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Exploring the Anticancer Potential of Marine Brown Algae as Estrogen Receptor Alpha Inhibitor

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Authors' Contribution
AJ conducted the methodology and drafted the manuscript. AB and AA contributed to figure preparation and manuscript revisions. AQ did the software. EZ proposed the study, supervised the research work, and provided critical review. MK contributed to manuscript review and guidance.

Key words
Breast cancer, Estrogen receptor alpha, Molecular docking, Drug discovery, Marine phytoactive compounds, Brown algae

ABSTRACT

Cancer is currently the second leading cause of death worldwide and continues to be a major global health concern. Breast cancer is one of the most prevalent cancers among women. Although the current breast cancer treatments are effective, they have disadvantages, including the possibility of cancer recurrence, negative side effects, and tamoxifen resistance. Novel targeted therapies are therefore always needed. This study aims to examine how phlorotannins from marine brown algae affect the estrogen receptor alpha (ERα) function in breast cancer cells. To predict the binding affinities between ERα (3ERT) and specific ligands, molecular docking studies were performed using AutoDock Vina. The binding pockets were identified with the help of CASTp analysis, which focuses on ligand-protein interactions. Using BIOVIA discovery studio, ligand-protein complexes were structurally visualized. The binding energies lie between -5.1 and -7.6 kcal/mol. Lowest binding energies of -7.6 and -7.3 kcal/mol, respectively, Eckol (PubChem ID: 145937) and 2, 4-diisobutyryl phloroglucinol (PubChem ID: 15659412) showed the strongest binding affinity to the ERα protein. Positive drug-likeness was predicted by ADMET by checking their properties. The docking results open the door for further *in vitro* and *in vivo* validation by highlighting the potential of plant-derived photoactive compounds as ERα inhibitors.

INTRODUCTION

Breast cancer, one of the most common cancers in women worldwide, is a cancerous tumor that is formed from breast cells, but also occurs in men (Cowin *et al*., 2005). Breast cancer, one of the most common types of cancer worldwide, is a condition of uncontrolled development of malignant cells in mammary epithelial tissue with gender variation and an abrupt rise with age (do Nascimento *et al*., 2020). Breast cancer is modulated by environmental, lifestyle and social-psychological variables with a contribution of genetic mutations and family background to 5%-10% of the cases (Obeagu and Obeagu, 2024). Cancer is a heavy worldwide health burden, with traditional treatments having limitations. Fungal, plant and sea creatures natural products have therapeutic activity like antioxidant, anti-inflammatory and anticancer action (Manzari-Tavakoli *et al*., 2024).

Marine macro algae, which contain anti-inflammatory, anti-cancer, immunomodulatory and antioxidant activities, hold vast potential in the application of the biomedical sector as a result of their peculiar chemical composition and capacity for adapting to the environment (Nova *et al*., 2024). Botanicals, rationally and wisely applied, can be a therapeutic system that is effective, economical, and less side-effect-causing in contemporary medicine (Mohd Zaid *et al*., 2023).

Although the rates of incidence are diverse within and among populations and geographic regions, breast cancer remains a significant adverse burden to both health services and individuals (Wilkerson *et al*., 2024), while underlining the need for continued prevention, early detection, and treatment efforts. The steroid hormone family known as estrogens regulates human reproductive system physiology, development, and growth. Estrogens also affect the skeletal, adipogenic, neuroendocrine and cardiovascular systems. The activity of estrogen receptor alpha (ERα) or ERβ in target organs balances to ensure

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selective activation or inhibition of estrogen signaling pathways (Lee *et al*., 2012). Estrogen plays an essential role in normal mammary gland development and growth, stimulating 50% of primary breast tumors, so Tamoxifen is the first-line treatment for ERα cancers (Palmieri *et al*., 2002). Additionally, through membrane-associated receptors, ERα can stimulate non-genomic signaling cascades that affect cell signaling pathways, including the PI3K and MAPK pathways (Arnal *et al*., 2017; Yin *et al*., 2024).

Scientists highlight the need to enhance breast cancer risk factors, backing screening programs with molecular docking in drug design and structural biology (Morris *et al*., 2009). Molecular docking is a method used to predict the favored position of a ligand in relation to a protein to create a stable compound. It plays a crucial role in drug design and drug discovery since it predicts drug affinity and activity towards protein targets (Chaudhary and Mishra, 2016).

