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Agonist potential of estrogen-β receptors from brown algae (Sargassum muticum) as molecular therapy for breast cancer: in-silico approach

Mila Karisma Fitriawati, Fakih Haikal, Fadia Fatiha, Ervina Setiawati, Rizky Prasiska Wulandari, Halwa Aulia Nurdin, dan Rina Fajri Nuwarda ✉

Department of Analytical Pharmacy and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia

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Abstract

Breast cancer is a malignant condition characterized by uncontrolled cell growth in breast tissue. Estrogen receptor-β have role as a tumor suppressor, so activating this receptor through specific agonists holds great promise for developing targeted and potential therapeutic agents for breast cancer treatment. This study aims to investigate the potential agonist activity of ten compounds of brown algae (Sargassum muticum) against estrogen-β receptors as candidates for breast cancer treatment through in-silico studies. The study was conducted using computational methods: Lipinski's Rule of Five (RO5) prediction, ADMET prediction, pharmacophore modeling, ligand and receptor preparation, method validation, molecular docking simulation and visualization. The results showed that of the 10 compounds evaluated from brown algae plants, all met the RO5 criteria, so they have potential as oral drug candidates. From the result, eckol compound has the smallest binding energy (-7.85) and inhibition constant (1.77 μM). Eckol interacts with several amino acid residues similarly to the way hydroxytamoxifen, the natural ligand, binds to estrogen-β. The study shows that Eckol has the potential to act as an estrogen receptor β agonist. However, further research, such as in vitro testing, is needed to confirm this agonistic activity.

Abstrak

Kanker payudara merupakan kondisi ganas yang ditandai dengan pertumbuhan sel yang tidak terkendali pada jaringan payudara. Reseptor estrogen-β memiliki peran sebagai penekan tumor, sehingga aktivasi reseptor ini melalui agonis spesifik memiliki potensi besar dalam pengembangan agen terapeutik yang lebih terarah untuk pengobatan kanker payudara. Penelitian ini bertujuan untuk mengkaji potensi aktivitas agonis dari sepuluh senyawa alga coklat (Sargassum muticum) terhadap reseptor estrogen-β sebagai kandidat terapi kanker payudara melalui studi in silico. Penelitian dilakukan menggunakan metode komputasi, meliputi prediksi Lipinski's Rule of Five (RO5), prediksi ADMET, pemodelan farmakofor, preparasi ligan dan reseptor, validasi metode, simulasi molecular docking, serta visualisasi. Hasil penelitian menunjukkan bahwa seluruh 10 senyawa yang dievaluasi memenuhi kriteria RO5 sehingga berpotensi sebagai kandidat obat oral. Dari hasil yang diperoleh, senyawa eckol memiliki energi ikatan paling kecil (-7,85) dan konstanta inhibisi sebesar 1,77 μM, serta berinteraksi dengan beberapa residu asam amino dengan cara yang mirip dengan hidroksitamoksifen sebagai ligan alami pada reseptor estrogen-β. Penelitian ini menunjukkan bahwa eckol memiliki potensi sebagai agonis reseptor estrogen-β, namun penelitian lanjutan seperti uji in vitro masih diperlukan untuk mengonfirmasi aktivitas agonis tersebut.

✉ Alamat korespondensi:
Jl. Raya Jatinangor, KM. 21 Jatinangor – Sumedang, West Java, Indonesia.
E-mail: rina.nuwarda@unpad.ac.id

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Introduction

Breast cancer is a malignant tumor characterized by uncontrolled cell growth and one of the primary causes of cancer-related mortality in women (Asif et al., 2016; Yang et al., 2024). Factors that cause breast cancer include genetics, lifestyle, and hormonal imbalances (Xu & Xu, 2023). External factors such as exposure to radiation or chemicals can also contribute to the development of breast cancer (Hussein & Alabbasy, 2022). Referring to the 2020 Global Burner of Cancer (GLOBOCAN) data, the percentage of breast cancer cases is greater than other cancers, amounting to 2.3 million new diagnoses and 684.996 deaths in women worldwide (Khaerunnisa et al., 2023). Therefore, prevention and treatment are needed to reduce the mortality rate of breast cancer.

