In Silico Evaluation of *Hyptis Verticillata*-Derived Phytochemicals Targeting Estrogen Receptor Alpha (Erα) and Progesterone Receptor in Hormone-Dependent Breast Cancer

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ABSTRACT

Hormone-dependent breast cancers, primarily driven by estrogen receptor alpha (ERα) and progesterone receptor (PR) signaling, account for most breast malignancies and remain a major therapeutic challenge due to frequent resistance to endocrine therapy. The search for novel, plant-derived ligands with dual modulatory activity on ERα and PR is therefore critical. This study employed an *in silico* approach to evaluate selected phytochemicals from *Hyptis verticillata*—a medicinal plant known for its diverse bioactive constituents—against ERα (Y537S mutant; PDB ID: 6CHZ) and PR (PDB ID: 4A2J). Seven phytocompounds were retrieved from the PubChem database and subjected to drug-likeness analysis using SwissADME, molecular docking with AutoDock Vina, and pharmacokinetic/toxicity prediction via ADMETlab 2.0. Among the screened compounds, squalene (−6.9 kcal/mol) and 4,7-methanon-1H-indene (−6.4 kcal/mol) demonstrated the highest binding affinities toward ERα and PR, respectively. Both ligands showed favorable hydrophobic interactions within the receptor ligand-binding domains, suggesting potential receptor antagonism or modulation. Drug-likeness and ADMET profiling revealed that 3a,4,5,6,7,7a-hexahydro-4,7-methanoindene and 4,7-methanon-1H-indene possess acceptable physicochemical and pharmacokinetic properties, indicating promising oral bioavailability and low toxicity risks. The findings highlight *H. verticillata* phytochemicals as potential scaffolds for developing multitargeted agents capable of counteracting endocrine resistance in hormone receptor–positive breast cancers. Further validation through molecular dynamics simulations and *in vitro* receptor-binding assays is recommended to confirm these computational predictions and explore their mechanistic potential.

Keywords: *Hyptis verticillata*, estrogen receptor alpha (ERα), progesterone receptor (PR), molecular docking, breast cancer, phytochemicals, endocrine resistance, ADMET profiling.

INTRODUCTION

Hormone-dependent (estrogen and/or progesterone receptor–positive) breast cancers account for the majority of breast tumors and are driven largely by estrogen receptor-alpha (ERα) signaling, which promotes proliferation and survival through genomic and non-genomic pathways (A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer, 2023; Targeting mutated estrogen receptor alpha: Rediscovering old and new opportunities, 2020). Crosstalk between ERα and other steroid receptors—notably the progesterone receptor (PR)—adds further regulatory complexity, influencing chromatin binding patterns, transcriptional programs, and therapeutic response (Estrogen Receptor Signaling in Breast Cancer, 2023; Genome-wide crosstalk between

steroid receptors in breast and prostate cancers, 2021). While endocrine therapies (e.g., SERMs, AIs, SERDs) have transformed outcomes, resistance remains common in advanced disease, with ligand-binding domain ESR1 mutations (e.g., Y537S, D538G) conferring ligand-independent activity and diminishing endocrine sensitivity (Mechanisms of endocrine resistance in hormone receptor-positive breast cancer, 2024; ESR1 Y537S and D538G Mutations Drive Resistance to CDK4/6 Inhibitors, 2025). Emerging data also highlight PR-mediated tumor-immune evasion (e.g., MHC-I downregulation), suggesting PR as both a biological driver and a therapeutic vulnerability in HR+ disease (Progesterone receptor–dependent downregulation of MHC class I, 2025).