Brown algae, bioactive chemicals such as phlorotannins, possess anti-inflammatory, anti-cancer, and antioxidant activities and can serve as therapeutic agents for alternative cancer therapies via apoptosis and angiogenesis (Pradhan and Ki, 2023; Remya *et al*., 2022). Recent studies have indicated that phenol-dense extracts of *Ecklonia cava*, a brown alga, suppress breast cancer cell growth and induce apoptosis through NF-κB activation repression (Nho *et al*., 2020). Dieckol, a phlorotannin molecule, had high anticancer activity against breast cancer cells by suppressing various molecular pathways related to carcinogenesis (Chen *et al*., 2018; Hakim and Patel, 2020). The study investigates phlorotannins of marine brown algae, like diphlorethol pentacetate, fucophloroethol and phloroglucinol triacetate, to prevent cell growth in breast cancer with web and desktop docking software.

MATERIALS AND METHODS

Protein preparation

The protein selected is 3ERT (human estrogen receptor alpha ligand-binding domain in complex with 4-hydroxytamoxifen) for docking. The structure of the PDB was converted from PDB to PDBQT format by AutoDock Tool (1.5.6). The already attached ligands were removed and water molecule were and adding polar hydrogen, Kollman charges were added to give the required structure.

Ligand preparation

The PubChem web database was queried for bioactive compounds, and the search results were downloaded in SDF format. Conversion of the 3D and 2D structures to PDB format was done using PyMol and converting them to PDBQT format using AutoDock Tool 1.5.6.

Molecular visualization of ERα complex

The ERα complexes were visualized via Discovery Studio 2025 and PyMOL. PyMOL is a molecular visualization program that can be employed to depict small molecule structures and also finds use in structural biology research and publications (Verma *et al*., 2025). A suite of molecular modeling biotechnology and pharmaceuticals, BIOVIA Discovery Studio Visualizer enables collaboration, speeds up research, simplifies procedures and provides predictive analytics (Naithani *et al*., 2024).

Grid box configuration

Ligand and protein, which are present in PDBQT format, are uploaded in Autodock Tool (1.5.6) Grid box was created with x, y, and z center as 22.396, 5.644 and 21.988 and size 40, 40, and 40 Å, respectively.

Active site prediction

The CASTp server (Computerized Atlas of Surface Topography of Proteins) application was utilized to assess the reactive sites of ERα. Additionally, it provides a visual representation of the binding pocket's volume and dimensions based on crystal structures (Dariya *et al*., 2021).

A total of 33 binding sites were predicted with the effective interactive amino acids including GLU353, LEU346, MET343, GLY390, THR347, LEU346, Pro324, LEU525, LEU346, THR347, ALA350, PRO324, LEU391, MET343 etc. The majority of ligands bind to Pocket 1 and a few bind to Pocket 2 and 3. Three binding pockets for the 3ERT as shown in the Figure 1. The majority of ligands bind to Pocket 1 and a few bind to Pocket 2 and 3.

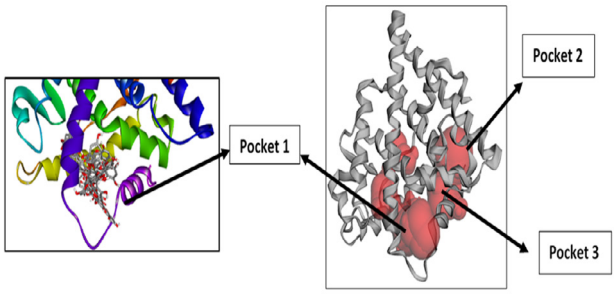

Fig. 1. Image obtained via DSV indicates that all the studied ligands are docked in binding pocket 1 on the left. CASTp predicted a total of 33 binding pockets of the protein (3ERT), of which three binding pockets 1, 2, and 3 are shown highlighted in red color on the right.

Physiochemical properties

The web tools pkCSM and Swiss ADME were utilized to calculate the Lipinski rule of five, ADMET analysis and the drug toxicity. Unique canonical smiles for each of the ligands were retrieved from PubChem, submitted to the ADMET tools and the ADMET evaluation and toxicity results were retrieved.

