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Molecular Docking of Phytochemicals from *Hyptis verticillata* (*Jacq)* Against Follicle Stimulating Hormone Receptor (FSHR) and Luteinizing Hormone Receptor (LHR): Insights into Natural Fertility Modulation

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Abstract

Hyptis verticillata is widely recognized in traditional medicine for its reproductive and fertility-enhancing benefits, yet the molecular mechanisms underlying these effects remain largely unexplored. This study employed structure-based molecular docking to elucidate the possible interaction of key phytochemicals from *H. verticillata* with the Follicle Stimulating Hormone Receptor (FSHR) and Luteinizing Hormone Receptor (LHR), two central regulators of ovarian folliculogenesis and ovulation. A curated library of plant-derived compounds was screened using Autodocking Vina, followed by binding affinity evaluation, interaction profiling, and in silico drug-likeness assessment. Three phytochemicals including; R-R, E-trans-Phytol, 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene, and 4,7-methano-1H-indene demonstrated the most favorable binding energies (−6.4 to −6.6 kcal/mol), The binding affinity of squalene (−5.4 kcal/mol) further supports moderate receptor compatibility among the plant constituents. ADMET predictions revealed acceptable pharmacokinetic characteristics for selected compounds, although several exhibited natural-product-typical deviations from classical drug-likeness rules. These findings provide the first computational evidence that *H. verticillata* harbors phytochemicals capable of engaging gonadotropic hormone receptors at meaningful affinity levels, offering a plausible molecular explanation for its ethnomedicinal use in fertility modulation.

Keywords: *Hyptis verticillata*, phytochemicals, molecular docking, follicle-stimulating hormone receptor (FSHR), luteinizing hormone receptor (LHR).

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Introduction

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, remains a global reproductive health challenge affecting both men and women. According to the World Health Organization (WHO 2023), approximately 17.5% of adult's worldwide experience infertility at some point in their lives. Among the numerous factors contributing to infertility, hormonal imbalance and dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis is predominant (Jack, *et al.,* 2022, Bensaad, *et al.,* 2024;). Two critical hormones that govern reproductive function are follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act through their respective receptors; FSHR and LHR located primarily in the gonads. These receptors are members of the G-protein coupled receptor (GPCR) family and play central roles in follicular maturation, ovulation, spermatogenesis, and steroidogenesis (Kumar and Idicula-Thomas, 2023; Duan, *et al.,* 2023). Alterations or dysfunctions in FSHR and LHR signaling can lead to conditions such as polycystic ovarian syndrome (PCOS), anovulation, hypogonadism, and infertility (Kaur, *et al.,* 2023). Infertility remains a major global health concern, with millions of couples affected by hormonal imbalances that disrupt normal ovulatory and spermatogenic processes. The limited accessibility, high cost, and side effects of conventional fertility treatments highlight the urgent need for safer and affordable alternatives. Although *Hyptis verticillata* has been traditionally used to improve reproductive health, the molecular basis of its action on critical reproductive hormone receptors such as FSHR and LHR remains poorly understood. Lack of mechanistic evidence hampers its rational use and scientific validation as a fertility modulator. Hence, there is a need to employ computational molecular docking techniques to elucidate the potential interactions between *H. verticillata* phytochemicals and these key receptors to provide insights into its mechanism of action and therapeutic potential. Conventional treatments for infertility often involve hormonal therapies such as clomiphene citrate, gonadotropins, or in vitro fertilization (IVF). However, these interventions are expensive, associated with adverse effects, and not always accessible, particularly in low- and middle-income countries (Danhof, *et al.,* 2020; Chiware, *et al.,* 2021). Hence, there is a growing scientific interest in identifying safe, affordable, and naturally derived fertility modulators that can enhance reproductive function through molecular interactions with key hormonal receptors.

Hyptis verticillata Jacq. (commonly known as bush tea or John Charles) is a medicinal plant belonging to the Lamiaceae family. It is traditionally used across the Caribbean, Central America, and parts of Africa for managing menstrual disorders, inflammation, and reproductive dysfunctions (Picking *et al.,* 2013; Egbung, *et al.,* 2017). Phytochemical investigations of *H. verticillata* have revealed the presence of flavonoids, terpenoids, phenolics, and essential oils with potent biological activities including antioxidant, anti-inflammatory, and hormonal-modulating effects (Picking, *et al.,* 2013; Picking, *et al.,* 2018; Ogar, *et al.,* 2019). Despite its traditional use in fertility enhancement, there is limited molecular-level evidence on how *H. verticillata* compounds interact with reproductive hormone receptors such as FSHR and LHR. Molecular docking, an in silico computational approach, provides a rapid and cost-effective method for predicting the binding affinity and interaction mechanisms of phytochemicals with specific protein targets (Ghosh, *et al.,* 2025). By modeling ligand–receptor interactions, docking studies can identify potential bioactive compounds that could modulate receptor function, thereby providing insights into the pharmacological mechanisms of medicinal plants. Therefore, exploring the molecular docking interactions between *H. verticillata* phytochemicals and the FSHR and LHR proteins could shed light on its potential as a natural fertility modulator. This study aimed to investigate the molecular interactions between bioactive phytochemicals from *Hyptis verticillata* and the reproductive hormone receptors; FSHR and LHR using in silico molecular docking techniques, to explore their potential role in natural fertility modulation.