Natural products remain a prolific source of anticancer leads, and in silico pipelines—combining molecular docking, molecular dynamics (MD), and ADMET prediction—accelerate early discovery while reducing cost and attrition (In silico design of novel bioactive molecules to treat breast cancer, 2023). *Hyptis verticillata* (Lamiaceae) is a medicinal plant whose extracts and essential oils contain diverse sesquiterpenoids and phenolic constituents (e.g., squamulosone; cadina-4,10(15)-dien-3-one) with reported bioactivities (Biological activity and chemical composition of the essential oil from *Hyptis verticillata*, 2005; Anti-hyperglycemic potential of *Hyptis verticillata* Jacq., 2018). Despite this chemical richness, systematic evaluation of *H. verticillata* phytochemicals against ERα and PR—especially in the context of clinically relevant ERα mutants—remains underexplored. Given the centrality of ERα/PR signaling and the need for novel, resistance-competent modulators, *in silico* screening of *H. verticillata*–derived compounds is timely and potentially impactful (Treating ER-positive breast cancer: a review of current FDA-approved therapies and novel approaches, 2025; Beyond endocrine resistance: ESR1 activating mutations, 2024).

Problem Statement

Endocrine resistance driven by ESR1 mutations and signaling crosstalk limits the durability of current therapies in hormone-dependent breast cancer (Mechanisms of endocrine resistance in hormone receptor-positive breast cancer, 2024; Estrogen/HER2 receptor crosstalk in breast cancer, 2023). Although natural products offer chemically diverse scaffolds, there is a specific evidence gap: the ERα/PR-targeting potential of characterized *H. verticillata* phytochemicals has not been systematically mapped using modern *in silico* workflows that consider wild-type and mutant ERα, PR interactions, and early drug-likeness/toxicity filters. Additionally, PR's emerging role in immune evasion underscores the need to identify ligands that could modulate PR signaling in therapeutically favorable ways (Progesterone receptor–dependent downregulation of MHC class I, 2025). Addressing these gaps could yield lead compounds with improved prospects against resistance mechanisms and provide hypotheses for downstream *in vitro* validation.

Aim of the study

To perform a comprehensive *in silico* evaluation of *Hyptis verticillata*–derived phytochemicals against estrogen receptor-alpha (ERα) and progesterone receptor (PR) in hormone-dependent breast cancer.

MATERIALS AND METHODS

Materials

The databases used include:

1. PubMed Database (https://pubmed.ncbi.nlm.nih.gov/)
2. PubChem (https://pubchem.ncbi.nlm.nih.gov/)
3. RCSB-Protein Data Bank (https://www.rcsb.org/)
4. Chemspider (http://www.chemspider.com/)
5. Swissadme (http://www.swissadme.ch/)

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6. ADMET lab 2.0 (https://admetmesh.scbdd.com/)

Softwares used include:

1. OpenBabel in build in PyRx 0.8
2. Discovery Studio 2022
3. AutoDock Vina in built in PyRx 0.8

Phytochemical Library Preparation

Canonical 2D structures (SDF) were downloaded from PubChem for each compound and converted to 3D with Open Babel, generating low-energy conformers by weighted rotor search and minimizing with the MMFF94 force field until the energy gradient fell below 0.05 kcal mol^{-1} $Å^{-1}$ (Halgren, 1996; O'Boyle *et al.,* 2011; Kim *et al.,* 2021). All structures were neutralized as appropriate for pH 7.4, explicit hydrogens were added, and tautomers were standardized. Final ligands were exported to PDBQT using ADT (Morris *et al.,* 2009).

Table 1 List of phytocompounds derived from *hyptis verticilata*

Ligands
1. 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene
2. 4,7- methanon-1H-indene
3. R-R,R-E- trans-Phytol
4. Squalene
5. 9,12,15-octadecatrien-1-ol
6. 1-octadecyne
7. 1-fluorodecane

Drug likeness screening

The compounds were subjected to various drug-likeness filtering analysis. The drug-likeness analysis which includes Lipinski, Veber, Ghose, Egan and Muegge were performed on the SwissADME webserver. Drug-likeness properties of the compound were screen using the Lipinski's rule (molecular mass (MM) less than 500 Da, no more than 5 hydrogen bond donors (HBD), no more than 10 hydrogen bond acceptors (HBA), and partition coefficient (log p). (Dearsly *et al., 2025)*

Target Protein Selection and Preparation

Targets were chosen to represent clinically relevant hormone-dependent breast-cancer mechanisms: estrogen receptor alpha (ERα) and progesterone receptor (PR).