RESULTS

Molecular docking analysis

The molecular docking analysis of the selected ligands against the estrogen receptor alpha (PDB ID: 3ERT) revealed varying binding affinities and interactions with key amino acid residues in the active site (Table I).

Phloroglucinol (PubChem ID: 359) showed a binding energy of -5.1 kcal/mol with a predicted inhibition constant of 1.76 µM. It formed hydrogen bonds with GLU353 (2.84 Å, 2.22 Å) and displayed hydrophobic interactions with PRO324 (4.15 Å) and LYS499 (4.99 Å). Phloroglucinol triacetate (PubChem ID: 76347) exhibited a better binding affinity of -6.3 kcal/mol (Ki 2.3 µM), forming hydrogen bonds with HIS524 (2.23 Å) and hydrophobic interactions with LEU346 (3.84 Å) as shown in Figure 2.

Table I. Protein (3ERT) interaction with respective ligands and amino acid residues with their distances and binding energies.

Ligand name (PubChem ID)	Interaction amino acid residues (Distance: Å)				Binding energy (Kcal/mol)	Inhibition constant (µM)
	Hydrogen bond	Hydrophobic	Electrostatic interaction	Other		
Phloroglucinol (359)	GLU353 (2.84 Å) GLU353(2.22 Å)	PRO324(4.15 Å)	LYS 499(4.99 Å) GLU353(3.61 Å)		-5.1	1.76
Phloroglucinol triacetate (76347)	HIS524 (2.23)	LEU346 (3.84 Å)			-6.3	2.3
Eckol (145937)	LEU346(2.22 Å) MET A:343(2.85 Å)	LEU525(3.81 Å) LEU346 (4.57 Å) LEU346(5.32 Å) LEU384(5.46 Å) LEU391(5.12 Å) LEU387(4.47 Å) ALA 350(5.10 Å) ALA350(4.37 Å)		MET343(5.59 Å) MET343(4.72 Å)	-7.6	2.55
Phloroglucinol dihydrate (80196)	PHE404 (2.68 Å)	LEU346 (5.18 Å) ALA350 (5.31 Å) LEU387 (5.04 Å) LEU391(4.98 Å)	GLU353 (4.38 Å)		-5.1	1.76
2,4-Diisobutyryl phloroglucinol (15659412)	ASP351(2.13 Å)	TRP383(3.93 Å) TRP383(3.54 Å) TRP383(5.43 Å) LEU354(4.10 Å) LEU536(4.01 Å) LEU525(5.13 Å) MET522(4.65 Å) TRP383(5.40 Å) LEU525(4.98 Å)			-7.3	4.23
Diphlorethol (14020558)	ARG394(2.67 Å) ILE386(2.47 Å) PRO325(2.1 Å) PRO324(1.70 Å) GLY390(3.65 Å)	PRO324(4.18 Å) PRO324(5.49 Å) ILE326(4.84 Å)	GLU353(3.54 Å)		-7.4	3.79

