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Lecanoric Acid As a Multi-Target Candidate Against Breast Cancer: *In Silico* Interactions With 17β-HSD1, ERα, EGFR, Bcl-xL and ADMET Profiling

Meme Kanserine Karşı Çok Hedefli Bir Aday Olarak Lekanorik Asit: 17β-HSD1, ERα, EGFR, Bcl-xL ile *In Silico* Etkileşimler ve ADMET Profillemesi

Feyza Burul[1,2], Selma Sezen[1]

[1] Agri Ibrahim Cecen University, Faculty of Medicine, Department of Medical Pharmacology, Agri, Türkiye

[2] Department of Medical Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Türkiye

ORCID ID: Feyza Burul: https://orcid.org/0009-0002-2193-1106, Selma Sezen: https://orcid.org/0000-0001-6575-6149

***Sorumlu Yazar / Corresponding Author:** Feyza Burul **e-posta / e-mail:** feyza.burul@hotmail.com

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Abstract

Aim Breast cancer is a common disease in women with high morbidity and mortality. Although various treatment modalities are available, chemoresistance remains a major problem in breast cancer. This study aimed to investigate the interactions of lecanoric acid, a natural compound with bioactive properties, with receptors considered therapeutic targets in breast cancer.

Materials and Methods The 3D structures of the target proteins 17β-HSD1 (1FDW), ERα (6CBZ), EGFR (1M17), and Bcl-xL (2W3L) were retrieved from the RCSB Protein Data Bank (RCSB PDB; https://www.rcsb.org) using their PDB IDs. The 3D structure of lecanoric acid was downloaded from the PubChem database and prepared for analysis. AutoDock Vina was used for molecular docking analyses. Ligand-receptor interactions were visualized using Discovery Studio 2021 (BIOVIA, USA). In addition, the physicochemical, medicinal chemistry, pharmacokinetic, and toxicity profiles of lecanoric acid as a drug candidate were comprehensively evaluated using ADMETlab 3.0.

Results Molecular docking analyses indicated that lecanoric acid bound to the target proteins with docking scores ranging from -7.1 to -7.7 kcal/mol. In addition, the probability of P-gp inhibition by lecanoric acid was predicted to be very low, and the radar plot showed that the evaluated ADMET parameters remained within the predefined lower and upper limits.

Conclusions Lecanoric acid was found to exhibit high binding affinity toward 17β-HSD1, ERα, EGFR, and Bcl-xL, which are of critical importance in breast cancer pathology. Although lecanoric acid appears to have favorable properties in terms of its physicochemical, medicinal chemistry, pharmacokinetic, and toxicity profiles, in vitro and in vivo studies are needed to validate its therapeutic potential.

Keywords 17β-HSD1, ADMET, breast cancer, EGFR, lecanoric acid, molecular docking

Öz

Amaç *Meme kanseri kadınlarda sık görülen, morbiditesi ve mortalitesi yüksek bir hastalıktır. Tedavide farklı yöntemler bulunmakla birlikte kemorezistans, meme kanserinde önemli bir problemdir. Bu çalışmada biyoaktif özelliklere sahip doğal bir bileşik olan lekanorik asitin meme kanserinde tedavi hedefi olarak değerlendirilen reseptörlerle etkileşiminin araştırılması amaçlanmıştır.*

Gereç ve Yöntem *Hedef proteinlerin 3D yapıları, 17β-HSD1 (1FDW), ERα (6CBZ), EGFR (1M17) ve Bcl-xL (2W3L) PDB kimlikleri kullanılarak RCSB Protein Veri Bankası'ndan (RCSB PDB; https://www.rcsb.org) elde edildi. Lekanorik asidin 3D yapısı PubChem veritabanından indirildi ve analizler için hazırlandı. Moleküler docking analizleri için AutoDock Vina kullanıldı. Ligand-reseptör etkileşimleri Discovery Studio 2021 (BIOVIA, ABD) kullanılarak görselleştirildi. Ayrıca lekanorik asidin ilaç adayı olarak fizikokimyasal, tıbbi kimya, farmakokinetik ve toksisite profilleri ADMETlab 3.0 kullanılarak kapsamlı bir şekilde değerlendirildi.*

Bulgular *Moleküler docking analizlerinde lekanorik asitin hedef proteinlere -7,1 ila -7,7 kcal/mol arasında değişen kenetlenme skorlarıyla bağlandığı belirlenmiştir. Ayrıca lekanorik asidin P-gp inhibisyonu olasılığının çok düşük olduğu ve değerlendirilen ADMET parametrelerinin önceden tanımlanmış alt ve üst sınırlar içinde kaldığı radar grafiğinde kaydedilmiştir.*

Sonuç *Lekanorik asitin meme kanseri patolojisinde kritik öneme sahip 17β-HSD1, ERα, EGFR, ve Bcl-xL ile yüksek bağlanma afinitesi gösterdiği belirlenmiştir. Fizikokimyasal, tıbbi kimya, farmakokinetik ve toksisite profilleri açısından olumlu özelliklere sahip olduğu belirlenen lekanorik asitin terapötik potansiyelinin doğrulanması için in vitro ve in vivo çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler *17β-HSD1, ADMET, meme kanseri, EGFR, lekanorik asit, moleküler docking*