Breast cancer is divided into different subtypes, such as luminal A, luminal B, HER2-positive and triple-negative breast cancer (TNBC) (Clusan et al., 2023), luminal A and luminal B refers to the presence of estrogen receptors (ER), indicating a major role for estrogen in cancer cell growth and development (Carvalho et al., 2025). The cellular action of estrogen is mainly mediated by nuclear ER α and ER β that couple with membrane G proteins (Clusan et al., 2023). A key difference between these two subtypes is their function, ER α is associated with increased cell proliferation in cancer development, especially breast cancer, whereas ER β has antiproliferative properties as a tumor suppressor (Song et al., 2022; Zlotos et al., 2023), in addition, ER β is highly expressed in ER α-negative breast cancer (BCa) and TNBC (Choi, 2022). ER β seems to counteract the effects of ER α on cell proliferation by regulating the expression of numerous genes regulated by ER α, including microRNA genes (Sellitto et al., 2020). In addition, it is known to have a tumor suppressor activity through DNA binding transcription that regulates gene expression and has a potential treatment target for various types of human cancer, including breast cancer (Zhou & Liu, 2020).

Estrogen receptor β has attracted attention in cancer research, especially breast cancer, due to its ability to reduce cell proliferation and increase apoptosis in cancer cells. Research conducted by Zhou and Liu (2020) demonstrated that patients with ER β expression greater than 75% have a lower risk of breast cancer. High expression of ER β is a good prognostic sign especially for patients undergoing chemotherapy (Zhou & Liu, 2020; Zlotos et al., 2023). While tamoxifen is one of the cancer therapies that works by binding to both ER α and ER β. Although often associated with ER α antagonism in the treatment of breast cancer, recent studies suggest tamoxifen can affect breast cancer through its agonistic effects on ER β, low ER β levels indicate of tamoxifen resistance, and treating breast cancer cells with ER β selective agonists can enhance the growth inhibitory effect of tamoxifen (Nagandla et al., 2024).

Indonesia is the home to one of the world's largest biodiversities, including marine resources. Marine organisms are a promising source of bioactive compounds, such as brown algae (Sargassum muticum), which contain various compounds including eckol and fucoidan. Several studies have shown that bioactive compounds in brown algae can act as antioxidants, antiproliferation, and anticancer (Frazzini & Rossi, 2025; Silva et al., 2024). However, the simulation molecular among compounds in brown algae with the ER β in molecular level are still limited. This study was conducted to investigate the interaction of 10 compounds from brown algae with the estrogen β receptor using in silico methods.

Method

Software and Materials. This *in-silico* study was conducted using an ASUS laptop equipped with an AMD A8-7410 APU processor (AMD Radeon R5 Graphics) and 8GB DDR4 RAM, operating on Windows 10 (64-bit). Several software and web-based tools were employed throughout the computational work. The chemical structures of hydroxytamoxifen and the test compound from brown algae were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/), which served as the initial input for subsequent analysis. Ligand preparation and geometry optimization were carried out using ChemDraw Ultra 12.0 and Chem3D Pro 12.0. The targeted receptor protein, estrogen receptor β, in complex with hydroxytamoxifen, was obtained from the Protein Data Bank (PDB ID: 2FSZ). SwissADME (http://www.swissadme.ch) and PreADMET (https://preadmet.webservice.bmdrc.org/adme/) were employed to predict pharmacokinetic and toxicity profiles, this serves as an assessment of the drug-likeness properties based on Lipinski's Rule of Five. Molecular docking was performed using AutoDock 4.2.6 with AutoDockTools version 1.5.6, while BIOVIA Discovery Studio 2020 was used to visualize 3D and interaction analysis between ligands and receptors. LigandScout 4.4.5 was used for pharmacophore analysis.