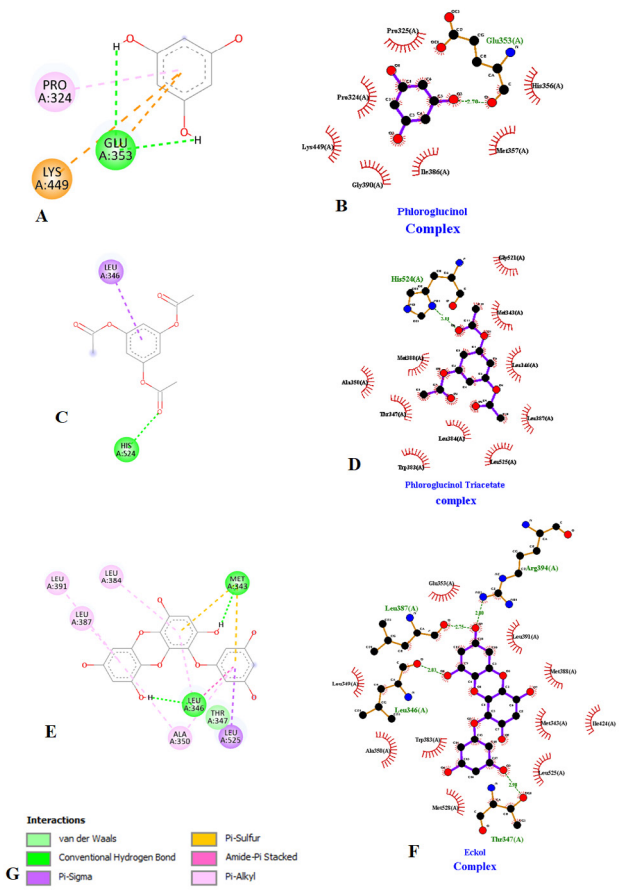

Fig. 2. Illustrating docked complexes. Phloroglucinol docked complex and its visualization (A and B). Phloroglucinol triacetate docked complex and its visualization (C and D). Eckol docked complex and its visualization (E and F). The different interaction types are shown in different colors (G).

Eckol (PubChem ID: 145937) demonstrated the strongest binding among the tested compounds, with a binding energy of -7.6 kcal/mol and an inhibition constant of 2.55 µM. It formed hydrogen bonds with LEU346 (2.22 Å) and hydrophobic contacts with residues including LEU525 (3.81 Å) and MET343 (5.59 Å) (Fig. 2). Phloroglucinol Dihydrate (PubChem ID: 80196) bound with an energy of -5.1 kcal/mol **(**Ki 1.76 µM**),** forming a hydrogen bond with PHE404 (2.68 Å) and hydrophobic interactions with LEU346 (5.18 Å) and ALA350 (5.31 Å) as shown in Figure 3.

2,4-Diisobutyryl Phloroglucinol (PubChem ID: 15659412) showed good affinity with -7.3 kcal/mol **(**Ki 4.23 µM**),** interacting via hydrogen bonding with ASP351 (2.13 Å) and hydrophobic contacts with TRP383 (3.93 Å) and LEU354 (4.10 Å). Diphlorethol (PubChem ID: 14020558) had a binding energy of -7.4 kcal/mol and a calculated inhibition constant of 3.79 µM**.** It interacted with ARG394 (2.67 Å) and ILE386 (2.47 Å) via hydrogen bonding, and displayed hydrophobic interactions with PRO324 (4.18 Å) and GLU353 (3.54 Å) (Fig. 3).

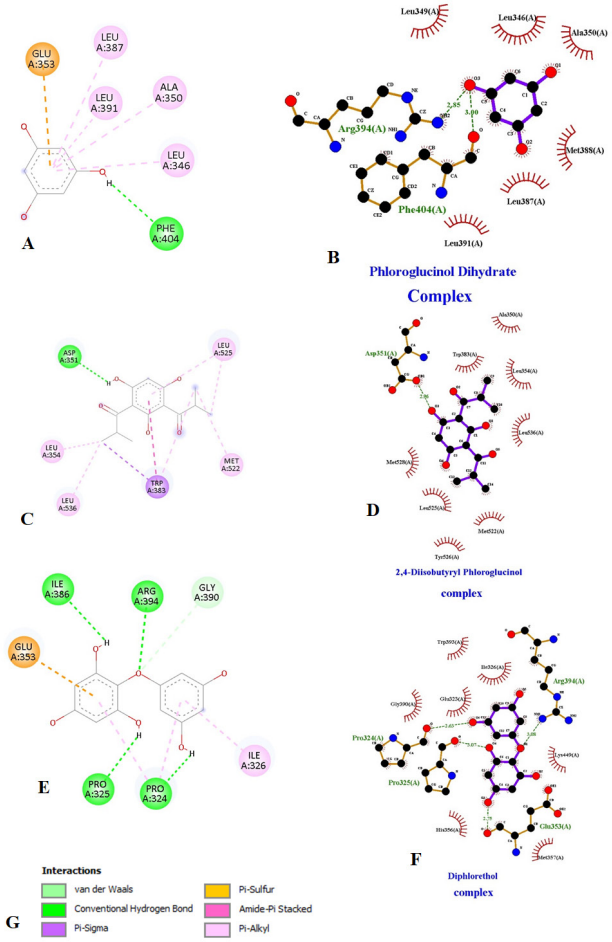

Fig. 3. Illustrating docked complexes. Phloroglucinol dehydrate docked complex and its visualization (A and B). 2,4-Diisobutyryl Phloroglucinol docked complex and its visualization (C and D). Diphlorethol docked complex and its visualization (E and F). The different interaction types are shown in different colors (G).