INTRODUCTION

Breast cancer is one of the most prevalent malignancies among women and is characterized by tumor formation resulting from the uncontrolled proliferation of breast cells.[1,2] Globally, approximately 2.3 million new cases are diagnosed each year, and this number is projected to reach nearly 3.2 million annually by 2050.[3-5]. In addition to its high incidence, the substantial mortality burden, estimated at around 670.000 deaths, further underscores breast cancer as a major global public health concern.[1]

In the current management of breast cancer, systemic therapies are widely employed alongside surgical resection and radiotherapy. These include selective estrogen receptor modulators (e.g., tamoxifen), aromatase inhibitors (anastrozole, letrozole, exemestane), LH-RH agonists (leuprolide, goserelin), and selective estrogen receptor degraders such as fulvestrant.[6] However, these treatment modalities have notable limitations, including off-target toxic effects on healthy tissues, particularly immune cells, and issues related to long-term tolerability in certain patient populations. Moreover, the development of resistance to chemotherapeutic agents remains a significant clinical challenge in breast cancer.[7,8] Despite advances in early diagnosis and therapeutic strategies, the etiology of breast cancer remains highly complex, with an expanding landscape of multifaceted molecular mechanisms being elucidated. Consequently, there is a continuing need for the development of biocompatible, target-specific therapeutic agents with reduced toxicity profiles.[9]

Breast cancer is a multifactorial disease that arises from the complex interplay of genetic predisposition, lifestyle, and hormonal factors. Hereditary susceptibility has been associated with germline mutations affecting one allele of genes such as BRCA1/2, CHEK2, PALB2, and TP539. Lifestyle-related contributors include environmental and behavioral factors such as radiation exposure, obesity, physical inactivity, alcohol consumption, and smoking3. In addition to these factors, hormonal influences, particularly estrogen, are known to play a central role in breast cancer development. Prolonged estrogen exposure increases breast cancer risk through conditions such as early menarche, late menopause, nulliparity, and lack of breastfeeding.[9] For estrogen to exert its biological effects, it must undergo activation following its synthesis. 17β-Hydroxysteroid dehydrogenase type 1 (17β-HSD1), which catalyzes the final step of estrogen biosynthesis, converts estrone (E1) into the more potent estradiol (E2), thereby enhancing estrogenic signaling. Increased expression and activity of 17β-HSD1 have been reported in malignant breast tissue compared with normal breast tissue. Moreover, reduced 17β-HSD1 levels have been associated with suppression of proliferative signaling, supporting its relevance as a potential therapeutic target.[8,10,11]

Activated estrogen exerts its carcinogenic effects predominantly through estrogen receptor alpha (ERα). Upon binding to ERα, estrogen activates the receptor and regulates the transcription of genes involved in cell proliferation, differentiation, and survival, thereby promoting tumor development and progression. Consistent with this role, ERα is reported to be expressed in more than 70% of breast cancers and is regarded as one of the most important biomarkers in diagnosis and treatment planning.[6,12] ERα is also known to be regulated independently of estrogen by several membrane receptor tyrosine kinases, most notably the epidermal growth factor receptor (EGFR). Activation of EGFR can stimulate downstream signaling cascades such as the mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) and phosphoinositide 3-kinase / protein kinase B (PI3K/AKT) pathways, leading to ligand-independent activation of ERα and sustained tumor cell proliferation even under low-estrogen conditions. This ER activation mediated by EGFR signaling is referred to as ligand-independent receptor activation.[13-15] At the same time, ERα signaling has also been shown to regulate EGFR expression and activity. This bidirectional crosstalk contributes to tumor progression and therapeutic resistance in breast cancer.[12,16] ERα and

EGFR-mediated signaling not only enhances cell proliferation but also activates downstream mechanisms that suppress apoptotic responses. Among the anti-apoptotic members of the B-cell lymphoma 2 (Bcl-2) protein family, B-cell lymphoma-extra large (Bcl-xL) is a key regulatory protein that plays a central role in determining whether a cell undergoes apoptosis. In breast cancer, however, Bcl-xL overexpression has been associated with increased chemoresistance, enhanced tumor cell survival, and disease progression.[17] In this context, inhibition of ERα, EGFR, and Bcl-xL represents an important therapeutic strategy in breast cancer.[12,17]