Materials and methods

Study Design Overview

This study adopted a computational molecular docking approach to evaluate the interactions between phytochemicals derived from *Hyptis verticillata* and two reproductive hormone receptors; Follicle Stimulating Hormone Receptor (FSHR) and Luteinizing Hormone Receptor (LHR). The procedure followed previously established docking protocols as described by Dearsly *et al.,* (2024a, 2024b, 2025), with minor modifications.

Materials and Databases

The study employed freely accessible bioinformatics and cheminformatics databases to retrieve ligand and protein structures, as well as analytical tools for docking and post-docking evaluations. The resources used includes: Protein Data Bank (PDB) for obtaining 3D crystallographic structures of FSHR and LHR, PubChem for downloading 2D/3D structures of identified phytochemicals from *H. verticillata*,

ADMET lab 2.0 for assessing drug-likeness and ADMET properties, Discovery Studio Visualizer 2021 – for visualization, structural optimization, and interaction analysis and AutoDock Vina integrated within PyRx 0.8 for virtual screening and docking simulations (Dearsly *et al.,* 2024a).

Ligand Selection and Preparation

Phytochemicals previously identified in *Hyptis verticillata* were obtained from literature and confirmed through PubChem. Ligand structures were downloaded in **SDF** format and converted to PDBQT format using Open Babel within PyRx (Table 1). Each compound was energy-minimized using the Universal Force Field (UFF) with a conjugate gradient algorithm to achieve the lowest possible energy conformation (Dearsly *et al.,* 2024b**)**.

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

Protein Preparation

The 3D structures of FSHR (PDB ID: 4MQW) and LHR (PDB ID: 1XP6) were retrieved from the RCSB Protein Data Bank. Non-essential heteroatoms, water molecules, and co-crystallized ligands were removed using Discovery Studio. Polar hydrogens were added, and Kollman charges were assigned using AutoDock Tools. The prepared protein structures were then saved in PDBQT format for docking (Dearsly *et al.,* 2025). To ensure receptor stability and reliability, each protein was validated using Ramachandran plot analysis and ProSA-web, confirming appropriate structural quality before docking.
Selected receptors in PCOS includes the following:
Follicle stimulating hormone (FSHR) (ID: 4MQW)
Luteinizing hormone (LHR) (ID: 1XP6)

Molecular Docking Procedure

Docking simulations were performed using AutoDock Vina through PyRx 0.8, following the docking workflow (Dearsly *et al.,* 2024a). The receptor active sites were defined based on known ligand-binding residues retrieved from literature (Dias *et al.,* 2018; Kumar and Idicula-Thomas, 2023). A grid box was generated to cover the entire binding pocket, ensuring that all potential interaction residues were included.

For each ligand, the binding affinity (kcal/mol) and interaction conformation were recorded. The best docked pose was selected based on the lowest binding energy and favorable orientation within the binding pocket.

Visualization and Interaction Analysis

Post-docking visualization and interaction analyses were carried out using Discovery Studio Visualizer 2021 and LigPlot+. Hydrogen bonds, hydrophobic interactions, van der Waals forces, and π–π stacking were analyzed to identify key amino acid residues involved in ligand binding. Comparative evaluation of binding affinities between ligands and reference fertility drugs (e.g., clomiphene citrate) was also performed (Dearsly *et al.,* 2024b).

Drug-Likeness and ADMET Analysis

Lead compounds with high binding affinities were subjected to pharmacokinetic screening using SwissADME (Daina, *et al.,* 2017) and pkCSM platforms (Pires, *et al.,* 2015). Drug-likeness was evaluated based on Lipinski's Rule of Five (Lipinski, *et al.,* 2012), Veber's Rule (Veber, *et al.,* 2002), and

Ghose filter parameters (Ghose, *et al.,* 1999). ADMET profiling assessed absorption, distribution, metabolism, excretion, and toxicity potentials to predict the in vivo suitability of each compound (Dearsly *et al.,* 2025).