Lipinski's rule of five

The selected ligands were tested for drug-likeness according to Lipinski's Rule of Five, keeping in view molecular weight (<500 g/mol), log P (<5), H-bond donors (<5) and H-bond acceptors (<10). From the table, we can see that all five ligands fall under the drug-ability criterion of molecular weight, log P and H-bond acceptor. Eckol only violates one rule despite having six hydrogen bond donors, which is slightly more than is advised. There are

also considerable variations in polar surface area (PSA), which affect drug absorption. While phloroglucinol has the lowest PSA (60.69 Å²), suggesting greater permeability, Eckol has the largest PSA (149.07 Å²), which can hinder absorption. In general, most ligands exhibit suitable PSA values and satisfy Lipinski's criterion, suggesting that they have the potential to be drug-like substances (Table II).

Drug likeness and toxicity

To confirm if the potential ligands were potential drugs, their ADMET properties were investigated. ADMET properties were predicted using the pkCSM web tool. The five ligands were well absorbed with a moderate to high level of human intestinal absorption (HIA). Highest absorption rates were for 2, 4-diisobutyryl phloroglucinol and phloroglucinol triacetate. All the compounds possessed low central nervous system (CNS) and blood-brain barrier (BBB) permeability, hence reducing the likelihood of CNS adverse effects. Drug-drug interaction risks were reduced by metabolic predictions that presented negligible inhibition of the CYP450 enzyme. Good renal or total clearance rates were presented by excretion parameters. Except for Eckol, which presented hepatotoxicity and one infringement of the Lipinski rule, most of the compounds possessed viable toxicity profiles and were AMES-negative and non-hepatotoxic. Drug-likeness of most of the ligands was generally validated by ADMET analysis, i.e., that they possessed the potential for further development as safe and effective oral therapeutic agents (Table III).

Table II. Lipinski rule of five analysis of selected ligands.

S. No	Ligands	Molecular weight < 500 (g/mol)	H-Bond acceptor < 10	H-Bond donors < 5	logP < 5 (WLOGP)	Polar surface area (Å2)
1	Phloroglucinol	126.11	3	3	0.8	60.69
2	Phloroglucinol triacetate	252.22	6	0	1.46	78.9
3	Eckol	372.28	9	6	3.61	149.07
4	Phloroglucinol dihydrate	162.14	5	5	0.67	79.15
5	2,4-Diisobutyryl phloroglucinol	266.29	5	3	2.48	94.83
6	Diphlorethol (14020558)	250.20	6	5	2.01	110.38

Table III. Drug likeness prediction using pkCSM online database server for the selected ligands.

ADMET		Phloro-glucinol	Phloroglucinol triacetate	Eckol	Phloroglucinol dihydrate	2,4-diisobutyryl phloroglucinol	Diphlore-thol
Absorption	Water solubility (LogS)ml/L	-1.408	-2.37	-2.899	-1.615	-2.43	-3.04
	Intestinal absorption (human)(%Ab-sorption)	83.55	96.67	67.17	61.7	73.88	70.93
	P-Glycoprptein I Inhibitors	No	No	No	No	No	No
	P-Glycoprptein II inhibitors	No	No	Yes	No	No	No
Distribution	VDss (human) (logL/kg)	0.13	-0.679	0.595	-0.136	0.102	0.99
	BBB permeability	-0.466	-0.686	-1.399	-0.72	-0.826	-1.36
	CNS permeability	-3.252	-3.114	-3.259	-3.392	-2.478	-3.23
Metabolism	CYP2D6 substrate	No	No	No	No	No	No
	CYP3A4 substrate	No	No	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No	No	No
	CYP 3A4 inhibitor	No	No	No	No	No	No
Excretion	Total clearance (Log ml/min / kg)	0.58	0.99	0.23	0.66	0.29	0.47
	Renal OCT 2 substrate	No	No	No	No	No	No
Toxicity	AMES toxicity categorical (Yes No/)	No	No	No	No	No	No
	Max. tolerable dose (log mg/kg/day)	0.107	Yes	0.476	0.172	0.591	0.50
	Hepatotoxicity	No	1.207	No	No	No	No