Natural compounds have played a major role in the development of therapeutic agents used in the treatment of various diseases, particularly cancer. One of the best-known examples is taxane, originally isolated from the bark of the Pacific yew tree (Taxus brevifolia).[18] Numerous anticancer agents derived from natural sources such as plants, fungi, and bacteria, including taxanes, berberine, rapamycins, and antroquinonol, have either already been approved for the treatment of different cancer types or are still under investigation.[19] Owing to their relatively low toxicity and broad spectrum of bioactivities, natural compounds continue to attract considerable interest in cancer research.[20-22] Lecanoric acid, a lichen-derived secondary metabolite with diverse reported bioactivities, has also been investigated in recent years for a range of potential biological effects (Figure 1). It has been identified in various lichen species inhabiting diverse environments, including Antarctica.[23] Previous studies have reported that lecanoric acid possesses antimicrobial, antiviral, anticancer, and antioxidant properties.[19,23,24] Its natural origin, together with its broad bioactivity profile, makes lecanoric acid a particularly attractive candidate for investigation in different disease contexts.[25] In a study evaluating the effects of lichen metabolites on different cell lines, lecanoric acid did not reduce cell viability in mouse fibroblast cells at concentrations up to 3 μg/mL. Conversely, at the same concentration, it significantly decreased viability in mouse leukemic macrophage (RAW264.7) and human cervical epithelial cancer (HeLa) cell lines. Moreover, following 24 hours of treatment, lecanoric acid was reported to arrest cell division in HCT-116 cells by significantly increasing the proportion of cells in the G2 phase even at a low concentration of 0.3 μg/mL.[24] In addition, the methanol extract of Parmotrema tinctorum, which contains lecanoric acid among its constituents, has been shown to exert antiproliferative effects against MCF-7 cells.[26] Nevertheless, current knowledge regarding the effects of lecanoric acid on breast cancer remains very limited.

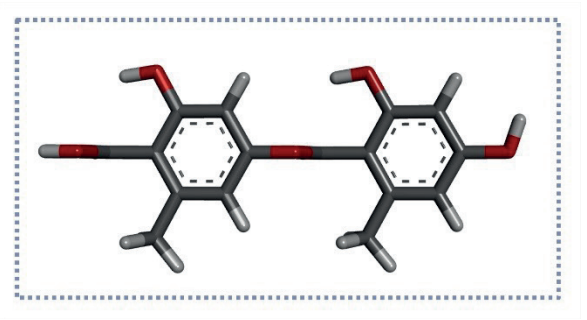

Figure 1. *Three-dimensional (3D) molecular structure of lecanoric acid generated using Discovery Studio Visualizer (BIOVIA, San Diego, CA, USA) based on data obtained from PubChem.*

In this study, the interactions between lecanoric acid and key therapeutic targets in breast cancer, 17β-HSD1, ERα, EGFR, and Bcl-xL, were investigated using molecular docking analyses. In addition, the ADMET profile of lecanoric acid was evaluated through the ADMETlab 3.0 platform. The findings indicate that lecanoric acid exhibits binding affinity toward these critical targets implicated in breast cancer and possesses a favorable pharmacokinetic and toxicity profile. To the best of our knowledge, this is the first study to comprehensively assess, *in silico*, the interaction of lecanoric acid with these four molecular targets simultaneously, highlighting its potential antiproliferative properties. Nevertheless, further *in vitro* and *in vitro* studies are required to validate these findings and to more fully elucidate its therapeutic potential.

MATERIALS and METHODS

Protein-Ligand Preparation and Molecular Docking Analysis

Before performing the molecular docking analyses, the receptors and the ligand, lecanoric acid, were prepared. A detailed literature review was conducted to determine the ID numbers of the target proteins.[27-30] The 3D structures of the breast cancer-related target proteins were retrieved from the RCSB Protein Data Bank (RCSB PDB; https://www.rcsb.org) using the following PDB IDs: 17β-HSD1 (1FDW), ERα (6CBZ), EGFR (1M17), and Bcl-xL (2W3L). Water molecules, heteroatoms, and any co-crystallized ligands were removed from the receptor structures using Discovery Studio 2021 (BIOVIA, USA). A blind docking approach was employed to allow the exploration of the entire protein surface. For this purpose, the grid box dimensions were set to 100 × 100 × 100 Å along the x, y, and z axes to ensure full coverage of the protein surface with AutoDockTools 1.5.7. The grid box centers for each receptor were determined according to the corresponding protein structures and are provided in Table 1. Subsequently, missing side chains that could affect docking accuracy were completed, and polar hydrogen atoms were added using AutoDockTools 1.5.7. After the assignment of Kollman and Gasteiger charges, the prepared proteins were saved in pdbqt format for molecular docking analysis.[31]

The 3D structure of lecanoric acid, used as the ligand in this study, was downloaded from the PubChem database. To obtain a more stable conformation, the ligand structure was energy-minimized using UCSF Chimera version 1.19. Torsions were then added to the ligand in AutoDockTools 1.5.7, and the final ligand structure was saved in pdbqt format. Molecular docking analyses of the prepared receptors and ligand were performed using AutoDock Vina to predict the binding affinity between lecanoric acid and the breast cancer-related target proteins (17β-HSD1, ERα, EGFR and Bcl-xL). The binding energies (affinity scores) were reported in kcal/mol, and values below -7.0 kcal/mol were considered indicative of strong interactions.[32-34] Finally ligand-receptor interactions were visualized in both 2D and 3D using Discovery Studio 2021 (BIOVIA, USA).[31]

In silico ADMET and Physicochemical Property Analysis

To comprehensively evaluate the drug candidacy of lecanoric acid, whose potential effects in breast cancer are to be investigated for the first time, its physicochemical, medicinal chemistry, pharmacokinetic, and toxicity profiles were assessed using ADMETlab 3.0.[35]

