

Research Article

Molecular Docking, Drug-Likeness, and Toxicity Profiling of *Taraxacum Officinale*-derived Phytochemicals Against Estrogen Receptor Alpha (ER α) in Breast Cancer

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Abstract

Public interest in the anticancer potential of dandelion (*Taraxacum officinale*) root has grown following reports that its extract can induce cell death in cancer cell lines, but whether individual *T. officinale* phytochemicals directly engage estrogen receptor alpha (ER α), the principal target in hormone receptor-positive breast cancer, has not been characterised. This study computationally evaluated eight bioactive phytochemicals reported from *T. officinale* root (taraxasterol, lupeol, β -sitosterol, chlorogenic acid, caffeic acid, chicoric acid, luteolin, and quercetin) as potential ER α inhibitors, benchmarked against tamoxifen. Molecular docking was performed using AutoDock Vina against the ER α ligand-binding domain (PDB: 3ERT), with docking protocol validity confirmed by redocking the native ligand and calculating the root-mean-square deviation (RMSD). Drug-likeness was assessed using SwissADME (Lipinski's Rule of Five), and pharmacokinetic and toxicity behaviour were predicted using pkCSM. Redocking reproduced the native ligand pose with an RMSD of 0.260 Å. Binding scores ranged from -4.5 (lupeol) to -8.5 kcal/mol (luteolin), versus -9.8 kcal/mol for tamoxifen. Luteolin, quercetin, chicoric acid, β -sitosterol, and chlorogenic acid showed the most favourable docking energies; luteolin and quercetin reproduced key hydrogen bonds seen for the native ligand, though none reproduced tamoxifen's Asp351 salt bridge. Chlorogenic acid, caffeic acid, luteolin, and quercetin showed zero Lipinski violations, and all eight phytochemicals were hepatotoxicity-inactive in silico, unlike tamoxifen. These findings offer a receptor-level perspective on dandelion's reported anticancer activity and identify candidates warranting experimental validation.

Keywords

Taraxacum Officinale, Estrogen Receptor Alpha, Molecular Docking, Tamoxifen, ADMET, Breast Cancer

1. Introduction

Breast cancer is the most common cancer in women across the globe and the leading cause of cancer associated mortality. The latest figures from GLOBOCAN, 2022, show 2,295,686 new cases and 665,684 deaths have been reported among

women globally, with breast cancer representing nearly 23.8% of all new cancer cases and 15.4% of all cancer-related deaths among women [1].

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Received: 8 September 2026; **Accepted:** 17 September 2026; **Published:** 9 October 2026



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Disease burden does not, however, fall equally on all regions: Asia had the highest total absolute incidence, with Europe and Northern America coming second and third, respectively, whereas Africa had the highest mortality-incidence ratio, highlighting disparities in early detection and treatment access [2]. Globally, the burden is anticipated to rise rapidly for several decades to come, with over 6 million future cases projected to occur by 2050 [2], again emphasizing an immediate and ongoing requirement for therapeutics that are efficacious, affordable, and compatible with a heterogeneous disease.

Breast cancer comprises a group of molecularly distinct subtypes, each with differing clinical course and response to treatment. Using gene expression profiling, breast cancer has been further placed into discrete molecularly defined subgroups (Luminal, HER2-Enriched, Basal-like and Normal-like) with different natural history and responsiveness to therapy [3]. Such a molecular taxonomy is for the most part captured in the clinic using hormone receptor and HER2 status, leading to four broad categories of breast cancer: hormone receptor-positive /HER2-negative cancers (closely corresponding to Luminal A subtype), hormone receptor-positive/ HER2-positive (Luminal B), HER2-enriched, and triple-negative breast cancer (TNBC). Luminal subtypes, which are defined by ER and/or PR status, are by far the most common in the clinical setting, whereas TNBC, which lacks ER, PR and HER2, accounts for 10-15% of all breast cancers and has the highest risk of recurrence with no tumour specific targeted therapies available [3].

Among these subtypes, ER-positive breast cancer occupies a position of particular clinical importance because it represents the largest proportion of cases and is amenable to hormonal manipulation. Reviews of ER-driven breast cancer report that approximately 70% of breast tumours are estrogen receptor-positive, making ER signalling the single most exploited therapeutic vulnerability in breast oncology [4]. Because ER-positive disease depends on estrogen-driven proliferative signalling for tumour growth and survival, pharmacological disruption of this axis, through selective estrogen receptor modulators, receptor downregulators, or aromatase inhibitors, has become the cornerstone of both adjuvant and long-term breast cancer management.

Ligand activated transcription factor of ER, ER alpha is encoded by the gene ESR1 and is known to regulate most estrogen-induced proliferation effects in the mammary epithelium. The protein includes AF (Activation Function) domains that drive breast cancer proliferation, metastasis and is also associated with the development of drug-resistance. These can also result through a non-genomic and a ligand-independent pathways in addition to classic genomic pathway [4]. Upon ligand binding, the receptor undergoes a conformational change that regulates recruitment of coactivator proteins to target gene promoters, driving transcriptional programmes that sustain cell cycle progression and inhibit apoptosis. Beyond its canon-

ical role in reproductive physiology, dysregulated ER α signalling has been implicated in a range of pathological conditions, including reproductive system-related disorders such as breast, ovarian, and prostate cancer, reflecting the receptor's broad influence on hormone-responsive tissues [5].

The centrality of ER α to luminal breast cancer biology has made it one of the most extensively validated and clinically actionable drug targets in oncology. Its ligand-binding domain possesses a well-defined hydrophobic pocket capable of accommodating structurally diverse small molecules, a feature that has enabled the rational design of antagonists that competitively displace estradiol and lock the receptor in an inactive conformation. Structural biology has been instrumental in this effort: crystallographic analysis of the human ER α ligand-binding domain bound to the active tamoxifen metabolite 4-hydroxytamoxifen showed that antagonist binding causes helix 12 to fold back over the surface region that would otherwise recruit transcriptional coactivator proteins, physically blocking this recruitment and thereby silencing receptor-driven transcription [6]. This structure, deposited as PDB 3ERT, remains a benchmark template for structure-based drug design targeting ER α and provides the receptor conformation used in the present docking study.

Tamoxifen, a first-generation selective estrogen receptor modulator (SERM), has been the mainstay of endocrine therapy for ER-positive breast cancer for over four decades. Mechanistically, tamoxifen and its active metabolites competitively bind the ER α ligand-binding domain, blocking the transcriptional activity of the receptor by directly binding to it, rather than degrading it, distinguishing SERMs from selective estrogen receptor downregulators such as fulvestrant [7]. Clinically, tamoxifen's importance is difficult to overstate: it has been used for four decades as endocrine therapy and has reduced breast cancer mortality by approximately 30% [7], cementing its role as one of the most successful targeted therapies in the history of oncology.

Despite this success, tamoxifen therapy is constrained by significant limitations. Its efficacy is undermined by both intrinsic and acquired resistance, with approximately 60% of patients with ER-positive breast cancer eventually experiencing some form of resistance to anti-estrogen therapy over the course of treatment [8]. Mechanistically, resistance has been linked to downregulation of ER α itself, alongside protective autophagy and dysregulated cell cycle regulators, reflecting the tumour's capacity to circumvent single-pathway blockade through multiple compensatory mechanisms [9]. Tamoxifen's tissue-selective pharmacology further compounds these challenges: while it behaves as an antagonist in breast tissue, it exhibits agonist activity in the endometrium, a property that is characterised by dose- and duration-dependent proliferative effects on uterine tissue [10]. Thus, long-term use of tamoxifen causes several clinically important effects; higher rates of endometrial cancer and venous thromboembolic disease [11], as well as frequently observed hot flashes and menopausal ef-

fects, occur among women receiving this therapy. These limitations collectively justify continued investigation into alternative or complementary ER α -targeting agents with potentially improved safety and resistance profiles.