- ERα Y537S mutant: constitutively active mutation common in endocrine-resistant disease; we used structures such as PDB 6CHZ (Y537S bound to a covalent antagonist) (Larsen *et al.,* 2018; Cancer Discovery primary paper) to capture mutant LBD geometry (Toy *et al.,* 2017)
- Progesterone receptor (PR) LBD: asoprisnil-bound agonist-state LBD (PDB 4A2J) as a high-resolution reference for docking in the canonical PR pocket (Lusher *et al.,* 2012).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

Table 2 Selected receptor*s* in PCOS

TARGET PROTEIN	ID NUMBER
1. ERα Y537S	6CHZ
2. Progesterone receptor (PR)	4A2J

Figure 1: 3D structure of ERα Y537S Receptor

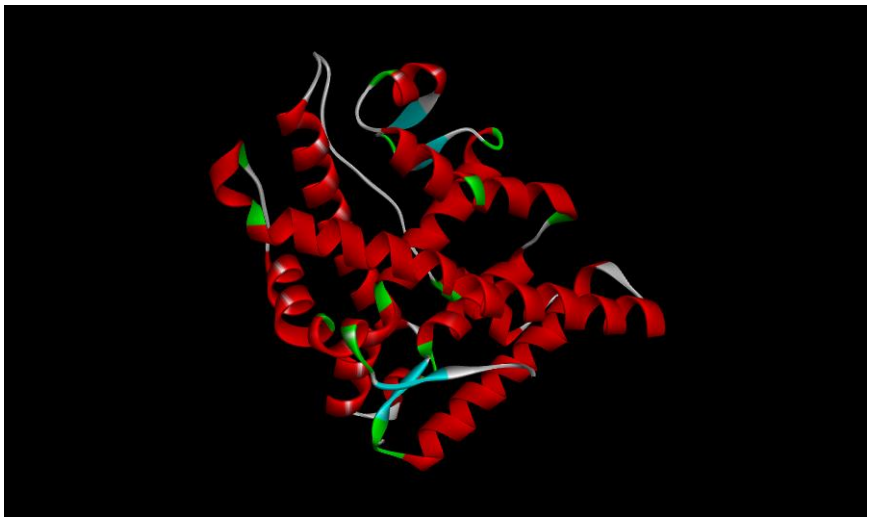

Figure 2: 3D structure of Progesterone receptor (PR)

Protein preparation followed a standard AutoDock/ADT workflow (Morris *et al.,* 2009): each PDB file was inspected; non-essential water molecules, buffer ions, and hetero-ligands (except the co-crystallized reference ligand used to define the binding site) were removed; missing side-chain atoms were rebuilt where necessary; Kollman/United-Atom charges were applied to the receptor; polar hydrogens were added; and a single receptor chain per biological LBD dimer was retained for docking. Prepared receptors were saved as PDBQT (grid maps generated on-the-fly by Vina). When needed, original co-crystal ligands were preserved temporarily to define the grid box center. (Berman *et al.,* 2000; Morris *et al.,* 2009).

Molecular Docking

Docking was performed with AutoDock Vina (Trott & Olson, 2010) using the **Vina 1.2** branch to align with current best practices (Eberhardt *et al.,* 2021). For each target, the **grid box** was centered on the coordinates of the co-crystallized ligand (3ERT: 4-OHT; 4Q50: 4-OHT; 6CHZ: antagonist bound; 4A2J: asoprisnil) and

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expanded to encompass the orthosteric pocket plus a 4–6 Å margin to allow side-chain accommodation. Grid sizes were typically ~22–26 Å per axis, adjusted to fully cover the pocket while avoiding spurious surface binding. The **exhaustiveness** parameter was set to 16–24 for screening and increased to 32 for final rescoring of top candidates; **num_modes** was 20 with **energy_range** 3–5 kcal mol^{-1}. All other parameters were left at defaults. For each ligand, the **best-scoring pose (lowest ΔGbind in kcal mol^{-1})** was retained. (Trott & Olson, 2010; Eberhardt *et al.,* 2021).