Data Analysis and Validation

Docking scores were recorded as mean binding energies (kcal/mol) and analyzed descriptively. The interaction residues were compared across ligands to identify conserved binding regions on both FSHR and LHR. Validation of docking results was achieved by redocking reference ligands to confirm the accuracy and reproducibility of the docking protocol (Dearsly *et al.,* 2025).

Results

Drug-likeness screening result

The drug-likeness screening showed that all the phytocompounds satisfied Lipinski's rule, indicating good basic drug-like properties. However, only 9,12,15-octadecatrien-1-ol and 1-fluorodecane passed most of the screening filters and were considered acceptable compounds. Other compounds failed some criteria, mainly due to their hydrophobic nature and molecular properties (Table 2).

Table 2: 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 docking scores of the compounds range from -4.5 to -6.9. The molecular docking results showed that R-R, R-E-trans-phytol had the highest binding affinity against both FSHR and LHR with docking scores of −6.6 kcal/mol. 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene and 4,7-methano-1H-indene also demonstrated strong interactions with both receptors. Squalene and 9,12,15-octadecatrien-1-ol showed moderate binding affinity, while 1-octadecyne and 1-fluorodecane exhibited weak interactions (Table 3). Overall, the results suggest that some phytochemicals from Hyptis verticillata may interact effectively with reproductive hormone receptors

Table 3: Docking score of phytochemicals from *Hyptis Verticillata* with receptor

Ligands	Binding Affinity	
	FSHR	LHR
1. 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene	-6.5	-6.5
2. 4,7- methanon-1H-indene	-6.4	-6.4
3. R-R,R-E- trans-Phytol	-6.6	-6.6
4. Squalene	-5.4	-5.4
5. 9,12,15-octadecatrien-1-ol	-6.0	-6.1
6. 1-octadecyne	-2.1	-3.8
7. 1-fluorodecane	-3.9	-4.8

The 2D structure of compounds with high binding affinity with Follicle stimulating hormone (FSHR)

The compound formed mainly hydrophobic interactions within the receptor binding pocket, contributing to its strong binding affinity (Figure 1), The interaction of R-R, R-E-trans-phytol with FSHR.showed stable binding within the receptor cavity through hydrophobic and van der Waals interactions. (Figure 2)

2D structure of compounds with high binding affinity with LHR

The interaction of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene with LHR. demonstrated favorable interaction within the receptor pocket, supporting its high docking score (Figure 3). Strong hydrophobic interactions were observed between R-R, R-E-trans-phytol with LHR, indicating stable ligand binding with the receptor (Figure 4).
Sample collections

ADMET (Adsorption, distribution, metabolism, excretion and toxicity) analysis result of the best phytocompounds in Hyptis Verticillata

The ADMET profile of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene showed acceptable pharmacokinetic and toxicity properties (Figure 5), while the ADMET analysis of R-R, R-E-trans-phytol, indicated favorable absorption and distribution properties with relatively low predicted toxicity (Figure 6)