Natural products have historically been a productive source of anticancer agents and continue to offer chemical scaffolds that are structurally distinct from synthetic libraries. Phytochemicals have been central to cancer therapeutics since the earliest antineoplastic drugs were discovered, and plant-derived compounds continue to constitute a substantial fraction of clinically used oncology drugs, exemplified by taxanes, vinca alkaloids, and camptothecin derivatives [12]. Natural compounds are valued in oncology not only for their direct cytotoxic potential but also for their roles as chemopreventive agents and as sensitisers that can overcome multidrug resistance. Importantly, since 1981, roughly a quarter of newly approved anticancer molecules have been derived from natural sources [13], reflecting sustained pharmaceutical interest despite the dominance of synthetic drug discovery pipelines. This track record provides a strong rationale for systematically evaluating phytochemicals from traditionally used medicinal plants against validated cancer targets such as ER α .

Taraxacum officinale (common dandelion) is one such plant with a long history of traditional use and recent scientific interest. Ethnomedicinally, dandelion has been used across diverse cultures for centuries; it has traditionally served as a diuretic, laxative, anti-inflammatory remedy, and digestive aid, with documented use in traditional Chinese medicine and European folk medicine for liver and urinary disorders [14]. Phytochemically, dandelion is a rich reservoir of bioactive constituents: phytochemical surveys reveal that dandelion contains a wide range of bioactive compounds, including polyphenols, phytosterols, flavonoids, carotenoids, terpenes, and coumarins, several of which act synergistically and contribute to antioxidant, antimicrobial, anti-inflammatory, and anticancer effects [15]. More than 197 compounds have been catalogued from *T. officinale* alone, with recent reviews expanding the genus-wide inventory considerably [16].

Dandelion, especially the root extract, has been increasingly noted by the public and scientific community because of its reported anticancer effects. Aqueous dandelion root extract caused selective apoptosis in colonic cancer cells. In the original research, an aqueous dandelion root extract has been shown to cause cell death in over 95 percent of colonic cancer cells in 48 hours but in healthy cells and to cause tumor growth reduction in xenograft models after oral administration [17]. This finding, alongside earlier reports of selective apoptosis induction in pancreatic cancer cells with no significant cytotoxic effect on non-cancerous fibroblasts [18] and in drug-resistant leukemia and melanoma cell lines, has contributed to considerable public interest in dandelion root as a potential anticancer agent. However, a crude extract producing selective cytotoxicity in a cell-based assay does not, on its own, establish which individual phytochemical is responsible, nor does it identify the molecular target through which any effect

is mediated, and this gap in mechanistic understanding motivates the present investigation.

This distinction matters because crude plant extracts are inherently complex mixtures containing dozens to hundreds of chemically diverse constituents that may act independently, additively, or synergistically, and whose relative concentrations vary with growing conditions, extraction method, and plant part used. Investigating individual, chemically defined bioactive compounds, rather than the whole extract, is therefore substantially more informative for mechanistic drug discovery: it allows a specific molecule to be linked to a specific molecular interaction with a specific target, enables rational structure-activity reasoning, and provides a tractable starting point for lead optimisation. Reviews of *Taraxacum*-derived oncotherapy candidates have specifically identified taraxasterol, chlorogenic acid, chicoric acid, and related constituents as promising agents capable of inhibiting tumour cell proliferation and modulating oncogenic pathways [30], underscoring that the anticancer potential of dandelion root is most plausibly attributable to a subset of its phytochemical constituents rather than to the extract as an undifferentiated whole.

Given the expense, time, and ethical burden associated with *in vitro* and *in vivo* pharmacological testing, computational approaches have become an indispensable first step in modern drug discovery. Molecular docking is one of the most commonly employed structure-based technique for this, facilitating computational modeling of the most energetically favourable position, orientation and conformation of a ligand within a target macromolecule's binding site, and thus offering an expedient approach to ranking of prospective molecules ahead of the expensive process of wet-laboratory validation [19]. However, the reliability of any docking protocol must first be established through validation: a standard approach involves redocking the co-crystallised ligand into its native binding site and calculating the root-mean-square deviation (RMSD) between the redocked and experimentally observed poses, with an RMSD value of ≤ 2.0 Å widely considered acceptable evidence of a reliable docking procedure [20]. Once validated, the docking protocol can be extended with confidence to score and rank candidate phytochemicals against the same target.

Docking alone, however, is insufficient to prioritise a viable drug candidate. Complementary *in silico* pharmacokinetic and toxicological profiling is equally essential, since a compound with excellent predicted binding affinity may nonetheless be unsuitable for development due to poor absorption, metabolic instability, or toxicity liabilities. Physicochemical drug-likeness filters such as Lipinski's Rule of Five remain a standard early screen, given that compounds analysed from thousands of successful oral drugs cluster within specific, well-defined property ranges [21], while dedicated servers such as SwissADME and pkCSM extend this assessment to pharmacokinetic behaviour, drug-likeness, and medicinal chemistry compatibility [22, 23], allowing rapid, cost-effective triage of candidate molecules prior to any experimental commitment. Tox-

icity prediction tools complete this pipeline by flagging potential mutagenic, hepatotoxic, or cardiotoxic liabilities early, further reducing the risk of late-stage attrition. Together, docking validation, drug-likeness assessment, ADMET prediction, and toxicity screening constitute a coherent, evidence-based in silico workflow that allows researchers to make a scientifically defensible case for or against a compound's therapeutic potential before any biological assay is performed.

Despite the accumulating evidence for the anticancer activity of *Taraxacum officinale* extracts, and despite the identification of specific bioactive constituents implicated in this activity, a critical gap remains in the literature: the direct molecular interaction between individual, major *T. officinale* phytochemicals and estrogen receptor alpha (the principal therapeutic target in hormone receptor-positive breast cancer) has not been systematically characterised. Existing anticancer studies of dandelion have relied predominantly on crude extracts and phenotypic cell-based assays, which, while valuable, do not establish whether any single constituent engages ER α in a manner comparable to established SERMs such as tamoxifen. Without this receptor-level mechanistic evidence, the relevance of dandelion's reported anticancer activity to hormone receptor-positive breast cancer specifically cannot be rationally assessed.

The aim of the present study was therefore to computationally evaluate eight bioactive phytochemicals reported from *Taraxacum officinale* root (taraxasterol, lupeol, β -sitosterol, chlorogenic acid, caffeic acid, chicoric acid, luteolin, and quercetin) as potential inhibitors of estrogen receptor alpha, using the ligand-binding domain co-crystallised with 4-hydroxytamoxifen (PDB: 3ERT) as the docking template, with tamoxifen employed as the reference standard. Following docking protocol validation through redocking and RMSD analysis, the binding affinities and interaction profiles of the test compounds were compared against the reference drug, and each compound was further assessed for drug-likeness, pharmacokinetic behaviour (via SwissADME and pkCSM), and predicted toxicity. This integrated in silico framework is intended to determine whether specific dandelion root phytochemicals possess molecular interactions with ER α consistent with anticancer potential, thereby providing a scientifically grounded foundation, independent of extract-level claims, for prioritising candidates for future experimental validation.