The physicochemical analysis performed using ADMETlab 3.0 included molecular weight (MW), number of hydrogen bond acceptors (nHA), number of hydrogen bond donors (nHD), number of rotatable bonds (nRot), number of rings (nRing), maximum ring size (MaxRing), number of heteroatoms (nHet), formal charge (fChar), number of rigid bonds (nRig), topological polar surface area (TPSA), logS, logP, and logD. To visually summarize the physicochemical property profile of lecanoric acid, a radar plot was generated by ADMETlab 3.0 based on these parameters. In the radar plot, the green area represented the lower acceptable limits, the blue area represented the upper acceptable limits, and the yellow line represented the physicochemical profile of lecanoric acid. In addition, medicinal chemistry-related parameters, including natural product-likeness score (NPscore), Lipinski rule, and GSK rule, were evaluated.

Pharmacokinetic assessment comprised absorption, distribution, metabolism, and excretion-related endpoints. Absorption was evaluated in terms of P-glycoprotein (P-gp) inhibitor potential, human intestinal absorption (HIA), and oral bioavailability threshold at 50% (F50%). Distribution was assessed by plasma protein binding (PPB), volume of distribution at steady state (VDss). Metabolic predictions included interactions with major cytochrome P450 isoenzymes, namely CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP2B6, and CYP2C8. Excretion was assessed using plasma clearance (CLplasma) and elimina-

tion half-life (T1/2).

The toxicity profile of lecanoric acid was evaluated using the endpoints drug-induced liver injury (DILI), AMES mutagenicity, human hepatotoxicity, drug-induced nephrotoxicity, hematotoxicity, genotoxicity, and drug-induced neurotoxicity. In addition, possible effects on selected Tox21 signaling pathways, including NR-ER were analyzed. For classification endpoints, the output values generated by ADMETlab 3.0 were interpreted as the probability of belonging to Category 1. Probability scores were categorized as --- (0–0.1), -- (0.1–0.3), - (0.3–0.5), + (0.5–0.7), ++ (0.7–0.9), and +++ (0.9–1.0), according to the ADMETlab 3.0 classification system. However, for the HIA and F50% endpoints, lower probability values indicated more favorable predicted absorption properties and were categorized as excellent (0–0.3), medium (0.3–0.7), or poor (0.7–1.0).[36]

RESULTS

The molecular docking analysis showed that lecanoric acid bound to all investigated breast cancer-related target proteins with docking scores ranging from -7.1 to -7.7 kcal/mol (Table 1). Among the tested receptors, the strongest binding affinity was observed for 17β-HSD1 (-7.7 kcal/mol), followed by EGFR (-7.5 kcal/mol), Bcl-xL (-7.3 kcal/mol), and ERα (-7.1 kcal/mol). It was determined that various amino acid residues play a role in these interactions of lecanoric acid with receptors (Table 1). Lecanoric acid interacted with 17β-HSD1 with residues TYR A:155, SER A:142, TYR A:218, SER A:222, VAL A:225, and LEU A:149 (Figure 2). Also, in the complex it forms with EGFR, it interacted with residues CYS A:751, THR A:830, ASP A:831, ASN A:818, LYS A:721, LEU A:820, and VAL A:70 (Figure 3).

Table 1. Molecular docking results for the lecanoric acid and breast cancer-related receptors

Receptor	**PDB ID**	**Resolution**	**Docking Score**	**Interacting Residues**	**Grid Box Centers***
17β-HSD1	1FDW	2.70 Å	-7.7 kcal/mol	TYR A:155, SER A:142, TYR A:218, SER A:222, VAL A:225, LEU A:149	x = 46.736 y = 2.739 z = 31.314
ERα	6CBZ	1.65 Å	-7.1 kcal/mol	GLU B:380, HIS B:547, HIS B:377, THR B:460, ALA B:546, SER B:456, HIS A:513, ARG B:515, HIS A:516, MET A:427	x = 13.241 y = 2.272 z = 19.238
EGFR	1M17	2.60 Å	-7.5 kcal/mol	CYS A:751, THR A:830, ASP A:831, ASN A:818, LYS A:721, LEU A:820, VAL A:702	x = 26.333 y = -3.03 z = 58.448
Bcl-xL	2W3L	2.10 Å	-7.3 kcal/mol	SER A:75, GLU A:119, LYS A:22, ARG B:66, TYR B:67, ARG A:68, VAL A:118, VAL A:115, ARG A:26	x = 20.583 y = 37.34 z = 13.251

*Grid dimensions of 100x100x100 points.
17β-HSD1, 17β-hydroxysteroid dehydrogenase type 1; ERα, estrogen receptor alpha; EGFR, epidermal growth factor receptor; Bcl-xL, B-cell lymphoma-extra large