Lipinski's Rule of Five Prediction. Ten active compounds from brown algae were retrieved from the PubChem website. The 2D structures of the compounds were generated using ChemDraw Ultra 12.0, subsequently converted into 3D models using Chem3D Pro 12.0. The compounds were then analyzed using SwissADME to predict their physicochemical properties included molecular weight, LogP, number of

hydrogen bond donors and acceptors. Finally, the obtained parameters were evaluated against the criteria defined in Lipinski's Rule of Five.

ADMET Prediction. ADMET properties were predicted using the PreADMET online tool. The 2D structure of each compound was uploaded, and ADMET Prediction and Toxicity Prediction modules were applied. These predictions cover Absorption, Distribution, Excretion, and Toxicity with parameters analyzed including human intestinal absorption (%HIA), cell permeability (CaCo-2), plasma protein binding (PPB), blood-brain barrier penetration (BBB), mutagenicity, and carcinogenicity.

Pharmacophore Modeling. Pharmacophore modeling was performed to identify potential lead compounds by analyzing common chemical features, such as hydrogen bonds, which might be essential for biological activity. Active and decoy compound sets were constructed using estrogen-β receptors (PDB ID: 2FSZ), which were obtained from the Directory of Useful Decoys - Enhanced (DUD-E) database (https://dude.docking.org/targets). Each model of active and decoy database was uploaded and subsequently validated by initiating the screening process using the "Perform Screening" function. Receiver Operating Characteristic (ROC) plots were used to visualize the screening performance of each model, and the best model was selected for further analysis based on the highest ROC value.

Afterward, the test pharmacophore model was transferred to the screening perspective using the "Load Screening Database" option. The test compound database was marked in green, while the other databases were unmarked. Subsequently, the best pharmacophore model was transferred to the screening perspective using the Ligand-Based perspective feature, and the detected compounds were displayed along with their pharmacophore fit score.

Ligand and Receptor Preparation. The 3D structure of the estrogen-β receptor (PDB ID: 2SFZ) was retrieved from the RCSB Protein Data Bank (www.rcsb.org) and prepared using AutoDockTools 1.5.6 by adding Kollman charges and polar hydrogens, followed by saving the file in .pbqt format. The test ligands were drawn in ChemDraw and initially saved in .pdb format. They were subsequently prepared by adding hydrogen atoms, assigning Gasteiger charges, and defining torsional flexibility using AutoDockTools 1.5.6. The ligands were then saved in .pdbqt format.

Method Validation. Molecular docking validation was carried out in AutoDockToos 1.5.6 by performing a redocking procedure using the control ligand hydroxytamoxifen, against the estrogen-β receptor (PDB ID: 2SFZ). In this step, the control ligand and receptor files were loaded in the exact position, and the size of the grid box was determined (Allo et al., 2023). The docking configurations were then saved in .dpf format. The key parameter evaluated in this validation is the root mean square deviation (RMSD) value, where an RMSD of less than 2.0 Å is considered.

Molecular Docking Simulation and Visualization. Molecular docking of the test ligands with receptor was performed using AutoDock 1.5.6 with Lamarckian genetic algorithm runs set to 100. The grid box parameters and docking settings are summarized in **Table 1**.

Table 1. Parameters of molecular docking

Parameters	Values
I. Grid Parameters	
Grid center	x = 96.096; y = 20.764; z = -4.375
Grid box	40 × 40 × 40 points with a distance of 0.375 Å
II. Docking Parameters	
Number of GA runs	100

The interaction between the ligands and the receptor was visualized in both 2D and 3D representations using AutoDock Tools and BIOVIA Discovery Studio 2020. The resulting visualizations were exported and saved in .jpg format.