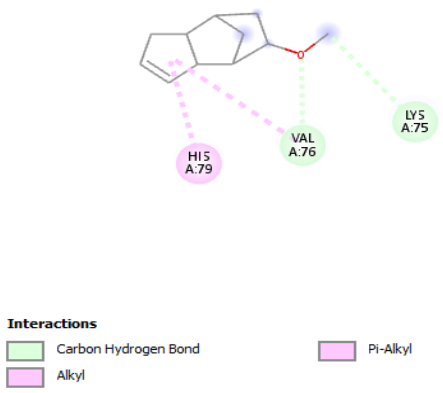

Figure 1: **2D result of** 3a.4,5,6,7,7a-hexahydro-4, 7-methanoindene with FSHR

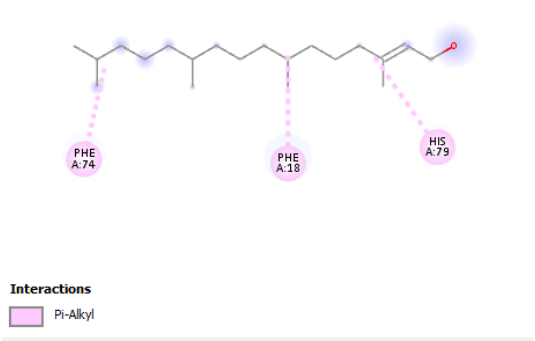

Figure 2: 2D result of R-R, R-E- trans-Phytol with FSHR

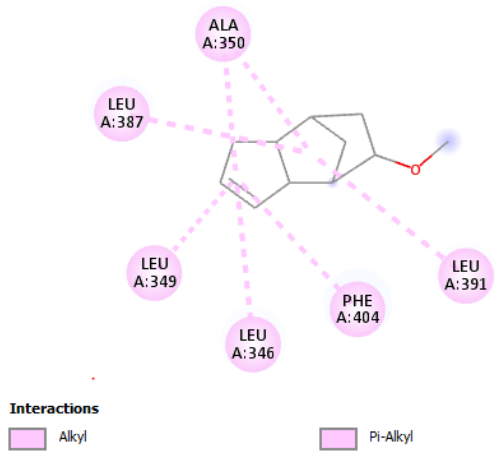

Figure 3: **2D result of** 3a.4,5,6,7,7a-hexahydro-4, 7-methanoindene with LHR

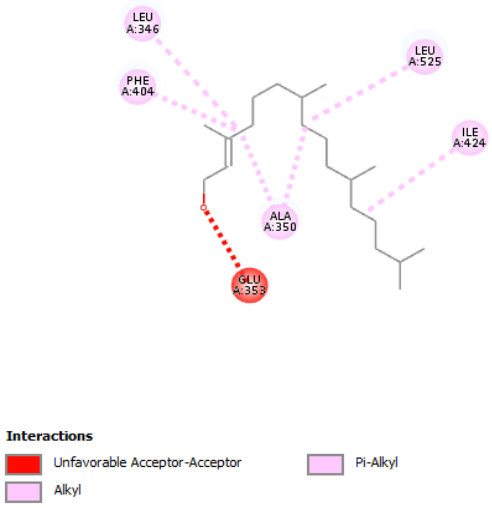

Figure 4: 2D result of R-R, R-E- trans-Phytol with LHR

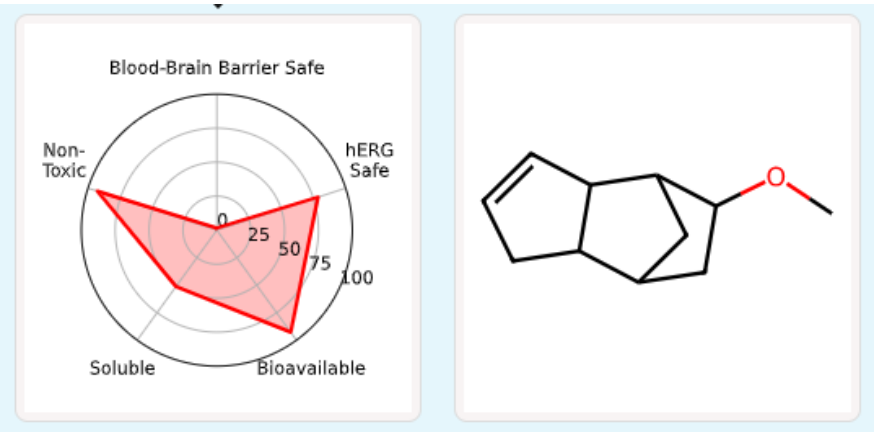

Figure 5: ADMET result of 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene

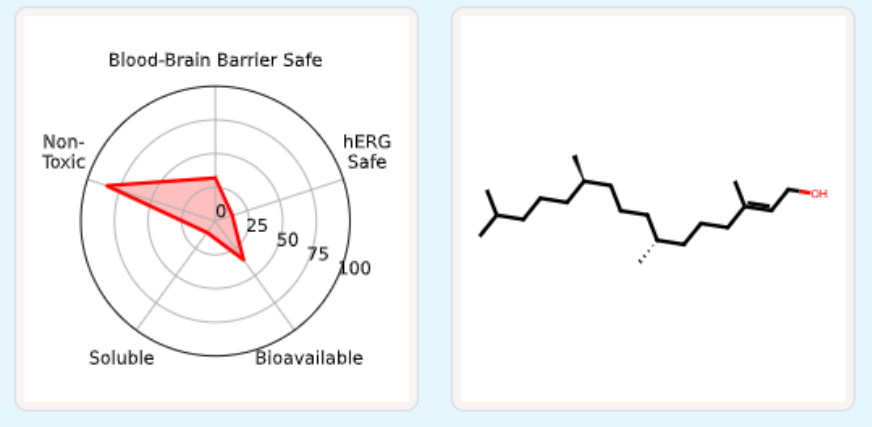

Figure 6: ADMET result of R-R, R-E- trans-Phytol

Discussion

This study employed structure-based molecular docking to explore the interaction potential of selected phytochemicals from *Hyptis verticillata* with two key gonadotropic receptors, FSHR and LHR. The objective is to examine whether these phytochemicals possess structural compatibility with functionally relevant binding regions of the receptors. The results indicate that several compounds exhibit moderate predicted binding affinities toward both targets, thereby providing a preliminary structural basis for potential receptor engagement.