DISCUSSION

A comprehensive molecular docking and *in silico* evaluation were conducted on five ligands: phloroglucinol, phloroglucinol triacetate, eckol, phloroglucinol dihydrate, and 2,4-diisobutyryl phloroglucinol. These compounds were selected based on their reported therapeutic potential, particularly their anti-cancer and estrogen receptor-modulating activities (Kim *et al*., 2015). Their interactions with estrogen receptor alpha (PDB ID: 3ERT) were analyzed alongside drug-likeness predictions using Lipinski's Rule of Five and ADMET properties (pkCSM server).

Among the tested ligands, eckol exhibited the highest binding affinity (–7.6 kcal/mol), suggesting strong and stable interactions with the receptor's active site. Eckol formed key hydrogen bonds with LEU346 and MET343, and hydrophobic interactions with LEU384, ALA350, and LEU387. Similar interactions between eckol and estrogen receptor-related targets have been reported previously, supporting its potential as a natural anti-cancer agent (Zhang *et al*., 2019). These interactions likely contribute to eckol's enhanced binding within the ligand-binding pocket of 3ERT, potentially modulating its biological activity.

All compounds had molecular weights within the acceptable range for oral drugs (<500 g/mol), consistent with desirable pharmacokinetic properties. However, eckol exceeded the recommended limit for hydrogen bond donors (six donors), which may hinder membrane permeability and oral bioavailability. Prior reports also noted that polyphenols with high polar surface area and multiple hydrogen bond donors often exhibit limited absorption through biological membranes (Teng and Chen, 2019). The low logP (–0.466) and high polar surface area (149.07 Å^2) of eckol indicate good water solubility but poor lipophilicity, factors that may further limit its absorption in the gastrointestinal tract (Karami *et al*., 2022).

In contrast, phloroglucinol and its derivatives complied with Lipinski's criteria, demonstrating favorable lipophilicity (logP 0.67–2.48) and hydrogen bond donor/acceptor profiles. These properties suggest better membrane permeability and oral absorption potential. 2,4-diisobutyryl phloroglucinol, in particular, exhibited a balanced profile with moderate lipophilicity and three hydrogen bond donors, indicating promising oral bioavailability. Similar derivatives of Phloroglucinol have shown good pharmacokinetics and bioactivity in earlier studies targeting cancer-related pathways (Kim *et al*., 2015; Sadeghi *et al*., 2024).

The ADMET analysis further supported the drug-likeness and safety profiles of the studied compounds. All ligands demonstrated acceptable water solubility, with Phloroglucinol showing the highest solubility (LogS –1.408) and diphlorethol the lowest (LogS –3.04). Intestinal absorption predictions indicated that phloroglucinol triacetate had the best absorption (96.67%) followed by phloroglucinol (83.55%), while eckol and phloroglucinol dihydrate exhibited relatively lower absorption (67.17% and 61.7%, respectively). None of the compounds were predicted to inhibit P-glycoprotein I, although eckol was identified as a P-glycoprotein II inhibitor, which may affect its efflux and distribution. Distribution data revealed that all compounds are unlikely to cross the blood-brain barrier (e.g., Eckol BBB permeability –1.399), minimizing potential central nervous system side effects. Importantly, none of the ligands were predicted to act as substrates or inhibitors of CYP2D6 or CYP3A4, suggesting a low risk of cytochrome P450-mediated drug-drug interactions. Excretion profiles indicated moderate clearance rates, with Phloroglucinol Triacetate showing the highest predicted clearance (log 0.99 ml/min/kg). Toxicity predictions were favorable across all compounds, as no AMES toxicity or hepatotoxicity was detected, and all ligands fell within a safe range of the maximum tolerable dose. Together, these ADMET characteristics support the potential of these compounds, particularly the Phloroglucinol derivatives, as promising candidates for further pharmacological evaluation.