Results and Discussion

Molecular docking is a data-driven chemical technique which relies on structured input in the form of computational data of the target protein and the ligand to calculate and predict the most stable interaction positions and energies, for discovering new compounds with potential as oral drugs based on their interaction with specific receptors (Tripathi & Bankaitis, 2017). This technique is also known as in silico and is becoming an important tool in drug development. This study begins with a molecular docking simulation using the Estrogen-β as a working target receptor in brown algae plants (*Sargassum muticum*), followed by an evaluation of the molecular characteristics of the derivative compounds to ensure optimal oral absorption and bioavailability.

The compound's capacity to efficiently assimilate in the gastrointestinal tract and penetrate biological membranes is closely correlated with Lipinski's Rule of Five (RO5) (Wu et al., 2024). This rule indicates that a compound is more likely to be orally active if it satisfies specific physicochemical criteria, such as a molecular weight of 500 Daltons or less, no more than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, and a log P value of less than five (Sellitto et al., 2020). The RO5 criteria were met by all ten compounds derived from *Sargassum muticum* in this study, suggesting that they have favorable molecular characteristics for oral administration. The potential of these compounds as promising oral drug candidates targeting the Estrogen-β receptor suggests that they may exhibit excellent membrane permeability and bioavailability. The brown algae-derived compounds exhibited comparable physicochemical profiles to hydroxytamoxifen, which also satisfies the RO5 requirements. The ten compounds in brown algae plants (*Sargassum muticum*) tested met the Rule of Five (RO5) criteria, as summarized in **Table 2**.

Table 2. Lipinski's Rule of Five Results

No	Compound Name	Molecular Weight (< 500 Da)	Log P (<5)	Hydrogen Bond		Remarks
				Donor (<5)	Acceptor (<10)	
1	Fucoidan	256.28 g/mol	-0.45	2	7	Meets the criteria
2	Gallic Acid	170.12 g/mol	0.21	4	5	Meets the criteria
3	3,4-Dihydroxybenzoic Acid	154.12 g/mol	0.65	3	4	Meets the criteria
4	Syringic Acid	198.17 g/mol	0.99	2	5	Meets the criteria
5	Salicylic Acid	138.12 g/mol	1.24	2	3	Meets the criteria
6	Caffeic Acid	180.16 g/mol	0.93	3	4	Meets the criteria
7	Ferulic Acid	194.18 g/mol	1.36	2	4	Meets the criteria
8	p-Coumaric acid	164.16 g/mol	1.26	2	3	Meets the criteria
9	Fukofloretol A	374.3 g/mol	1.52	8	9	Meets the criteria
10	Eckol	372.28 g/mol	1.83	6	9	Meets the criteria (1 violation)

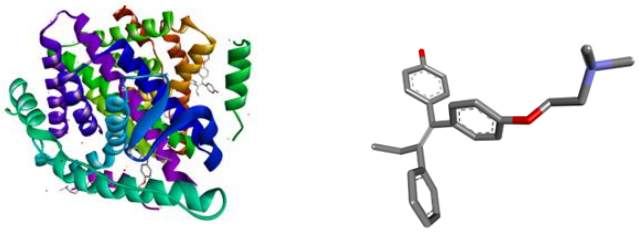
Table 3. ADMET Determination Results

No	Compounds	Absorption		Distribution		Toxicity		
		HIA (%)	CaCO2 (nm/sec)	PPB (%)	BBB	Mutagen	Carsinogen	
							Rat	Mice
1	Fucoidan	40.443	5.856	35.693	0.091	Mutagen	-	+
2	Gallic Acid	53.696	13.849	65.384	0.348	Mutagen	-	+
3	3,4-Dihydroxybenzoic Acid	74.749	18.304	27.115	0.442	Mutagen	-	+
4	Syringic Acid	82.027	18.832	69.775	0.539	Mutagen	-	+
5	Salicylic Acid	88.138	20.314	8.772	0.643	Mutagen	-	-
6	Caffeic Acid	82.301	21.107	40.290	0.497	Mutagen	-	+
7	Ferulic Acid	90.603	21.117	50.414	0.758	Mutagen	-	+
8	p-Coumaric acid	92.095	21.109	63.055	0.694	Mutagen	+	+
9	Fukofloretol A	28.870	11.355	100.000	0.228	Non mutagen	-	+
10	Eckol	55.597	4.205	100.000	0.255	Mutagen	-	+