2. Materials and Methods

2.1. Protein and Ligand Retrieval

The three-dimensional crystal structure of human estrogen receptor alpha ligand-binding domain in complex with 4-hydroxytamoxifen (PDB ID: 3ERT; resolution 1.90 Å) was retrieved from the RCSB Protein Data Bank [6, 24]. This structure was selected as the docking template because it captures the antagonist-bound conformation of ER α , in which helix

12 occludes the coactivator-binding groove, making it directly relevant to the identification of antagonist-type ER α ligands. The three-dimensional structures of the eight test phytochemicals reported from *Taraxacum officinale* root (taraxasterol, lupeol, β -sitosterol, chlorogenic acid, caffeic acid, chicoric acid, luteolin, and quercetin), together with tamoxifen, the reference drug, were retrieved in structure-data file (SDF) format from the PubChem database [25] using the following PubChem Compound Identifiers (CIDs): taraxasterol (CID 115250), lupeol (CID 259846), β -sitosterol (CID 222284), chlorogenic acid (CID 1794427), caffeic acid (CID 689043), chicoric acid (CID 5281764), luteolin (CID 5280445), quercetin (CID 5280343), and tamoxifen (CID 2733526).

2.2. Protein and Ligand Preparation

Structure preparation was carried out in PyMOL (Schrödinger, LLC) [26]. The co-crystallised 4-hydroxytamoxifen ligand, all crystallographic water molecules, and other heteroatoms were removed from the 3ERT protein structure to generate a clean receptor file, and the extracted native ligand was retained separately for the docking validation procedure described below. Polar hydrogen atoms and Gasteiger partial charges were subsequently added to both the receptor and each ligand using AutoDockTools (ADT), and all structures were converted to the PDBQT format required for docking, following the standard AutoDock preparation protocol [27].

2.3. Molecular Docking Protocol

Molecular docking of the eight test phytochemicals and tamoxifen against the prepared ER α receptor was performed using AutoDock Vina with the following configuration: exhaustiveness = 8, num_modes = 8; grid box centre coordinates center_x = 31.575, center_y = -1.590, center_z = 25.599; grid box dimensions size_x = 16.5 Å, size_y = 12 Å, size_z = 16.5 Å. The grid box was centred on the native ligand-binding pocket occupied by 4-hydroxytamoxifen in the crystal structure, ensuring that the entire search space encompassed the residues known to line the antagonist-binding site [28]. For each ligand, the pose with the most favourable (most negative) predicted binding free energy, expressed in kcal/mol, was selected as the representative binding mode for subsequent interaction analysis.

2.4. Docking Validation

To validate the reliability of the docking protocol, the native co-crystallised ligand (4-hydroxytamoxifen) was extracted from the 3ERT structure and redocked into its original binding site under identical grid box and search parameters. The redocked pose was then superimposed on the original crystallographic pose of the native ligand, and the root-mean-square deviation (RMSD) between heavy-atom coordinates of the

two poses was calculated in PyMOL using the align function [26]. A redocking RMSD of 2.0 Å or less is generally accepted as evidence that a docking protocol can reliably reproduce the experimentally observed binding geometry and can therefore be extended with confidence to score novel ligands against the same target [20]. As an additional confirmatory step, the native ligand was independently redocked a second time under the validated protocol and its interaction profile with the ER α binding pocket was analysed alongside the redocking RMSD result.

2.5. Protein-Ligand Interaction Analysis

Two-dimensional and three-dimensional visualisation of protein-ligand interactions for each docked complex was performed in BIOVIA Discovery Studio Visualizer (Dassault Systèmes BIOVIA), which classifies non-bonded contacts into conventional hydrogen bonds, van der Waals contacts, alkyl and Pi-alkyl interactions, Pi-sulfur interactions, Pi-sigma interactions, salt bridges, Pi-cation interactions, and unfavourable steric or electrostatic clashes. For each ligand, the amino acid residues participating in these interaction types were identified and tabulated for comparison against the reference drug, tamoxifen.

2.6. Drug-Likeness, ADMET, and Toxicity Prediction

The physicochemical and drug-likeness properties of all nine compounds, molecular weight, LogP (octanol-water partition coefficient), topological polar surface area (TPSA), and the number of Lipinski Rule-of-Five violations, were evaluated using the SwissADME web server [22], applying the criteria of Lipinski et al. [21]. Absorption, distribution, metabolism, and excretion (ADME) parameters, including human intestinal absorption (HIA, %), apparent Caco-2 cell permeability (log Papp), blood-brain barrier permeability (log BB), steady-state volume of distribution (Vss, log L/kg), inhibitory activity against cytochrome P450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and total predicted clearance (log mL/min/kg), were predicted using the pkCSM server [23]. Acute oral toxicity was estimated as the median lethal dose (LD50, mg/kg) with corresponding Globally Harmonised System (GHS) toxicity classification, and hepatotoxicity liability was predicted for each compound using the same in silico platforms.

3. Results

3.1. Docking Validation

Redocking of the native 4-hydroxytamoxifen ligand into the ER α binding site of 3ERT reproduced the experimentally observed crystallographic pose with a root-mean-square deviation (RMSD) of 0.260 Å (Figure 1). This value is well below the generally accepted threshold of 2.0 Å for a reliable docking protocol [20], and the near-complete superimposition of the aromatic core, the alkyl side chain, and the dimethylaminoethoxy tail of the redocked and native poses confirms that the docking parameters faithfully reproduce the true binding geometry of the ER α ligand-binding pocket. This validated protocol was subsequently applied without modification to score the eight test phytochemicals and the reference drug, tamoxifen.

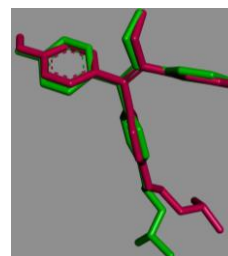


Figure 1. Superimposition of the native (pink) and redocked (green) pose of 4-hydroxytamoxifen within the ER α binding site (PDB: 3ERT). RMSD = 0.260 Å.

3.2. Molecular Docking of Test Compounds

All eight phytochemicals from *Taraxacum officinale* root docked successfully within the ER α ligand-binding pocket defined by the validated grid box. Binding scores ranged from -4.5 kcal/mol (lupeol) to -8.5 kcal/mol (luteolin), compared with -9.8 kcal/mol for tamoxifen, the reference drug (Table 1). Five compounds, luteolin (-8.5 kcal/mol), chicoric acid (-8.4 kcal/mol), quercetin (-8.0 kcal/mol), β -sitosterol (-7.9 kcal/mol), and chlorogenic acid (-7.4 kcal/mol), showed the most favourable docking energies among the test compounds, approaching but not matching the docking energy of tamoxifen. Luteolin was the strongest binder among the flavonoids, chicoric acid the strongest among the phenolic acids, and β -sitosterol the strongest among the triterpenoid/phytosterol subgroup. Taraxasterol (-5.6 kcal/mol), lupeol (-4.5 kcal/mol), and caffeic acid (-6.4 kcal/mol) showed less favourable docking energies and were not carried forward for detailed interaction analysis.

Table 1. Predicted binding scores of *Taraxacum officinale* phytochemicals and tamoxifen against ER α (PDB: 3ERT).

Compound	PubChem CID	Binding score (kcal/mol)
Taraxasterol (CPD1)	115250	-5.6
Lupeol (CPD2)	259846	-4.5
β -Sitosterol (CPD3)	222284	-7.9
Chlorogenic acid (CPD4)	1794427	-7.4
Caffeic acid (CPD5)	689043	-6.4
Chicoric acid (CPD6)	5281764	-8.4
Luteolin (CPD7)	5280445	-8.5
Quercetin (CPD8)	5280343	-8.0
Tamoxifen (reference drug)	2733526	-9.8

3.3. Protein-Ligand Interaction Analysis

Detailed two- and three-dimensional interaction analysis was performed for the five most promising phytochemicals (β -

sitosterol, chlorogenic acid, chicoric acid, luteolin, and quercetin) and for tamoxifen, in both its PubChem-derived reference-drug docking and its native-ligand (4-hydroxytamoxifen) revalidation docking. A summary of the interaction profiles is presented in Table 2, followed by compound-specific descriptions and figures.