Among the screened compounds, R-R, E-trans-phytol, 3a.4,5,6,7,7a-hexahydro-4,7-methanoindene, and 4,7-methano-1H-indene demonstrated the most favorable docking scores (−6.4 to −6.6 kcal/mol) against both FSHR and LHR. In virtual screening studies involving GPCR targets, binding energies within this range are generally considered indicative of moderate affinity interactions, particularly for small, hydrophobic natural products (Lenselink *et al.*, 2016). However, it is important to emphasize that such docking scores reflect predicted binding stability under rigid receptor conditions and do not directly translate to biological potency, efficacy, or receptor activation. FSHR and LHR are class A G-protein coupled receptors with complex activation mechanisms involving conformational rearrangements, allosteric modulation, and downstream signaling bias (Duan *et al.,* 2023; Lazzaretti *et al.,* 2023). Ligand binding alone does not establish agonism, antagonism, or functional modulation (Lazzaretti *et al.,* 2023). Therefore, while the observed docking affinities suggest structural compatibility with receptor cavities, they should not be interpreted as definitive evidence of fertility modulation. Instead, these findings identify scaffold candidates that may warrant further investigation through

molecular dynamics simulations, free-energy calculations, and receptor activation assays.

Interestingly, the top-performing ligands exhibited comparable binding energies across both FSHR and LHR. This pattern may reflect shared structural features within the transmembrane domains of gonadotropin receptors, which possess conserved hydrophobic cavities capable of accommodating lipophilic ligands. The dominance of van der Waals and hydrophobic interactions observed in the interaction profiles is consistent with the largely nonpolar nature of the tested phytochemicals (Fekadu *et al.,* 2022). Given that the orthosteric sites of FSHR and LHR typically bind large glycoprotein hormones (Duan *et al.,* 2023; Kumar & Idicula-Thomas, 2023), the smaller phytochemicals evaluated here are more plausibly interacting within transmembrane or potential allosteric regions rather than the canonical extracellular hormone-binding domain. This distinction is critical and further supports the need for dynamic and functional validation.

Squalene demonstrated a slightly lower binding affinity (−5.4 kcal/mol) yet remained within the moderate interaction range (Lenselink *et al.,* 2016). Considering its highly hydrophobic and membrane-associated characteristics, its predicted binding may reflect nonspecific hydrophobic stabilization rather than selective receptor targeting. Similar considerations apply to long-chain hydrocarbons such as 1-octadecyne, which showed weaker binding energies and may lack structural features required for selective receptor interaction.

Benchmarking against typical GPCR docking studies suggests that affinities stronger than −7.0 kcal/mol are generally associated with higher-confidence binders, while values between −5.0 and −6.5 kcal/mol require cautious interpretation (Lenselink *et al.,* 2016). Therefore, the affinities observed in this study should be regarded as exploratory rather than confirmatory. Nonetheless, the consistent ranking of certain ligands across both receptors strengthens internal reliability of the docking workflow.

Drug-likeness and ADMET analyses were performed to evaluate general pharmacokinetic plausibility and structural developability. As expected for natural terpenoid-rich compounds, several ligands violated classical drug-likeness filters, primarily due to hydrophobicity and molecular size (Lipinski *et al.*, 2012; Ghose *et al.,* 1999). Such deviations are common among natural products and do not negate biological activity (Ghosh *et al.,* 2025) however, they highlight potential limitations in solubility and bioavailability that would require optimization if therapeutic development were pursued.

Collectively, the present findings provide computational evidence that selected phytochemicals from *Hyptis verticillata* can structurally associate with FSHR and LHR at moderate predicted affinity levels. These interactions do not establish receptor modulation but identify plausible molecular interaction candidates that may contribute to the plant's reported ethnomedicinal reproductive effects. Experimental validation - including receptor signaling assays, binding displacement studies, and in vivo reproductive models - will be necessary to determine whether these computationally predicted interactions translate into biological activity.

Overall, this study provides computational evidence that selected constituents of *Hyptis verticillata* can interact with key reproductive hormone receptors at moderate predicted affinity levels. These findings generate a hypothesis for future mechanistic validation through molecular dynamics simulations, receptor signaling assays, and in vivo reproductive models to determine their true biological relevance.

Conclusion

The results highlight promising scaffold candidates for future optimization and warrant comprehensive validation through molecular dynamics simulations, receptor activation assays, and in vivo reproductive studies

Conflict of interest

Author declares no conflict of interest

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