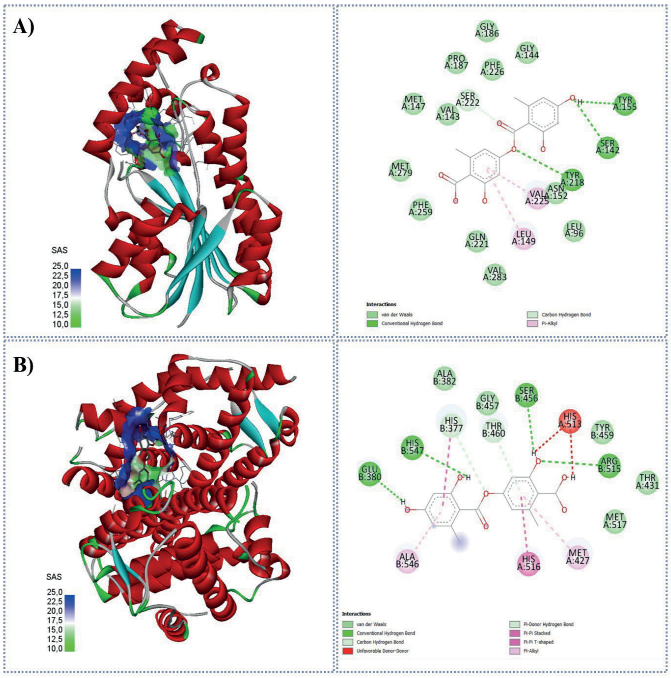

Figure 2. *3D and 2D representations of molecular docking interactions of lecanoric acid with breast cancer-associated target receptors. (A) Lecanoric acid-17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1; PDB ID: 1FDW) complex. (B) Lecanoric acid-estrogen receptor alpha (ERα, PDB ID: 6CBZ) complex.*

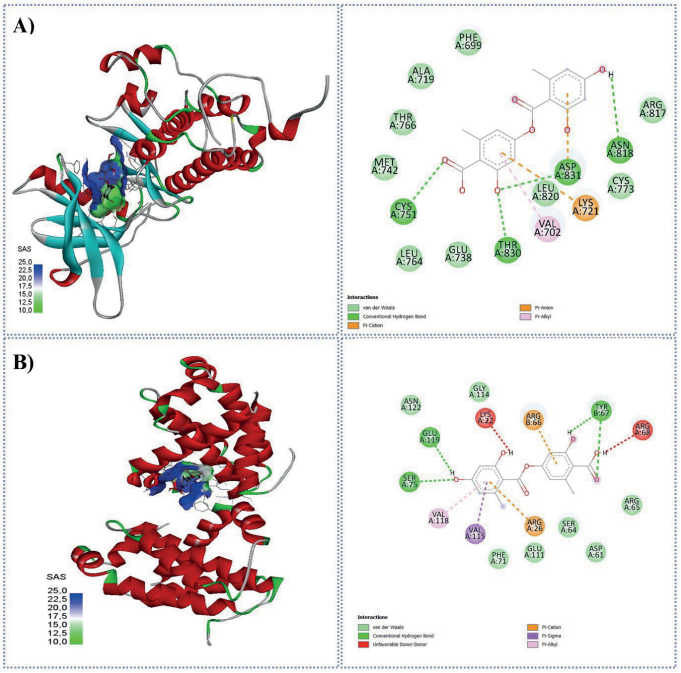

Figure 3. *3D and 2D representations of molecular docking interactions between lecanoric acid and breast cancer-associated target receptors. (A) Lecanoric acid–epidermal growth factor receptor (EGFR; PDB ID: 1M17) complex. (B) Lecanoric acid-apoptosis regulator B-cell lymphoma 2 (Bcl-xL; PDB ID: 2W3L) complex*

The physicochemical analysis revealed that lecanoric acid had a molecular weight of 318.07 g/mol. Additionally, within the ADMET analysis, the hydrogen bonding capacity, closely associated with aqueous solubility, was evaluated and lecanoric acid was found to possess 7 hydrogen bond acceptors and 4 hydrogen bond donors. The compound had a formal charge of 0 and possessed 14 rigid bonds (Table 2).

Table 2. Lecanoric acid ADMET analysis evaluation results (ADMETlab 3.0)

Category	Property	Predicted Value
Physicochemical Property	Molecular Weight (MW)	318.07 g/mol
	nHA	7.0
	nHD	4.0
	nRot	4.0
	nRing	2.0
	MaxRing	6.0
	nHet	7.0
	fChar	0.0
	nRig	14.0
	TPSA	124.29 Å²
	logS	-3.38
	logP	3.412
	logD	2.159
Medicinal Chemistry	NPscore	0.799
	Lipinski Rule	0.0
	GSK Rule	0.0
Absorption	Pgp-inhibitor	0.001
	HIA	0.019
	F50%	0.736
Distribution	PPB	96.309 %
	VDss	-0.84 L/kg
Metabolism	CYP1A2 inhibitor	0.722
	CYP2C19 inhibitor	0.056
	CYP2C9 inhibitor	0.211
	CYP2D6 inhibitor	0.044
	CYP3A4 inhibitor	0.437
	CYP2B6 inhibitor	0.005
	CYP2C8 inhibitor	0.996
Excretion	CLplasma	1.606 mL/min/kg
	T1/2	1.519 hour
Toxicity	DILI	0.714
	AMES Mutagenicity	0.317
	Human Hepatotoxicity	0.334
	Drug-induced Nephrotoxicity	0.335
	Hematotoxicity	0.1
	Genotoxicity	0.586
	Drug-induced Neurotoxicity	0.102
Tox21 pathway	NR-ER	0.037