Table 2. Summary of key protein-ligand interactions within the ER α binding pocket.

Compound	H-bond residues	Hydrophobic/alkyl/pi contacts	Other notable interactions
β -Sitosterol (CPD3)	None observed	Leu346, Leu525, Ala350, Phe404, Leu387, Leu391, Leu384, Met388, Trp383, Met343	Purely hydrophobic binding mode; no polar anchoring
Chlorogenic acid (CPD4)	Glu353, Arg394	Ala350 (Pi-alkyl)	Two conventional H-bonds stabilise the caffeoyl carbonyl and quinic acid moiety
Chicoric acid (CPD6)	Gly521, His524, Glu419, Arg394	Leu387 (Pi-sigma), Leu525	Pi-sulfur contacts with Met421, Met343; most extensive H-bond network of all test compounds
Luteolin (CPD7)	Glu353, Glu419, His524, Gly420	Leu387, Leu384, Ala350 (Pi-alkyl)	Pi-sulfur with Met421
Quercetin (CPD8)	Glu353, Glu419, His524, Gly420	Leu387, Leu384, Ala350 (Pi-alkyl)	Pi-sulfur with Met421; additional B-ring hydroxyl vs. luteolin
Tamoxifen (PubChem reference)	None (ionic/aromatic anchoring)	Met421, Phe404, Leu346, Leu387, Ala350 (alkyl/Pi-alkyl)	Salt bridge and Pi-cation with Asp351 via protonated dimethylaminoethyl side chain
4-Hydroxytamoxifen (native, revalidation)	None (unfavourable contact noted)	Met421, Leu346, Leu387, Ala350, Leu349, Leu391 (alkyl/Pi-alkyl)	Unfavourable acceptor-acceptor clash with Glu353

β -Sitosterol (CPD3)
 β -Sitosterol (-7.9 kcal/mol) occupied the ER α binding

pocket entirely through hydrophobic contacts, engaging Leu346, Leu525, Ala350, Phe404, Leu387, Leu391, Leu384,

Met388, Trp383, and Met343 via alkyl and Pi-alkyl interactions (Figure 2). No conventional hydrogen bonds were observed, indicating that the steroidal scaffold of β -sitosterol is accommodated within the hydrophobic sub-pocket of the re-

ceptor in a manner reminiscent of the non-polar core of tamoxifen's triphenylethylene skeleton, but without the polar anchoring contributed by tamoxifen's dimethylaminoethoxy side chain.

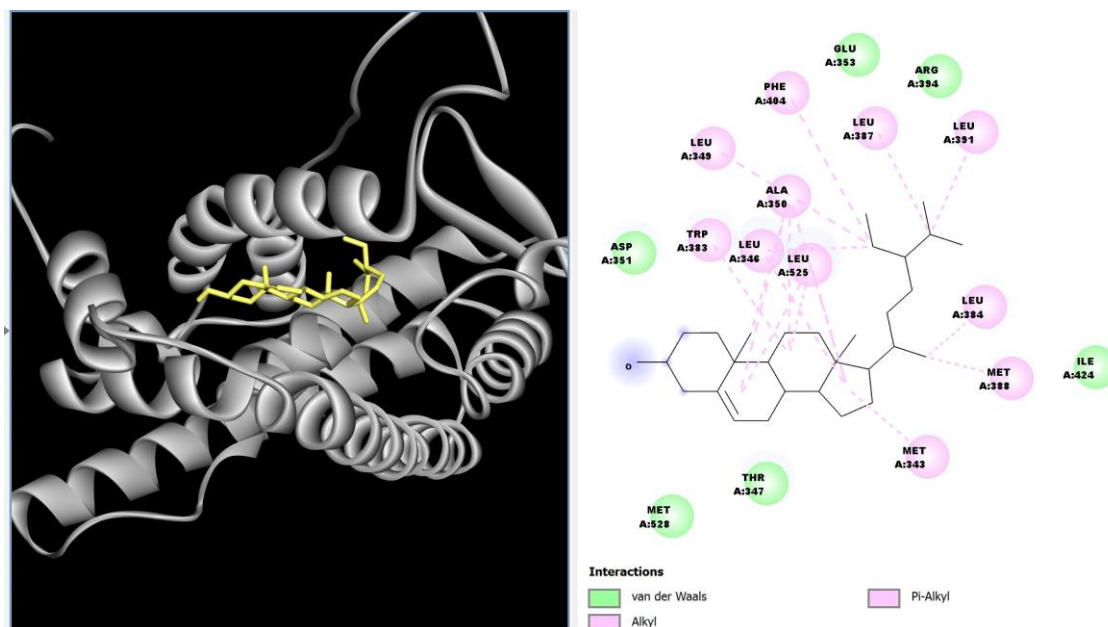


Figure 2. Predicted binding pose and 2D interaction diagram of β -sitosterol within the ER α binding pocket.

Chlorogenic acid (CPD4)

Chlorogenic acid (-7.4 kcal/mol) formed two conventional hydrogen bonds with Glu353 and Arg394, in addition to a Pi-alkyl contact with Ala350 (Figure 3). The caffeoyl-quinic acid

ester structure of chlorogenic acid allowed its carbonyl and hydroxyl groups to engage in polar interactions with the receptor, a binding mode distinct from the purely hydrophobic engagement seen with β -sitosterol.

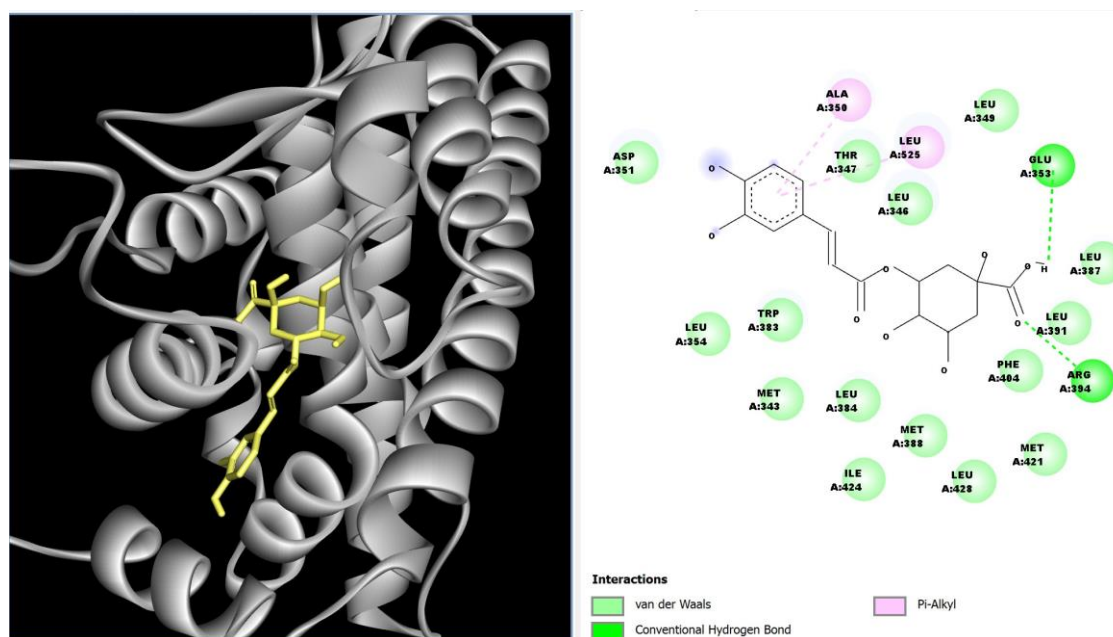


Figure 3. Predicted binding pose and 2D interaction diagram of chlorogenic acid within the ER α binding pocket.