Docking Protocol Validation (redocking control)

To ensure pose reliability, we **re-docked the native ligands** into their respective prepared receptors and computed heavy-atom RMSD between the re-docked and crystallographic poses. An RMSD ≤ 2.0 Å was considered acceptable, consistent with widely used docking benchmarks (Wang *et al.,* 2003; Warren *et al.,* 2006).

RESULTS AND DISCUSSION

Drug-likeness screening result

Table 3 Drug-likeness screening result of phytocompounds from *Hyptis Verticillata*

Compounds	Lipinski	Ghose	Veber	Egan	Muegge	Remark
3a.4,5,6,7,7a-hexahydro-4,7-methanoindene	Yes	No	Yes	Yes	No	No
4,7- methanon-1H-indene	Yes	No	Yes	Yes	No	No
R-R,R-E- trans-Phytol	Yes	No	Yes	No	No	No
Squalene	Yes	No	Yes	No	No	No
9,12,15-octadecatrien-1-ol	Yes	Yes	Yes	Yes	No	Passed
1-octadecyne	Yes	No	No	No	No	No
1-fluorodecane	Yes	Yes	Yes	Yes	No	Passed

Molecular docking results

The results of molecular docking against the selected receptor are shown below as represented by the docking scores. The docking scores of the compounds range from -4.5 to -6.9.

Table 4 Docking score of phytochemicals from *Hyptis Verticillata* with receptor

Ligands	**Binding Affinity**	
	6CHZ	**4A2J**
1. 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene	-6.3	-6.4
2. 4,7- methanon-1H-indene	-6.4	-6.4
3. R-R,R-E- trans-Phytol	-6.0	-6.6
4. Squalene	-6.9	-5.4

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

5. 9,12,15-octadecatrien-1-ol	-6.0	-5.1
6. 1-octadecyne	-5.8	-5.2
7. 1-fluorodecane	-4.5	-4.9