For classification endpoints, the output value represents the probability of belonging to Category 1 in ADMETlab 3.0. Probability values were expressed as --- (0–0.1), -- (0.1–0.3), - (0.3–0.5), + (0.5–0.7), ++ (0.7–0.9), and +++ (0.9–1.0). Category 1 definitions are endpoint-specific. However for the HIA and F50% endpoints, lower probability values indicated more favorable predicted absorption properties and were categorized as excellent (0–0.3), medium (0.3–0.7), or poor (0.7–1.0). MW, molecular weight; nHA, number of hydrogen bond acceptors; nHD, number of hydrogen bond donors; nRot, number of rotatable bonds; nRing, number of rings; MaxRing, number of atoms in the largest ring; nHet, number of heteroatoms; fChar, formal charge; nRig, number of rigid bonds; TPSA, topological polar surface area; logS, logarithm of aqueous solubility; logP, logarithm of the n-octanol/water partition coefficient; logD, logarithm of the distribution coefficient; NPscore, natural product-likeness score; HIA, human intestinal absorption; F50%, oral bioavailability threshold at 50%; PPB, plasma protein binding; VDss, volume of distribution at steady state; CYP, cytochrome P450; CLplasma, plasma clearance; T1/2, elimination half-life; DILI, drug-induced liver injury; AMES, Ames mutagenicity; NR-ER, estrogen receptor.

The compound also exhibited a topological TPSA of 124.29 Å², along with logS, logP, and logD values of -3.38, 3.412, and 2.159, respectively.

The radar plot further illustrated the physicochemical profile of lecanoric acid and showed that the evaluated parameters generally remained within the predefined lower and upper limits (Figure 4). The yellow profile line indicated a balanced distribution across the assessed descriptors, with relatively prominent values observed for logP, logS and TPSA.

In the medicinal chemistry assessment, lecanoric acid showed an NPscore of 0.799, indicating a favorable natu-

ral product-likeness profile (Table 2). In addition, both the Lipinski rule and GSK rule outputs were 0.0, suggesting no predicted violation signal according to these rule-based filters.

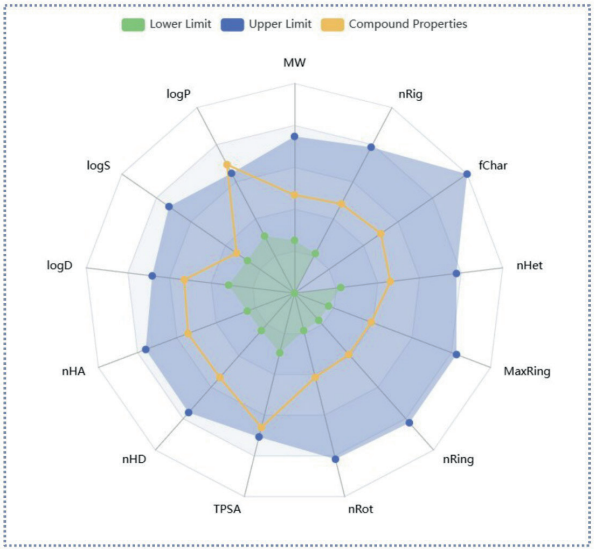

Figure 4. *Radar plot showing the physicochemical property profile of lecanoric acid. The green area indicates the lower limits, the blue area indicates the upper limits, and the yellow line represents the properties of the investigated compound. The plot includes molecular weight (MW), number of rigid bonds (nRig), formal charge (fChar), number of heteroatoms (nHet), maximum ring size (MaxRing), number of rings (nRing), number of rotatable bonds (nRot), topological polar surface area (TPSA), number of hydrogen bond donors (nHD), number of hydrogen bond acceptors (nHA), and the logD, logS, and logP parameters.*

Pharmacokinetic analysis indicated that lecanoric acid has a very low probability of P-gp inhibition (probability score: 0.001). The compound was predicted to exhibit high intestinal absorption, whereas its oral F50% value was classified as medium (Table 2). Distribution-related predictions showed a plasma protein binding (PPB) value of 96.309% and VDss of -0.84 L/kg, indicating high PPB, low VDss. For metabolism-related endpoints, the highest predicted probabilities were observed for CYP2C8 (0.996) and CYP1A2 (0.722), whereas CYP3A4 (0.437) showed an intermediate value. Lower probabilities were obtained for CYP2C9 (0.211), CYP2C19 (0.056), CYP2D6 (0.044), and CYP2B6 (0.005). Excretion analysis yielded a CLplasma of 1.606 mL/min/kg and an elimination half-life (T1/2) of 1.519 h.

The ADMET toxicity analysis indicated that the predicted probabilities for AMES mutagenicity, human hepatotoxicity, drug-induced nephrotoxicity, hematotoxicity, and drug-induced neurotoxicity ranged between 0.1 and 0.3, suggesting an overall low toxicity potential. Comparatively higher probabilities were observed for DILI (0.714) and genotoxicity (0.586). Regarding the Tox21 pathway analysis, the predicted value was 0.037 for NR-ER, indicating generally low activity probabilities across these pathway-related endpoints (Table 2).