Chicoric Acid (CPD6)

Chicoric acid (-8.4 kcal/mol), a dicaffeoyltartaric acid derivative, formed the most extensive polar interaction network among all test compounds, with conventional hydrogen bonds to Gly521, His524, Glu419, and Arg394, alongside Pi-sulfur

interactions with Met421 and Met343 and a Pi-sigma interaction with Leu387 (Figure 4). The presence of two caffeoyl moieties in the chicoric acid structure appears to allow simultaneous polar and hydrophobic engagement with residues at both ends of the ER α binding pocket.

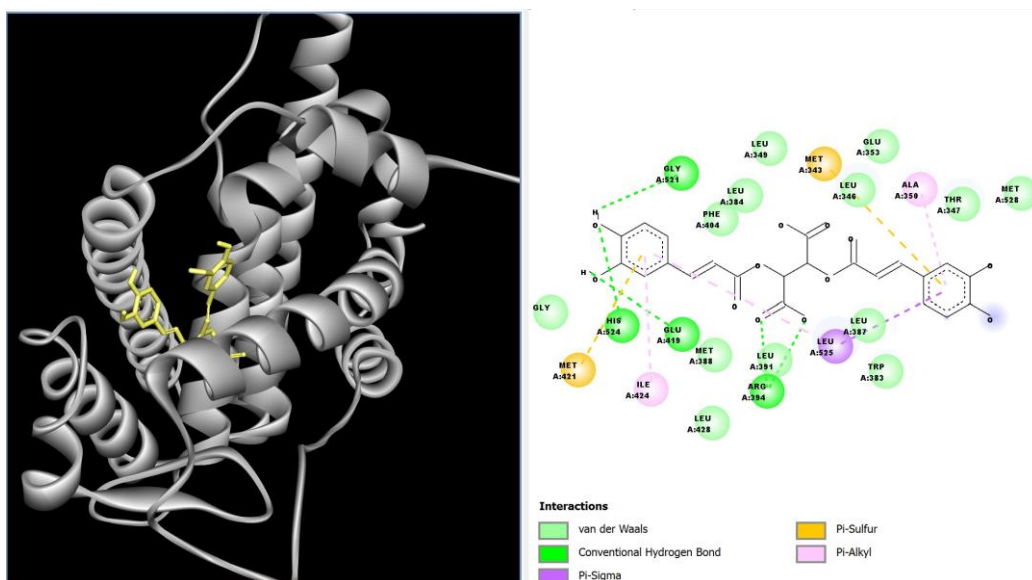


Figure 4. Predicted binding pose and 2D interaction diagram of chicoric acid within the ER α binding pocket.

Luteolin (CPD7)

Luteolin (-8.5 kcal/mol), the strongest-binding phytochemical overall, formed conventional hydrogen bonds with Glu353, Glu419, His524, and Gly420, together with Pi-alkyl contacts (Leu387, Leu384, Ala350) and a Pi-sulfur interaction with Met421 (Figure 5). The flavone backbone of luteolin,

bearing hydroxyl substituents at the 5-, 7-, 3'-, and 4'-positions, positioned its catechol-like B-ring hydroxyls to donate hydrogen bonds to Glu419 and His524, closely paralleling the hydrogen-bonding pattern seen for the native 4-hydroxytamoxifen ligand at the same receptor site.

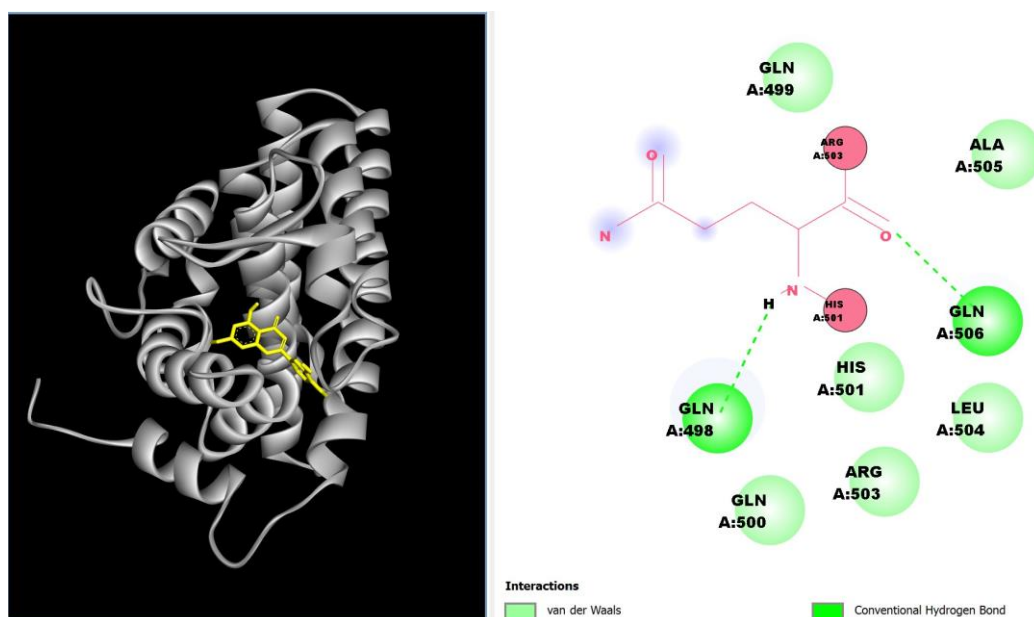


Figure 5. Predicted binding pose and 2D interaction diagram of luteolin within the ER α binding pocket.

Quercetin (CPD8)

Quercetin (-8.0 kcal/mol) shares an identical flavone core with luteolin, differing only by an additional hydroxyl group on the B-ring, and accordingly produced a near-identical interaction fingerprint: conventional hydrogen bonds with Glu353, Glu419, His524, and Gly420, Pi-alkyl contacts with

Leu387, Leu384, and Ala350, and a Pi-sulfur interaction with Met421 (Figure 6). The additional hydroxyl substituent did not markedly change the binding score relative to luteolin, but the conserved hydrogen-bonding network across both flavonoids reinforces the reproducibility of this polar anchoring mode within the ER α pocket.

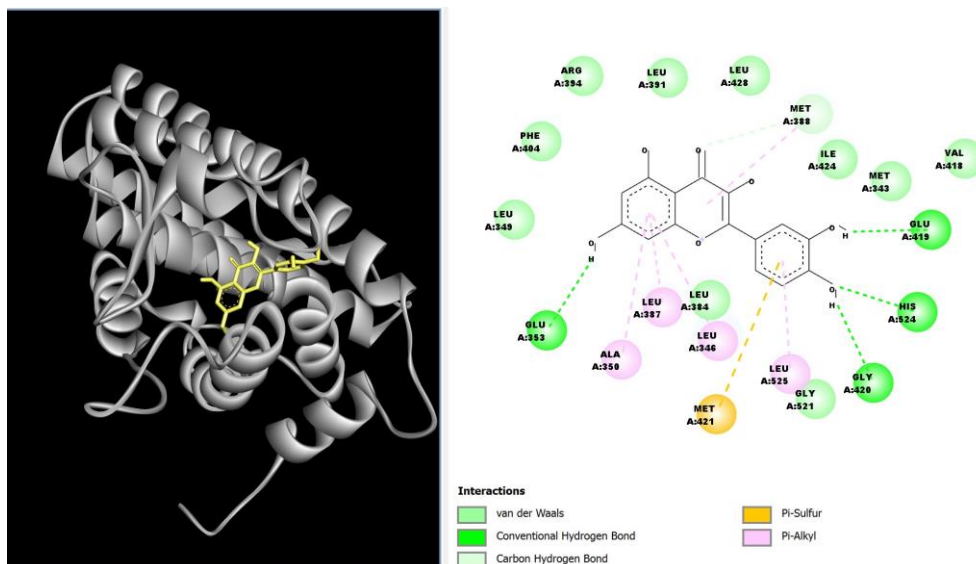


Figure 6. Predicted binding pose and 2D interaction diagram of quercetin within the ER α binding pocket, including a Pi-sulfur interaction with Met421.