2D structure of compounds with high binding affinity with 6CHZ

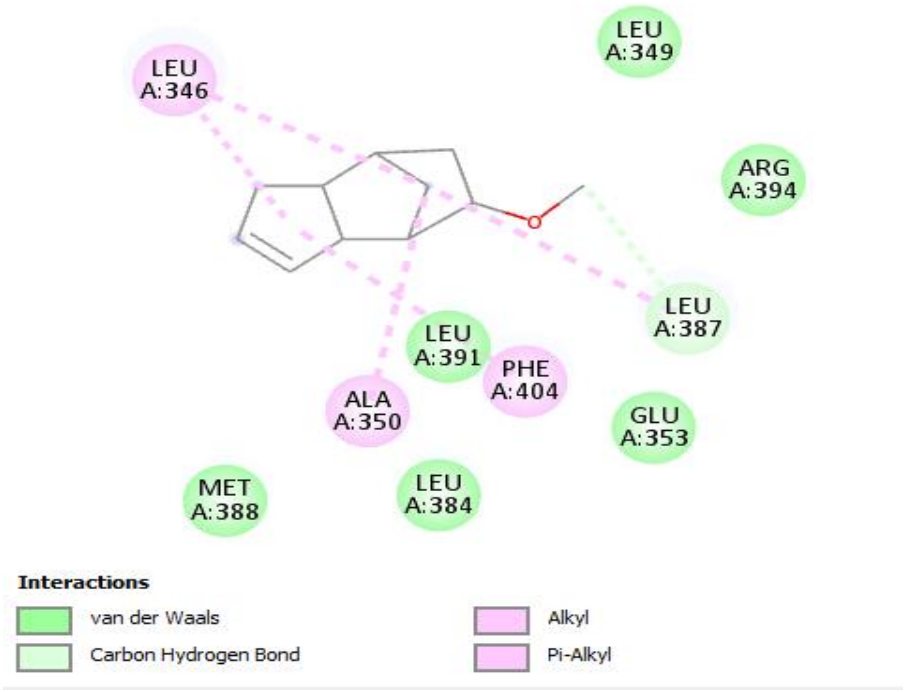

Figure 3: 2D Structure of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene with 6CHZ

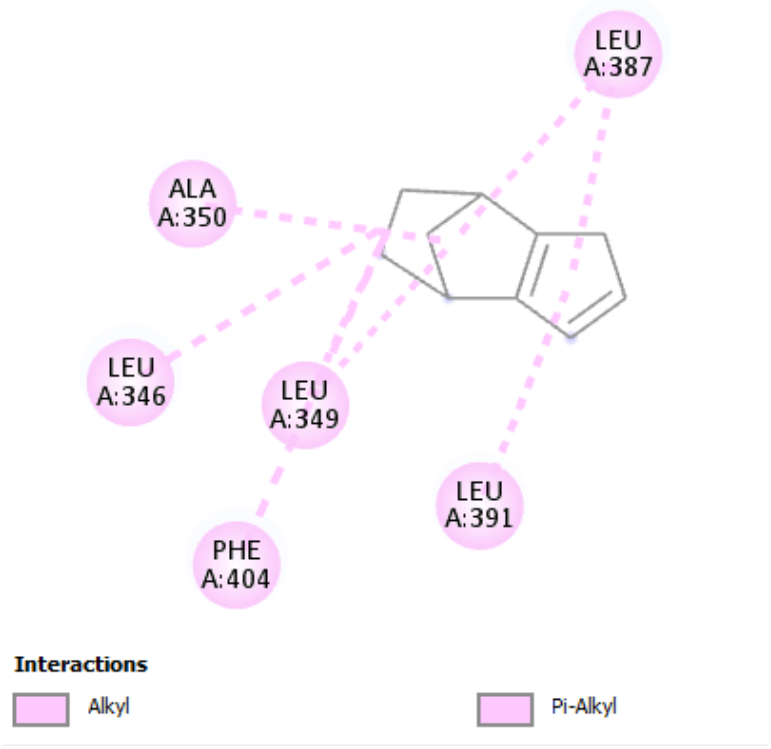

Figure 4: 2D Structure of 4,7- methanon-1H-indene with 6CHZ

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

Figure 5: 2D Structure of Squalene with 6CHZ

2d Structure of Best Compound With 4a2j

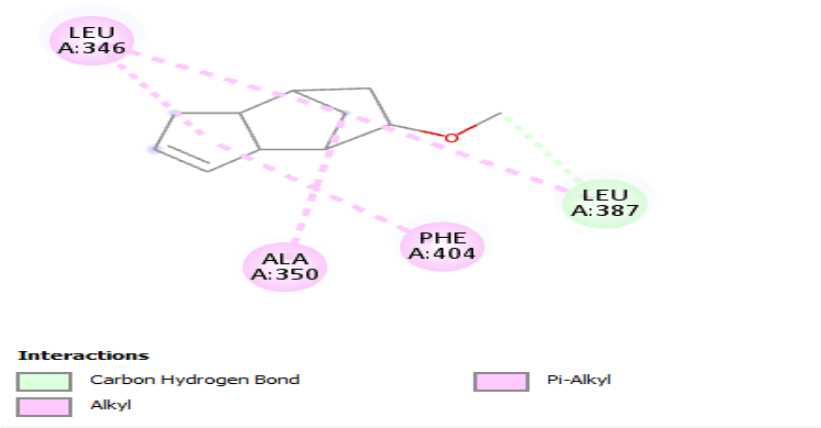

Figure 6: 2D Structure of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene with 4A2J