The suitability of these compounds as oral drug candidates was then further tested through predictions of absorption, distribution, metabolism, excretion, and toxicity (ADMET). The ADMET prediction results

obtained are summarized in Table 3. Human Intestinal Absorption (HIA) and Caco-2 cell permeability (Caco-2) parameters are used to evaluate the absorption ability of a compound, while Plasma Protein Binding (PPB) and Blood–Brain Barrier (BBB) parameters are used to assess the distribution ability of the compound. The results showed that six compounds had good intestinal absorption (HIA 70-100%) with moderate cellular permeability, and four other compounds were moderately absorbed in the body (%HIA 20-70%) reinforcing the potential for oral bioavailability. However, the distribution aspect presented challenges, particularly for two compounds (Eckol and Fucofloretol A) that showed very strong PPB of 100,000%, which could significantly limit the availability of free drug for therapeutic activity, it was also found that nine compounds could penetrate well into the brain barrier (BBB 2.0-0.1) and one compound penetrated poorly (BBB <0.1). Additionally, toxicity results raise critical concerns as nine compounds are predicted to be mutagenic, the results of the toxicity test showed that there was only one compound (fucofloretol) that was a non-mutagen and one compound that was non-carcinogenic to rats.

Next, Estrogen-β receptor preparation results and natural ligands that were originally four chains have been separated into one chain, as shown in **Figure 1**. Ten compounds from brown algae plants were also prepared as test compounds.



(a) (b)

Figure 1. (a) Estrogen receptor-β structure (PDB ID: 2FSZ) and (b) Structure of Natural Ligand Hydroxytamoxifen

Validation results are obtained based on RMSD values,with values below 2 Å considered acceptable. A low RMSD also indicates that the re-docking results are similar to the crystallographic conformation. The RMSD value obtained from the re-docking between the natural ligand (hydroxytamoxifen) and the estrogen-β receptor 2FSZ is 1.014 Å. Based on these results, it can be concluded that the docking parameters are valid for application in the molecular docking process of the test ligand as the RMSD value falls within the accepted threshold (≤ 2 Å). This indicates a similarity in the position of the natural ligand before and after the re-docking process. A visualization of the position of the natural ligand before and after re-docking can be seen in **Figure 2.**

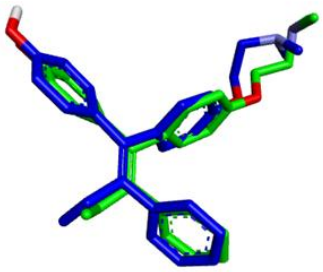


Figure 2. Overlay of Hydroxytamoxifen Before (Green) and After Re-Docking Process (Blue), RMSD value was 1.014 A

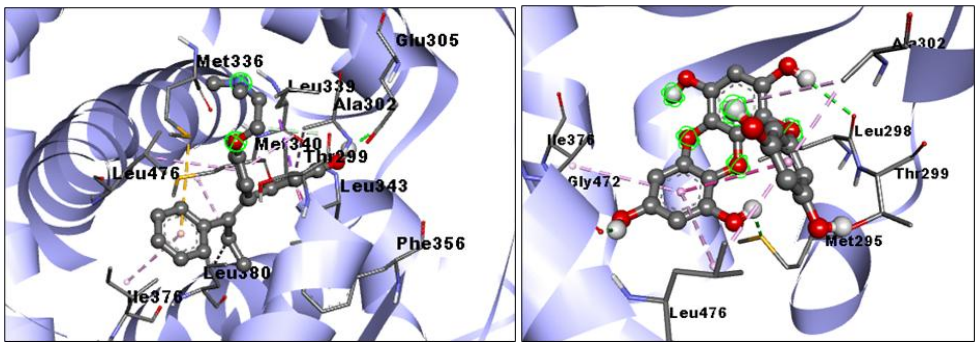
The results of the molecular docking simulation between estrogen- β and hydroxytamoxifen, as well as the test compounds, are presented in Table 4. The results indicate the presence of natural ligands binding to amino acid residues GLU305 and THR299 through hydrogen bonds. Some test ligands also showed bonding with GLU305. The hydroxytamoxifen compound had a binding energy of -10.79 kcal/mol and an inhibition constant of 12.4 nM. The test compound with the lowest binding energy and inhibition constant is Eckol, with values of -7.85 and 1.77 μ M, respectively