CONCLUSION

In summary, the present study highlights the potential of marine-derived phlorotannins, particularly phloroglucinol derivatives and eckol, as promising candidates for targeting estrogen receptor alpha (ERα) in breast cancer therapy. Consistent with previous reports on the cytotoxic and anticancer activities of phlorotannins from brown algae, our molecular docking results suggest that these compounds can effectively interact with key residues within the ERα binding pocket, possibly modulating its activity. Among the tested ligands, phloroglucinol triacetate and 2,4-diisobutyryl phloroglucinol exhibited favorable drug-likeness profiles according to Lipinski's rule of five and ADMET predictions, supporting their potential as orally bioavailable therapeutic agents. However, the predictive nature of *in silico* analyses warrants validation through comprehensive *in vitro* and *in vivo* studies. Such experimental work will be essential to confirm the molecular mechanisms, efficacy, and safety of these compounds and to advance them towards clinical application in breast cancer treatment.

DECLARATIONS

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Generative AI or AI-assisted technology statement

No genarative AI or AI-assisted technology was used for this study.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Arnal, J.F., Lenfant, F., Metivier, R., Flouriot, G., Henrion, D., Adlanmerini, M. and Katzenellenbogen, J., 2017. Membrane and nuclear estrogen receptor alpha actions from tissue specificity to medical implications. *Physiol. Rev.*, **97**: 1045-1087. https://doi.org/10.1152/physrev.00024.2016

Chaudhary, K.K. and Mishra, N., 2016. A review on molecular docking: Novel tool for drug discovery. *Databases*, **3**: 1029.

Chen, L., Hu, J.S., Xu, J.L., Shao, C.L. and Wang, G.Y., 2018. Biological and chemical diversity of ascidian-associated microorganisms. *Mar. Drugs*, **16**: 362. https://doi.org/10.3390/md16100362

Cowin, P., Rowlands, T.M. and Hatsell, S.J., 2005. Cadherins and catenins in breast cancer. *Curr. Opin. Cell Biol.*, **17**: 499-508. https://doi.org/10.1016/j.ceb.2005.08.014

Dariya, B., Muppala, S., Srivani, G., Momin, S., Alam, A. and Saddala, M.S., 2021. Targeting STAT proteins via computational analysis in colorectal cancer. *Mol. Cell. Biochem.*, **476**: 165-174. https://doi.org/10.1007/s11010-020-03893-6

do Nascimento, R.G. and Otoni, K.M., 2020. Histological and molecular classification of breast cancer: What do we know? *Mastology*, **30**: 1-8. https://doi.org/10.29289/25945394202020200024

Lee, H.R., Kim, T.H. and Choi, K.C., 2012. Functions and physiological roles of two types of estrogen receptors, ERα and ERβ, identified by estrogen receptor knockout mouse. *Lab. Anim. Res.*, **28**: 71-76. https://doi.org/10.5625/lar.2012.28.2.71

Manzari-Tavakoli, A., Babajani, A., Tavakoli, M.M., Safaeinejad, F. and Jafari, A., 2024. Integrating natural compounds and nanoparticle-based drug delivery systems: A novel strategy for enhanced efficacy and selectivity in cancer therapy. *Cancer Med.*, **13**: e7010. https://doi.org/10.1002/cam4.7010

Mohd Zaid, N.A., Sekar, M., Bonam, S.R., Gan, S.H., Lum, P.T., Begum, M.Y. and Fuloria, S., 2023. Promising natural products in new drug design, development, and therapy for skin disorders: An overview of scientific evidence and understanding their mechanism of action. *Drug Design Develop. Ther.,* pp. 23-66. https://doi.org/10.2147/DDDT.S326332

Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K., Goodsell, D.S. and Olson, A.J., 2009. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J. Comput. Chem.*, **30**: 2785-2791. https://doi.org/10.1002/jcc.21256

Naithani, U. and Guleria, V., 2024. Integrative computational approaches for discovery and evaluation of lead compound for drug design. *Front. Drug Disc.*, **4**: 1362456. https://doi.org/10.3389/fddsv.2024.1362456

Nho, J.A., Shin, Y.S., Jeong, H.R., Cho, S., Heo, H.J., Kim, G.H. and Kim, D.O., 2020. Neuroprotective effects of phlorotannin-rich extract from brown seaweed *Ecklonia cava* on neuronal PC-12 and SH-SY5Y cells with oxidative stress. *J. Microbiol. Biotechnol.*, **30**: 359. https://doi.org/10.4014/jmb.1910.10068