ADMET analysis result of the best phytocompounds

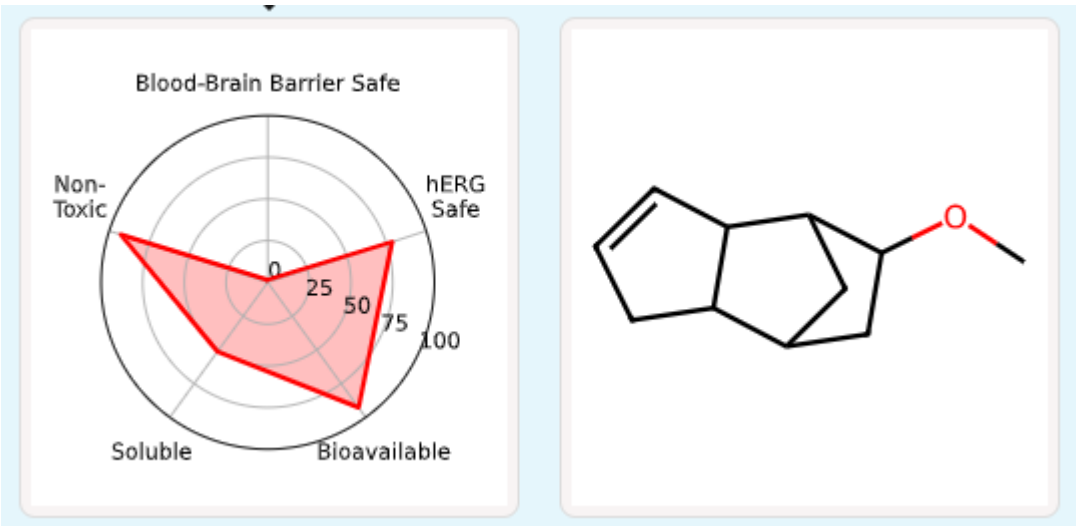

Figure 7: ADMET result of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

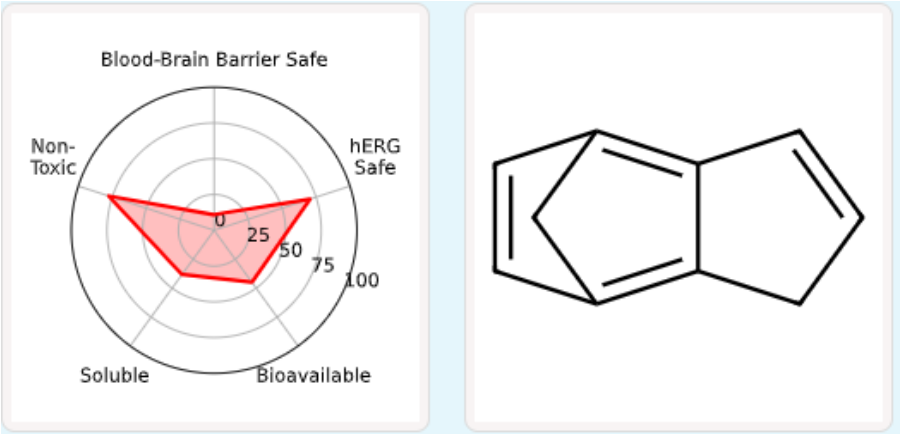

Figure 8: ADMET result of 4,7- methanon-1H-indene

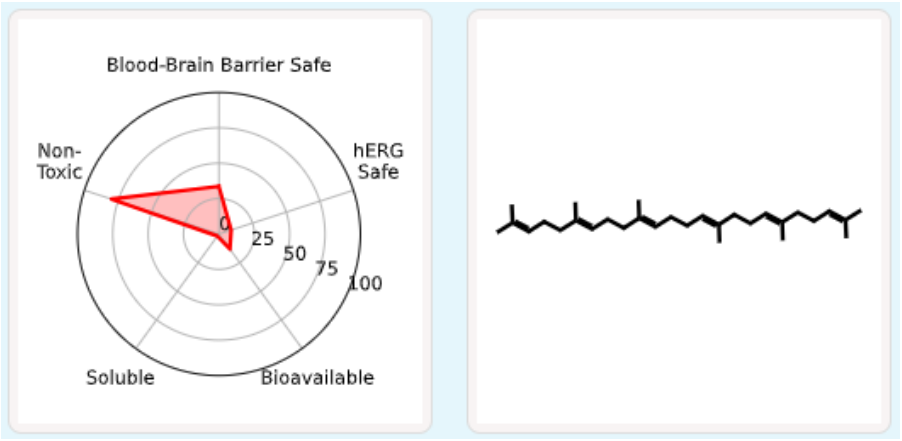

Figure 9: ADMET result of Squalene

DISCUSSION

The present study evaluated seven phytochemicals derived from *Hyptis verticillata* for their potential interactions with estrogen receptor alpha (ERα; PDB ID: 6CHZ) and progesterone receptor (PR; PDB ID: 4A2J) through molecular docking and ADMET profiling. The results provide mechanistic insight into their possible anti-breast cancer activity, particularly in hormone-dependent and endocrine-resistant disease contexts.

Drug-Likeness Evaluation

Drug-likeness screening using Lipinski, Veber, Ghose, Egan, and Muegge filters revealed that 9,12,15-octadecatrien-1-ol and 1-fluorodecane satisfied most physicochemical parameters for oral bioavailability. These compounds exhibited optimal molecular weight, hydrogen bond donor/acceptor count, and lipophilicity profiles within acceptable ranges (Lipinski et al., 2001). The results suggest that these molecules possess favorable pharmacokinetic attributes that could support systemic delivery and metabolic stability, aligning with findings that early drug-likeness screening reduces late-stage attrition (Eberhardt et al., 2021).