Table 4. Molecular Docking Simulation Output

No	Compound Name	Cluster	Binding Energy (kkal/mol)	Ki	Interaction With Amino Acid	
					Hydrogen Bond	Etc
1	Hydroxytamoxifen (Natural Ligand)	1	-10.79	12.4 nM	GLU305 THR299	ALA302 LEU343 MET340 LEU380 ILE376 LEU476 PHE356 MET336 LEU 339
2	Fucoidan	1	-5.14	171.4 µM	ARG346 GLU305	MET 340 LEU343 LEU380 LEU298 PHE356
2	Gallic Acid	1	-4.24	784.86 µM	ARG346 GLU305 LEU298	LEU343 PHE356 ALA302
3	3,4-Dihydroxybenzoic Acid	1	-4.32	687.0 µM	GLU305 ARG346 MET336	MET340 LEU339 LEU343 ALA302 PHE356
4	Syringic Acid	1	-4.04	1.09 mM	GLU305 LEU339	LEU343 LEU298 ALA302 PHE356
5	Salicylic Acid	1	-4.44	560.18 µM	GLU305	ALA302 LEU301 LEU339 LEU298 PHE356
6	Caffeic Acid	1	-4.96	231.0 µM	GLU305	LEU339 LEU343
7	Ferulic Acid	1	-5.01	212.37 µM	GLU305 LEU298	ALA302 LEU301 LEU339 PHE356 LEU343
8	p-Coumaric acid	1	-4.73	338.6 µM	GLY472 LEU298 GLU305 ARG346 LEU339	ALA302 LEU476 LEU343 PHE356 MET336

No	Compound Name	Cluster	Binding Energy (kkal/mol)	Ki	Interaction With Amino Acid	
					Hydrogen Bond	Etc
						MET295 LEU339
9	Fukofloretol A	1	-7.55	2.91 µM	GLY472 LEU298 GLU305 ARG346 LEU339	LEU476 ALA302 LEU343 PHE356 MET295 MET336 LEU339
10	Eckol	1	-7.85	1.77 µM	GLY472 MET295 LEU298 THR299	ALA302 ILE376 LEU476

Hydroxytamoxifen was shown to occupy a specific binding pocket within the Estrogen-β receptor (ERβ) ligand-binding domain, forming strong hydrogen bond interactions with key residues GLU305 and THR299 that are essential for ligand stabilization and receptor modulation. Several brown algae-derived compounds exhibited comparable binding behavior, particularly through shared interactions with THR299, while eckol additionally shared GLU305 as a binding residue. Eckol demonstrated a broader interaction network within the same binding cavity, involving hydrogen bonds with THR299, ALA302, MET295, LEU298, and GLY472, as well as hydrophobic and van der Waals contacts with ILE376 and LEU476. This interaction pattern closely resembles, and in some aspects extends beyond, that of hydroxytamoxifen, suggesting enhanced stabilization through multiple contact points. Furthermore, other compounds such as fucoidan, gallic acid, 3,4-dihydroxybenzoic acid, p-coumaric acid, and fucofloretol A interacted with ARG346, a residue known to play a critical role in ERβ agonist activity. The extensive hydrogen bonding capacity of eckol, attributed to its multiple hydroxyl groups, may confer higher binding affinity and subtly alter receptor conformation compared to hydroxytamoxifen. Collectively, these findings indicate that brown algae-derived compounds, particularly eckol, may function as natural estrogen receptor modulators by mimicking key interaction features of hydroxytamoxifen, highlighting their potential relevance in anticancer drug development.