DISCUSSION

In this study, we present the first *in silico* evidence suggesting that lecanoric acid, a compound with notable bioactive properties, may represent a potential drug candidate for the treatment of breast cancer. Our molecular docking analyses demonstrated that lecanoric acid exhibits strong binding interactions with the target proteins 17β-HSD1 (-7.7 kcal/mol), ERα (-7.1 kcal/mol), EGFR (-7.5 kcal/mol), and Bcl-xL (-7.3 kcal/mol), all of which are implicated in breast cancer. These binding profiles suggest that lecanoric acid may interact with multiple molecular pathways involved in tumor progression and therefore may hold promise as a multi-target therapeutic agent. In addition, findings from *in silico* ADMET predictions indicate that lecanoric acid may possess an overall favorable pharmacokinetic and safety profile.

Data derived from computer-aided computational analyses and medicinal chemistry provides a critical foundation for the evaluation of candidate compounds for cancer treatment and for generating preliminary evidence to guide subsequent studies.[37] By reducing the cost and time burden of experimental research, *in silico* approach-

es support a more rapid and efficient drug discovery process while also enabling the prediction of how potential candidate compounds may interact with disease-related molecular mechanisms.[36] The current literature indicates that estrogen plays a central role in breast cancer pathology and that inhibition of estrogen-related targets may suppress disease progression by reducing estrogen levels.38 Among these targets, 17β-HSD1 has attracted considerable attention in breast cancer research. In a study in which several ligands targeting 17β-HSD1 were evaluated *in silico*, the binding energy of epirubicin hydrochloride, a known 17β-HSD1 inhibitor, was reported as -8.2 kcal/mol, whereas the binding scores of other candidate ligands ranged from -8.0 to -9.9 kcal/mol.[8] In the present study, the binding score of lecanoric acid with 17β-HSD1 was determined to be -7.7 kcal/mol. This value suggests that lecanoric acid may possess a noteworthy interaction potential with the 17β-HSD1 target. ERα, like 17β-HSD1, is another key mediator of estrogen signaling and is closely associated with breast cancer progression.[6] Although the clinical benefit of tamoxifen and other selective estrogen receptor modulators in patients with ERα-positive breast cancer is well established, the emergence of tamoxifen resistance following long-term treatment has prompted the search for new ERα-targeted agents. In this context, one study reported that the phytochemical drug candidates designated ZINC69481841 and ZINC95486083 exhibited binding energies of -10.47 and -11.88 kcal/mol toward ERα, respectively, whereas tamoxifen showed a binding energy of -8.32 kcal/mol.[39] In our study, lecanoric acid exhibited a binding score of -7.1 kcal/mol with ERα, indicating a meaningful interaction with the receptor and suggesting that the compound may have the potential to directly modulate estrogen signaling through ERα.

A well-established crosstalk exists between ERα and EGFR in breast cancer, influencing signaling networks associated with proliferation, survival, and resistance to endocrine therapy. For this reason, the simultaneous targeting of ERα and EGFR may be important for the multidimensional suppression of estrogen-related tumor progression.[13-15] In an in silico study, the docking scores of six secondary metabolites derived from Origanum majorana in their interactions with EGFR were reported to range from -3.12 to -5.98 kcal/mol. Among these metabolites, the lowest binding energy was observed for α-terpinene at -5.98 kcal/mol, while limonene and sabinene showed binding energies of -5.32 and -5.12 kcal/mol, respectively.[40] In the present study, lecanoric acid exhibited a binding score of -7.5 kcal/mol toward EGFR. This value suggests that, compared with these natural metabolites, lecanoric acid displays a lower binding energy and therefore a stronger binding tendency. This interaction further indicates that lecanoric acid may also have the potential to modulate estrogen-related signaling pathways indirectly. Nevertheless, it should be taken into account that direct comparison of docking scores across different studies may be influenced by methodological differences.

In breast cancer, alterations in estrogen signaling are accompanied by the reprogramming of cell survival and apoptotic pathways. Particularly in ER+ breast cancer, considering the overexpression of anti-apoptotic Bcl-2 family proteins, reduction of Bcl-xL levels or suppression of its function has been associated with enhanced apoptosis and increased treatment sensitivity[41]. In a study evaluating the binding scores of 52 bioactive metabolites against Bcl-xL, the binding energies of the docked compounds were reported to range from -5.3 kcal/mol to -10.1 kcal/mol. In the same study, the reference drug Obatoclax showed a binding score of -8.4 kcal/mol against Bcl-xL.[29] In another study investigating the anti-hepatocarcinoma activity of lichen extracts containing lecanoric acid, the binding energy of lecanoric acid with Bcl-xL was reported as -7.3 kcal/mol.[26] Consistent with this finding, lecanoric acid also exhibited a binding energy of -7.3 kcal/mol toward Bcl-xL in our study. This score is in agreement with the literature and suggests that lecanoric acid may have the potential to contribute to the modulation of apoptotic pathways through its interaction with the Bcl-xL target.