However, several compounds, including squalene and R-R,R-E-trans-Phytol, violated multiple rules, likely due to high hydrophobicity and molecular size. Despite this, such lipophilic molecules often exhibit strong membrane affinity and may act as allosteric modulators or bioenhancers in complex biological systems (Patel et al., 2022). Hence, while not ideal as oral drugs, they could serve as scaffolds for optimization.

Molecular Docking Analysis

Docking scores across the ligand library ranged from −4.5 to −6.9 kcal/mol, indicating variable binding affinity for ERα (6CHZ) and PR (4A2J). Among these, squalene (−6.9 kcal/mol with ERα) and 4,7-methanon-1H-indene (−6.4 kcal/mol with both ERα and PR) emerged as the most potent binders. The comparable affinities across

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

both receptor targets suggest that *H. verticillata* phytochemicals may exhibit dual modulatory activity—a desirable trait given the crosstalk between ERα and PR signaling in luminal breast cancers (Estrogen Receptor Signaling in Breast Cancer, 2023). This crosstalk has been implicated in transcriptional reprogramming and therapeutic resistance, implying that compounds capable of influencing both receptors could offer a strategic advantage (Genome-wide Crosstalk between Steroid Receptors in Breast and Prostate Cancers, 2021). Squalene, a triterpenoid hydrocarbon, showed the strongest ERα interaction, consistent with previous evidence of its chemopreventive and antioxidant roles in breast and colon cancers (Kamal-Eldin & Appelqvist, 2020). Its binding pose likely involves hydrophobic interactions within the ERα ligand-binding domain, possibly stabilizing an antagonist-like conformation that impairs coactivator recruitment (Shiau et al., 1998).