Tamoxifen (Reference Drug, PubChem)

Tamoxifen (-9.8 kcal/mol), docked as the reference drug using its PubChem-derived structure, engaged the ER α pocket through an extensive alkyl and Pi-alkyl network (Met421, Phe404, Leu346, Leu387, Ala350) together with a salt bridge

and Pi-cation interaction between its protonated dimethylaminoethyl side chain and Asp351 (Figure 7). This ionic anchoring interaction, absent from all eight phytochemicals evaluated, is consistent with the established mechanism by which SERM side chains engage Asp351 to displace helix 12 and antagonise receptor activation [6].

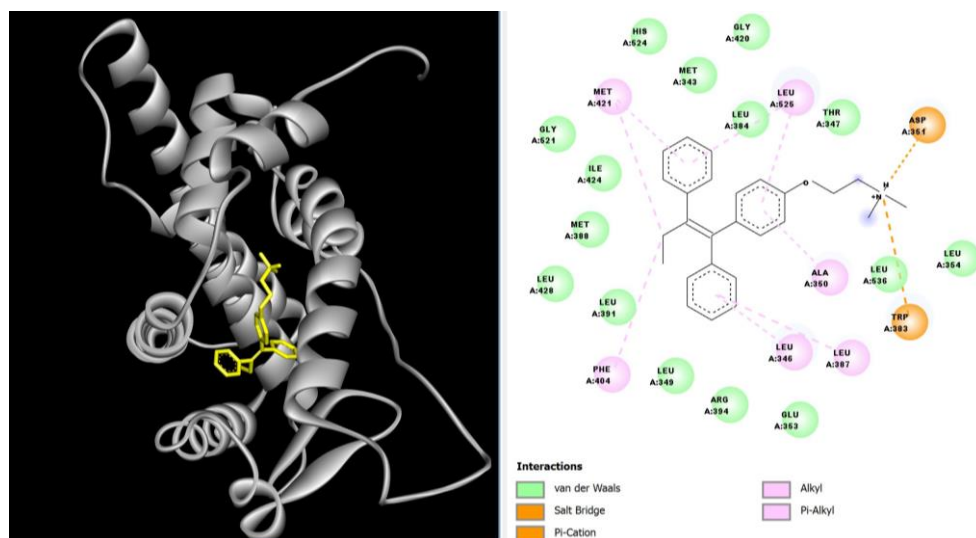


Figure 7. Predicted binding pose and 2D interaction diagram of tamoxifen (PubChem CID 2733526) within the ER α binding pocket, showing salt bridge/Pi-cation interaction with Asp351.

4-Hydroxytamoxifen (Native Ligand, Revalidation Docking)

As part of the docking validation exercise, the native ligand extracted from 3ERT (4-hydroxytamoxifen) was independently redocked and its interaction profile examined. This pose reproduced the same alkyl/Pi-alkyl hydrophobic network observed for the PubChem tamoxifen docking (Met421,

Leu346, Leu387, Ala350, Leu349, Leu391) but showed an unfavourable acceptor-acceptor clash with Glu353 involving the ligand's phenolic hydroxyl group (Figure 8). This finding is consistent with known steric sensitivity of the 4-hydroxy substituent within this sub-pocket and does not detract from the high fidelity of the redocking RMSD, since RMSD reflects positional accuracy rather than interaction favourability.

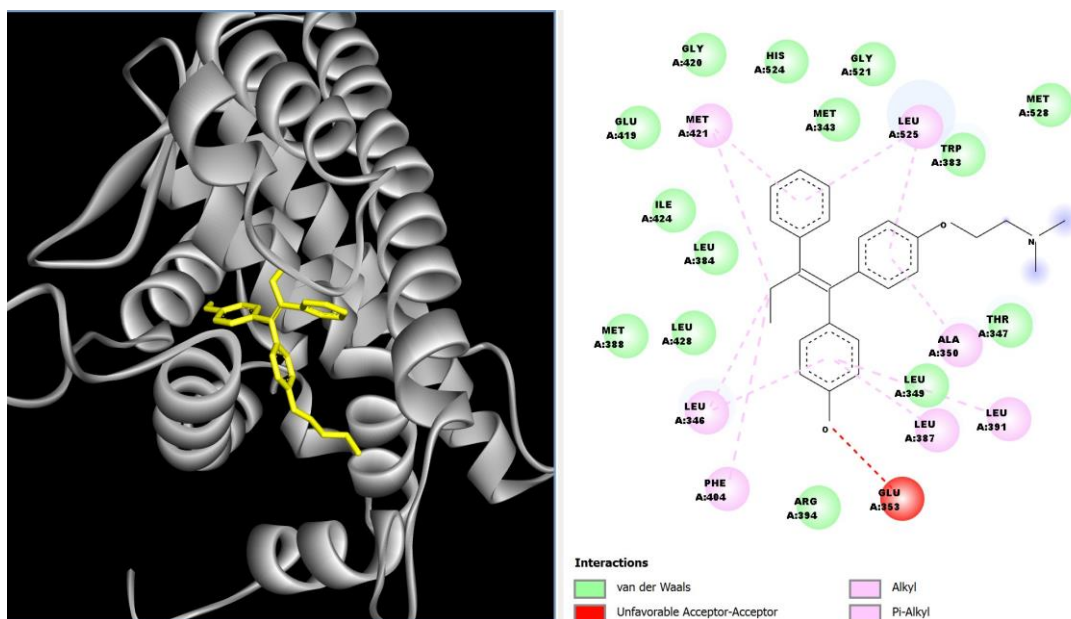


Figure 8. Predicted binding pose and 2D interaction diagram of the redocked native ligand (4-hydroxytamoxifen) within the ER α binding pocket, showing an unfavourable acceptor-acceptor interaction with Glu353.

3.4. Drug-Likeness, ADMET, and Toxicity Profile

All eight phytochemicals and tamoxifen were evaluated for physicochemical drug-likeness, pharmacokinetic behaviour, and predicted toxicity (Tables 3 and 4). Six of the eight test compounds carried zero or one Lipinski Rule-of-Five violations, indicating broadly favourable oral drug-likeness across the panel; taraxasterol, lupeol, and β -sitosterol each carried one Lipinski violation on account of elevated LogP. Chlorogenic acid, caffeic acid, luteolin, and quercetin recorded zero violations, matching or exceeding the drug-likeness profile of tamoxifen itself, which carried one violation (LogP = 6.06).