Nova, P., Gomes, A.M. and Costa-Pinto, A.R., 2024. It comes from the sea: Macroalgae-derived bioactive compounds with anti-cancer potential. *Crit. Rev. Biotechnol.*, **44**: 462-476. https://doi.org/10.1080/07388551.2023.2174068

Obeagu, E.I. and Obeagu, G.U., 2024. Breast cancer: A review of risk factors and diagnosis. *Medicine*, **103**: e36905. https://doi.org/10.1097/MD.0000000000036905

Palmieri, C., Cheng, G.J., Saji, S., Zelada-Hedman, M., Weihua, Z., Van Noorden, S. and Gustafsson, J.A., 2002. Estrogen receptor beta in breast cancer. *Endocr. Relat. Cancer*, **9**: 1-13. https://doi.org/10.1677/erc.0.0090001

Pradhan, B. and Ki, J.S., 2023. Antioxidant and chemotherapeutic efficacies of seaweed-derived phlorotannins in cancer treatment: A review regarding novel anticancer drugs. *Phytother. Res.*, **37**: 2067-2091. https://doi.org/10.1002/ptr.7809

Remya, R.R., Samrot, A.V., Kumar, S.S., Mohanavel, V., Karthick, A., Chinnaiyan, V.K. and Muhibbullah, M., 2022. Bioactive potential of brown algae. *Adsorpt. Sci. Technol.*, **2022**: 9104835. https://doi.org/10.1155/2022/9104835

Sadeghi, A., Rajabiyan, A., Nezhad, N.M., Nabizade, N., Alvani, A. and Zarei-Ahmady, A., 2024. A review on Persian Gulf brown algae as a potential source for anticancer drugs. *Algal Res.*, pp. 103446. https://doi.org/10.1016/j.algal.2024.103446

Verma, V.V., Vimal, S., Mishra, M.K. and Sharma,

V.K., 2025. A comprehensive review on structural insights through molecular visualization: Tools, applications, and limitations. *J. Mol. Model*., **31**: 1-15. https://doi.org/10.1007/s00894-025-06402-y

Wilkerson, A.D., Gentle, C.K., Ortega, C. and Al-Hilli, Z., 2024. Disparities in breast cancer care how factors related to prevention, diagnosis, and treatment drive inequity. *Healthcare,* **12**: 462. MDPI. https://doi.org/10.3390/healthcare12040462

Yin, G., Liu, L., Yu, T., Yu, L., Feng, M., Zhou, C. and Yu, Z., 2024. Genomic and transcriptomic analysis of breast cancer identifies novel signatures associated with response to neoadjuvant chemotherapy. *Genom. Med.*, **16**: 11. https://doi.org/10.1186/s13073-024-01286-8

Hakim, M.M. and Patel, I.C., 2020. A review on phytoconstituents of marine brown algae. *Fut. J. Pharma. Sci.*, **6**: 1-11. https://doi.org/10.1186/s43094-020-00147-6

Kim, R.K., Uddin, N., Hyun, J.W., Kim, C., Suh, Y. and Lee, S.J., 2015. Novel anticancer activity of phloroglucinol against breast cancer stem-like cells. *Toxicol. appl. Pharmacol.*, **286**: 143-150. https://doi.org/10.1016/j.taap.2015.03.026

Karami, T.K., Hailu, S., Feng, S., Graham, R. and Gukasyan, H.J., 2022. Eyes on lipinski's rule of five: A new "rule of thumb" for physicochemical design space of ophthalmic drugs. *J. Ocular Pharmacol. Therapeut.*, **38**: 43-55. https://doi.org/10.1089/jop.2021.0069

Teng, H. and Chen, L., 2019. Polyphenols and bioavailability: An update. *Crit. Rev. Fd. Sci. Nutr.*, **59**: 2040-2051. https://doi.org/10.1080/10408398.2018.1437023

Zhang, M.Y., Guo, J., Hu, X.M., Zhao, S.Q., Li, S.L. and Wang, J., 2019. An *in vivo* anti-tumor effect of eckol from marine brown algae by improving the immune response. *Fd. Funct.*, **10**: 4361-4371. https://doi.org/10.1039/C9FO00865A