Natural compounds offer significant potential for modern drug development in breast cancer due to their relatively low toxicity profiles, structural diversity, wide availability, and broad spectrum of biological activities.[37] However, they also present certain limitations, including restricted bioavailability, low stability, and pharmacokinetic variability.[42] In this context, the combined evaluation of both the target protein interaction potential and ADMET properties of natural compounds such as lecanoric acid may provide a valuable basis for the development of therapeutic strategies in breast cancer. Our *in silico* ADMET findings indicate that lecanoric acid has high intestinal absorption and a very low probability of P-gp inhibition. Taken together, these results suggest that its bioavailability may not be substantially compromised by efflux mechanisms. However, the moderate oral F50% value may indicate some variability in oral bioavailability. Evaluation of the distribution parameters revealed high plasma protein binding (PPB) and a low steady-state volume of distribution (VDss), suggesting that lecanoric acid is likely to remain largely within the systemic circulation with limited tissue distribution. This may raise concerns regarding whether sufficient pharmacologically active concentrations can be achieved in breast tumor tissue. Nevertheless, drug distribution to tumor sites is not solely dependent on VDss[43], and the ability of lecanoric acid to reach effective concentrations in target tissues should be confirmed through further experimental studies.

Drug metabolism is a key determinant of drug concentrations in the body. Cytochrome P450 (CYP) enzymes play a central role in drug metabolism and constitute the primary basis of drug-drug interactions. Inhibition or induction of these enzymes can alter plasma drug levels, thereby influencing both clinical efficacy and toxicity.[44] From a metabolic perspective, lecanoric acid was predicted to act as a strong inhibitor, particularly of CYP2C8 and CYP1A2 enzymes. Considering that combination and supportive therapies are commonly used in patients with breast cancer, drug-drug interactions represent a clinically significant risk factor.[45,46] Conversely, Saha et al. reported, based on their ADMET analyses, that lecanoric acid may not exhibit inhibitory activity against CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4.[26] These discrepancies among ADMET findings may be attributable to differences in computational tools and software platforms used in the analyses. In this context, it should be considered that lecanoric acid may increase the plasma concentrations of co-administered drugs through CYP enzyme inhibition, potentially leading to toxicity in breast cancer patients. Taking interindividual variability into account, the inhibitory potential of lecanoric acid on metabolic enzymes should be further validated through *in vivo* studies.

According to our *in silico* analyses, lecanoric acid exhibits a low-risk profile in terms of AMES mutagenicity, hepatotoxicity, nephrotoxicity, hematotoxicity, and neurotoxicity. Given the well-known adverse effects of current anticancer therapies on the hematological system, liver, kidneys, and nervous system[47], this finding suggests that lecanoric acid may have a relatively favorable side-effect profile. However, the predicted probability values for drug-induced liver injury (DILI) and genotoxicity were comparatively higher, indicating that careful monitoring may be warranted, particularly under conditions requiring higher doses or prolonged exposure. In our molecular docking analyses, lecanoric acid showed high binding affinity toward ERα, whereas ADMET/Tox21 analysis predicted a low probability of NR-ER activation. This may suggest that, although the compound is capable of binding to the receptor, it may not strongly activate estrogen-related signaling pathways, and therefore could possess a safer effect profile in the context of breast cancer.

Limitations

The principal limitation of this study is that the findings are based solely on *in silico* predictive analyses. Furthermore, the absence of molecular dynamics (MD) simulations represents an additional limitation of the *in silico* component of the study. The differences between data ob-

tained from *in silico* approaches and those observed in the *in vivo* biological environment should not be overlooked. In addition, although the potential effects of lecanoric acid on breast cancer were evaluated through some of the best-established disease-related targets, 17β-HSD1, ERα, EGFR, and Bcl-xL, it is well recognized that many additional molecular mechanisms contribute to breast cancer pathogenesis. Therefore, the results should be interpreted within the broader context of the disease's complex molecular landscape, and the *in silico* findings should be regarded as preliminary.

CONCLUSION

The complex pathogenesis of breast cancer on a global scale, together with the limited efficacy of current treatment options, necessitates the exploration of new therapeutic candidates. *In silico* methods can provide valuable insights into disease mechanisms and help predict the interactions of candidate compounds with target proteins. In the present study, lecanoric acid was found to exhibit strong binding interactions with well-established breast cancer-related targets, including 17β-HSD1, ERα, EGFR, and Bcl-xL. In addition, ADMETlab 3.0 analyses indicated that lecanoric acid may possess noteworthy properties as a potential drug candidate. Taken together, these findings suggest that lecanoric acid merits further investigation as a natural candidate compound for breast cancer. However, *in vitro* and *in vivo* studies are required to validate this potential.

Ethical Approval

This study does not require ethics committee approval.

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.S., Design: S.S., F.B., Supervision: S.S., Resources: S.S., F.B., Data Collection or Processing: S.S., F.B., Analysis or Interpretation: S.S., F.B., Literature Search: S.S., F.B., Writing: S.S., F.B., Critical Review: S.S.

Conflict of Interest

The authors declare no conflict of interest.

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