Predicted human intestinal absorption (HIA) varied considerably across the panel. The triterpenoid/phytosterol compounds (taraxasterol, lupeol, and β -sitosterol) showed high predicted HIA (94.25-94.80%), comparable to tamoxifen (96.89%), consistent with their high lipophilicity (LogP 5.82-7.91). Caffeic acid (69.40%) and quercetin (75.20%) showed moderate predicted absorption, luteolin showed similarly moderate absorption (81.13%), while chlorogenic acid (36.30%) and, most markedly, chicoric acid (0.69%) showed

poor predicted intestinal absorption, reflecting their high topological polar surface area (164.75 Å² and 208.12 Å², respectively) and multiple ionisable carboxylic acid groups. None of the nine compounds, including tamoxifen, were predicted to cross the blood-brain barrier, which is a favourable safety feature for compounds intended to act peripherally on breast tissue ER α rather than centrally.

Cytochrome P450 interaction predictions distinguished the flavonoids from the remaining phytochemicals: luteolin was predicted to inhibit CYP1A2 and CYP2C9, and quercetin was predicted to inhibit CYP1A2, CYP2C9, and CYP2C19, raising a theoretical potential for drug-drug interactions upon co-administration with substrates of these isoforms. Tamoxifen itself was predicted to inhibit CYP1A2 and CYP3A4, the latter being the isoform principally responsible for its own metabolic activation to endoxifen [29], whereas none of the triterpenoid, phytosterol, or simple phenolic acid compounds (taraxasterol, lupeol, β -sitosterol, chlorogenic acid, caffeic acid, chicoric acid) showed predicted inhibition of any of the five CYP isoforms evaluated.

Acute oral toxicity predictions indicated favourable safety margins for most test compounds. Taraxasterol, chlorogenic acid, and chicoric acid showed the highest predicted LD50

values (5000 mg/kg, GHS Class 5, the least hazardous classification), followed by caffeic acid (2980 mg/kg, Class 5) and lupeol (2000 mg/kg, Class 4). β -Sitosterol (890 mg/kg, Class 4) and luteolin (3919 mg/kg, Class 5) also fell within acceptable ranges. Quercetin showed the lowest predicted LD50 among the phytochemicals (159 mg/kg, GHS Class 3), placing it in a more hazardous acute toxicity category than the other

seven compounds, though still less severe than the most acutely toxic GHS classes. Tamoxifen showed a predicted LD50 of 1190 mg/kg (GHS Class 4) and was the only compound in the panel flagged as having an active hepatotoxicity liability; all eight phytochemicals were predicted to be hepatotoxicity-inactive.

Table 3. Physicochemical properties and drug-likeness parameters (SwissADME).

Ligand	MW (g/mol)	LogP	TPSA (Å ²)	Lipinski viol.	HIA (%)	Caco-2 (log Papp)	BBB (log BB)
Taraxasterol	426.72	5.82	20.23	1	94.25	1.21	No
Lupeol	426.72	7.91	20.23	1	94.80	1.23	No
β -Sitosterol	414.71	7.78	20.23	1	94.50	1.20	No
Chlorogenic acid	354.31	-0.71	164.75	0	36.30	-0.84	No
Caffeic acid	180.16	0.92	77.76	0	69.40	0.60	No
Chicoric acid	474.37	1.01	208.12	1	0.69	-1.12	No
Luteolin	286.24	1.10	111.13	0	81.13	0.10	No
Quercetin	302.24	0.79	131.36	0	75.20	0.18	No
Tamoxifen	371.51	6.06	12.47	1	96.89	1.10	No

Table 4. Predicted pharmacokinetic, cytochrome P450 interaction, and toxicity parameters (pkCSM).

Ligand	Vss (log L/kg)	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	Cl. (log mL/min/kg)	LD50 (mg/kg)	GHS class	Hepa-tox.
Taraxasterol	0.13	No	No	No	No	No	0.12	5000	5	Inactive
Lupeol	0.12	No	No	No	No	No	0.15	2000	4	Inactive
β -Sitosterol	0.20	No	No	No	No	No	0.63	890	4	Inactive
Chlorogenic acid	-0.58	No	No	No	No	No	0.30	5000	5	Inactive
Caffeic acid	-1.0	No	No	No	No	No	0.51	2980	5	Inactive
Chicoric acid	0.09	No	No	No	No	No	0.08	5000	5	Inactive
Luteolin	0.12	Yes	Yes	No	No	No	0.5	3919	5	Inactive
Quercetin	-0.23	Yes	Yes	Yes	No	No	0.42	159	3	Inactive
Tamoxifen	0.83	Yes	No	No	No	Yes	0.60	1190	4	Active

4. Discussion

The present study set out to determine whether individual,

chemically defined phytochemicals from *Taraxacum officinale* root show molecular interactions with estrogen receptor alpha, providing a receptor-level complement to previous extract-based reports of dandelion's anticancer activity. The redocking validation, which reproduced the crystallographic

pose of 4-hydroxytamoxifen with an RMSD of 0.260 Å, provides a high degree of confidence that the docking energies and interaction profiles reported here reflect geometrically reliable predictions of ligand pose within the ER α binding pocket, rather than artefacts of an unvalidated docking protocol [20].

Among the eight phytochemicals evaluated, luteolin, chicoric acid, quercetin, β -sitosterol, and chlorogenic acid emerged as the compounds with the most favourable predicted ER α docking energies (-7.4 to -8.5 kcal/mol), approaching the docking energy calculated for tamoxifen (-9.8 kcal/mol). Notably, the two flavonoids, luteolin and quercetin, reproduced a hydrogen-bonding pattern similar to that of the native 4-hydroxytamoxifen ligand, engaging Glu419 and His524 through their catechol-like B-ring hydroxyls. This convergence in predicted binding mode suggests that the flavone scaffold, independent of the steroidal or triphenylethylene chemotypes typical of estrogenic and anti-estrogenic ligands, may be capable of accessing the same polar recognition elements of the ER α ligand-binding domain that underlie tamoxifen's antagonist activity, although docking energies and shared contact residues indicate potential interaction rather than demonstrated biological efficacy. This observation is consistent with a substantial body of prior work establishing flavonoids such as quercetin and luteolin as phytoestrogen-like ER α ligands capable of both agonist and antagonist behaviour depending on cellular and structural context [5].

Chicoric acid's comparatively favourable docking energy (-8.4 kcal/mol) and extensive hydrogen-bonding network (the most polar-interaction-rich profile among all eight phytochemicals) is consistent with its dicaffeoyltartaric acid structure, which presents two catechol-like caffeoyl termini capable of simultaneous polar engagement at opposite ends of the binding pocket. This is the same class of compound previously highlighted in reviews of *Taraxacum*-derived oncotherapy candidates as a promising tumour-modulating constituent [30], and the present docking data provide, to our knowledge, the first structural evidence suggesting that chicoric acid may interact with the ER α ligand-binding domain specifically, rather than acting solely through the non-receptor-mediated apoptotic or oxidative-stress mechanisms previously reported for crude dandelion extracts [17]; this predicted interaction would need to be confirmed experimentally.

β -Sitosterol's binding mode, by contrast, was purely hydrophobic, lacking any hydrogen-bond anchoring within the pocket. This is consistent with its steroidal, non-polar structure, which lacks the phenolic or carboxylic acid groups available to the flavonoids and phenolic acids in this panel. While its binding score (-7.9 kcal/mol) was competitive, the absence of polar anchoring residues typically associated with high-affinity, selective ER α antagonism raises the possibility that its predicted affinity reflects a more generic hydrophobic-pocket fit rather than the specific polar recognition pattern that distinguishes established SERMs. This distinction underscores the value of interaction-level analysis over binding score alone

when prioritising candidates for further study.