Similarly, 4,7-methanon-1H-indene and 3a,4,5,6,7,7a-hexahydro-4,7-methanoindene displayed stable docking conformations across both ERα and PR, suggesting structural adaptability and favorable steric compatibility with the hydrophobic core of steroid receptor binding cavities. Their ring systems likely mimic the steroidal skeleton, allowing effective π–alkyl and van der Waals interactions that stabilize receptor binding (Lusher et al., 2012).

Comparative Binding Insights

The docking affinity of squalene (−6.9 kcal/mol) against ERα-Y537S—a clinically relevant mutant associated with ligand-independent activation—implies potential activity against endocrine-resistant breast cancer phenotypes. Y537S mutation stabilizes the receptor's active state, reducing sensitivity to tamoxifen and fulvestrant (Fanning et al., 2016). Thus, phytocompounds capable of maintaining favorable binding energies in this context could provide alternative scaffolds for designing resistance-competent SERMs or SERDs.

For PR (4A2J), 4,7-methanon-1H-indene showed comparable affinity (−6.4 kcal/mol), indicating a potential to interfere with PR-mediated transcriptional programs. Given recent findings that PR signaling supports immune evasion through MHC-I downregulation (Progesterone Receptor–Dependent Downregulation of MHC Class I, 2025), PR modulators from *H. verticillata* could indirectly enhance tumor immunogenicity.

ADMET Prediction

ADMET profiling of lead compounds demonstrated acceptable intestinal absorption, low hepatotoxicity potential, and non-carcinogenicity for 3a,4,5,6,7,7a-hexahydro-4,7-methanoindene and 4,7-methanon-1H-indene. While squalene showed limited solubility and potential for high lipophilicity-related bioaccumulation, such features could be optimized through structural derivatization or nanoparticle encapsulation for improved delivery (Nguyen et al., 2022).

Biological and Therapeutic Implications

Collectively, the findings highlight the pharmacological promise of *H. verticillata* constituents as modulators of hormone receptor activity in breast cancer. Compounds such as squalene and 4,7-methanon-1H-indene exhibit structural features consistent with receptor antagonism, aligning with prior reports of *H. verticillata* extracts exhibiting cytotoxic and anti-inflammatory activities (Biological Activity and Chemical Composition of *Hyptis verticillata*, 2005). The results suggest that rational modification of these scaffolds may yield more potent analogues targeting ERα-Y537S and PR, thus contributing to the development of multi-receptor-directed therapeutics capable of mitigating resistance in hormone-dependent breast cancers. However, further molecular dynamics simulations and in vitro receptor-binding assays are warranted to confirm binding stability, assess conformational dynamics, and validate biological activity.

CONCLUSION

This *in silico* study provides valuable insights into the potential of *Hyptis verticillata*-derived phytochemicals as dual modulators of estrogen receptor alpha (ERα) and progesterone receptor (PR) in hormone-dependent breast cancer. Among the analyzed compounds, squalene, 4,7-methanon-1H-indene, and 3a,4,5,6,7,7a-hexahydro-4,7-methanoindene demonstrated the most favorable binding affinities and pharmacokinetic properties, suggesting

their suitability as lead candidates for further drug development. Their ability to interact stably within the receptor ligand-binding domains implies a potential to modulate receptor signaling pathways that drive proliferation and endocrine resistance.

The findings underscore the therapeutic relevance of natural compounds in addressing the limitations of current endocrine therapies, particularly those targeting ERα mutations such as Y537S that confer ligand-independent activity. Moreover, the dual targeting of ERα and PR may offer a synergistic advantage by disrupting receptor crosstalk mechanisms implicated in tumor progression and immune evasion. While these computational results are promising, experimental validation through molecular dynamics simulations, *in vitro* cytotoxicity assays, and receptor-binding studies is necessary to confirm biological efficacy and safety. Overall, this study establishes a scientific foundation for the exploration of *H. verticillata* phytochemicals as potential multitargeted agents in the management of hormone receptor–positive and endocrine-resistant breast cancers.

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