(a) (b)

Figure 3. 3D visualization of ligand–receptor interactions within the Estrogen-β receptor (ERβ). (a) hydroxytamoxifen and (b) eckol.

Next, the results of molecular docking of the best compound (eckol) were visualized 3D using BIOVIA Discovery Studio, as shown in Figure 3. Hydroxytamoxifen demonstrates several stabilizing interactions with key residues, including hydrogen bonds and hydrophobic contacts, which are consistent

with its established binding mode. In comparison, Eckol also forms multiple favorable interactions with residues such as Leu476, Phe356, and Met336, suggesting that its polyphenolic structure is capable of occupying the ER β active pocket effectively. The interaction pattern observed in Figure 3b supports the hypothesis that Eckol may mimic the receptor-binding behavior of the standard ligand.

Then, ten pharmacophore models were generated and validated, and Model 8 demonstrated the best performance, yielding the highest number of hit compounds (306 hits) and superior statistical parameters (AUC = 0.98; EF = 1.6), thus fulfilling the criteria for a valid and robust pharmacophore model (AUC > 0.5 and EF > 1.0) and exceeding the threshold for a good model (AUC > 0.7). Pharmacophore-based virtual screening identified eight active compounds, namely fucoidan, 3,4-dihydroxybenzoic acid, salicylic acid, caffeic acid, ferulic acid, p-coumaric acid, fucofloretol A, and eckol. Among these, eckol exhibited the highest pharmacophore fit score (44.66), as illustrated in Figure 4, indicating optimal alignment with the essential pharmacophoric features required for Estrogen-β receptor (ERβ) interaction. The pharmacophore analysis further revealed that eckol matched five key features, including aromatic rings, hydrogen bond donors, hydrogen bond acceptors, and hydrophobic interactions, highlighting its strong structural compatibility and supporting its potential role as a promising brown algae–derived lead compound with selective affinity toward ERβ targets

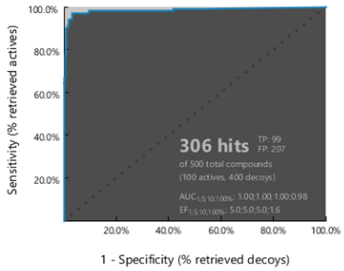


Figure 4. Pharmacophore Modeling Results Model 8

Notably, these in silico findings are consistent with previous biological evidence. Zhang et al (2019) reported that eckol inhibited tumor growth in a mouse xenograft model by inducing apoptosis (upregulation of Caspase-3 and Caspase-9, downregulation of Bcl-2 and EGFR) and enhancing immune responses (activation of dendritic cells and an increased CD4+/CD8+ ratio) (Zhang et al., 2019). Such experimental results provide further support that the strong ERβ interaction profile observed here may translate into meaningful anticancer activity, positioning eckol as a promising candidate for further exploration in ERβ-targeted therapies.

Conclusion

In silico analysis of brown algae (Sargassum muticum) against the Estrogen- β receptor using ChemOffice, AutoDock, BIOVIA Discovery Studio, and LigandScout showed that all ten compounds evaluated met Lipinski's Five Rules, indicating their potential as oral drug candidates. Further ADMET predictions supported their favorable absorption, distribution, and safety profiles. Among them, eckol emerged as the most promising compound, showing the best pharmacophore fit score and major interactions with residues THR299, ALA302, ILE376, and LEU476, which are similar to hydroxytamoxifen. These findings suggest that eckol from brown algae could serve as a potential source of estrogen-B receptor agonists.

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