Taraxasterol, lupeol, and caffeic acid showed the least favourable docking energies in the panel (-5.6, -4.5, and -6.4 kcal/mol, respectively) and were therefore not carried forward to detailed interaction analysis. These differences are plausibly explained by molecular structure. Taraxasterol and lupeol are both large, rigid pentacyclic triterpenoids that, unlike β -sitosterol, lack a flexible side chain capable of extending toward polar residues at the periphery of the ER α pocket; their bulk may also restrict optimal orientation within the binding cavity, limiting the number of favourable contacts relative to their molecular size. Caffeic acid, by contrast, is the smallest phenolic acid in the panel (180.16 g/mol) and possesses only a single catechol ring with no ester linkage to a second polar moiety, unlike chlorogenic acid (which adds a quinic acid ester) or chicoric acid (which presents two caffeoyl termini); this more limited polar surface area and reduced molecular complexity likely restrict caffeic acid to fewer simultaneous contacts within the pocket. Their comparatively modest predicted affinity for ER α does not exclude a role in dandelion's previously reported anticancer activity, since non-ER α mechanisms (including direct pro-apoptotic, pro-autophagic, and oxidative-stress-mediated pathways) have been implicated in the cytotoxic effects of dandelion root extract in prior cell-based studies [17, 18]. Rather, these findings suggest that if dandelion root extract exerts any ER α -mediated component of anticancer activity, this is more plausibly attributable to its flavonoid and phenolic acid constituents than to its triterpenoid fraction.

Critically, no phytochemical in this panel reproduced tamoxifen's ionic anchoring interaction with Asp351, mediated by the protonated dimethylaminoethyl side chain that is characteristic of triphenylethylene SERMs [6]. This structural feature is widely regarded as central to the specific, high-affinity antagonism exhibited by tamoxifen and related SERMs, since it positions the ligand precisely to displace helix 12 and block coactivator recruitment. Its absence across all eight test compounds indicates that, while several dandelion phytochemicals, particularly the flavonoids and chicoric acid, show predicted molecular interactions consistent with ER α engagement, none is likely to reproduce tamoxifen's mechanism of action with equivalent specificity. These docking results indicate potential interaction with the ER α ligand-binding domain that warrants experimental validation, rather than demonstrating that these compounds function as ER α antagonists or possess anticancer efficacy.

From a translational perspective, the ADMET and toxicity profile of the panel is broadly encouraging in silico. Chlorogenic acid, caffeic acid, luteolin, and quercetin each showed zero Lipinski violations, a physicochemical drug-likeness profile at least as favourable as that of tamoxifen [21]. None of the nine compounds evaluated, including tamoxifen, was predicted to cross the blood-brain barrier, a favourable feature for a receptor target expressed principally in peripheral hormone-responsive tissue. The predicted absence of hepatotoxicity

across all eight phytochemicals, contrasting with tamoxifen's own flagged hepatotoxicity liability, is a notable finding given that tamoxifen-associated hepatotoxicity, including rare cases of hepatocellular injury and an increased risk of non-alcoholic fatty liver changes, is a recognised, if uncommon, clinical concern [31]. These compounds therefore displayed more favourable predicted hepatotoxicity profiles *in silico* than tamoxifen; whether this translates into an improved hepatic safety margin *in vivo* would need to be confirmed experimentally, since *in silico* hepatotoxicity models do not capture dose, exposure duration, or metabolic activation in a living system.

The most important caveat concerns quercetin's predicted acute oral toxicity (LD50 = 159 mg/kg, GHS Class 3), which places it in a more hazardous category than every other phytochemical evaluated, despite its otherwise favourable drug-likeness and ER α -binding profile. Quercetin and luteolin were also the only two phytochemicals flagged for potential CYP1A2 and CYP2C9 inhibition (with quercetin additionally flagged for CYP2C19 inhibition), raising a theoretical risk of pharmacokinetic drug-drug interactions. These findings do not disqualify quercetin as a compound of interest, since *in silico* LD50 predictions carry considerable uncertainty and quercetin has an extensive history of dietary and supplemental human exposure at far lower doses than those associated with acute toxicity thresholds in rodent models, but they do indicate that any future experimental work with quercetin in this context should include a careful dose-ranging toxicological assessment.

Taken together, these findings help to narrow the mechanistic space underlying dandelion root's reported anticancer activity. Prior cell-based studies established extract-level cytotoxicity in colorectal and pancreatic cancer cell lines [17, 18] but did not identify a specific molecular target. The present *in silico* analysis provides structural evidence that at least five individual *T. officinale* phytochemicals (β -sitosterol, chlorogenic acid, chicoric acid, luteolin, and quercetin) show docking energies and, in several cases, hydrogen-bonding patterns comparable to a validated SERM reference standard, suggesting potential interaction with the ER α ligand-binding domain that warrants experimental validation. Rather than dandelion root acting as an undifferentiated cytotoxic agent, these data point to specific constituents, particularly the flavonoids, as candidates for targeted experimental follow-up, rather than the extract as a whole.

5. Conclusions

This study employed a validated molecular docking protocol (redocking RMSD = 0.260 Å) to evaluate eight bioactive phytochemicals from *Taraxacum officinale* root as potential estrogen receptor alpha inhibitors, benchmarked against tamoxifen. Luteolin, chicoric acid, quercetin, β -sitosterol, and chlorogenic acid showed the most favourable docking energies, with luteolin and quercetin in particular reproducing key hydrogen-bonding interactions characteristic of the native

ER α ligand within the same pocket. None of the eight phytochemicals reproduced tamoxifen's signature ionic interaction with Asp351, indicating that these compounds are unlikely to act as direct tamoxifen mimetics, but several nonetheless show docking patterns consistent with potential ER α interaction that warrants experimental validation. Drug-likeness and ADMET profiling further identified chlorogenic acid, caffeic acid, luteolin, and quercetin as possessing favourable oral drug-likeness with zero Lipinski violations, and all eight phytochemicals displayed more favourable predicted hepatotoxicity profiles *in silico* than tamoxifen. Quercetin's comparatively lower predicted LD50 warrants caution and further scrutiny in any future experimental work. Collectively, these findings offer a receptor-level perspective on dandelion root's reported anticancer activity and identify specific phytochemical candidates, most notably luteolin, quercetin, and chicoric acid, for prioritised experimental validation, including *in vitro* ER α binding assays, transcriptional reporter assays, and cell-based proliferation studies in ER-positive breast cancer models, before any conclusions regarding *Taraxacum officinale*'s therapeutic relevance to hormone receptor-positive breast cancer can be drawn.

Abbreviations

ER α	Estrogen Receptor Alpha
SERM	Selective Estrogen Receptor Modulator
PDB	Protein Data Bank
RMSD	Root-Mean-Square Deviation
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
TPSA	Topological Polar Surface Area
HIA	Human Intestinal Absorption
BBB	Blood-Brain Barrier
CYP	Cytochrome P450
LD50	Median Lethal Dose
GHS	Globally Harmonised System
MW	Molecular Weight
CID	PubChem Compound Identifier
SDF	Structure-Data File
PDBQT	Protein Data Bank, Partial Charge (Q), and Atom Type (T) File Format
V _{ss}	Steady-State Volume of Distribution
Papp	Apparent Permeability
TNBC	Triple-Negative Breast Cancer
HER2	Human Epidermal Growth Factor Receptor 2
ER	Estrogen Receptor
PR	Progesterone Receptor
ESR1	Estrogen Receptor 1 (gene)
AF	Activation Function
GLOBOCAN	Global Cancer Observatory

Acknowledgments

I sincerely acknowledge Mrs Modupe Ajike Lawrence and Mr. Ayodele Idris Aminu for the support and encouragement received during the course of this work.

Author Contributions

Osakuade Ayodeji Sunday: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing

Ikor Kelvin Okibe: Methodology, Supervision, Validation, Writing – review & editing

Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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