

Integration of Network Pharmacology and Molecular Docking with Computational Toxicology to Investigate the Predicted Anti-Prostate Cancer Potential of *Ficus exasperata* Leaf Phytochemicals

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ABSTRACT: Background: *Ficus exasperata* (*F. exasperata*) is used in African traditional medicine for inflammatory and urinary disorders, but its phytochemical interactions with prostate cancer targets remain insufficiently characterized computationally. **Objective:** This study used network pharmacology, molecular docking, pharmacokinetic prediction, and computational toxicology to explore the predicted anti-prostate cancer potential of *F. exasperata* leaf ethanol extract. **Methods:** GC-MS characterized phytochemicals. SwissADME assessed drug-likeness and pharmacokinetics. SwissTargetPrediction identified targets; prostate cancer genes were retrieved from GeneCards, Open Targets, and DisGeNET. GO and KEGG enrichment were performed. Docking and MM-GBSA were done against the androgen receptor (PDB: 2AX6). PASS, ProTox-3.0, and StopTox predicted activities and toxicity. **Results:** GC-MS identified eight phytoconstituents; two had favorable pharmacokinetics. Network pharmacology located 174 phytochemical targets, 3,388 prostate cancer genes, and 97 common targets. Docking yielded XP Glide scores of -1.866 kcal/mol for hexadecanoic acid, ethyl ester and -2.609 kcal/mol for enzalutamide; XP MM-GBSA values were -38.29 and -31.99 kcal/mol, respectively. PASS predicted testosterone 17β -dehydrogenase inhibition ($Pa=0.781$), TP53 enhancement ($Pa=0.719$), and alpha-methylacyl-CoA racemase inhibition ($Pa=0.665$) for the phytochemical. Toxicity prediction indicated a higher LD₅₀ but possible skin sensitization. **Conclusions:** Computational analyses suggest *F. exasperata* phytochemicals may interact with prostate cancer networks and AR. Hexadecanoic acid, ethyl ester warrants further study. These are predictions, not experimental evidence; AR-binding studies, molecular dynamics, cellular assays, and in vivo validation are needed.

KEYWORDS: *Ficus exasperata*; Prostate cancer; Network pharmacology; Molecular docking; Androgen receptor; SwissADME; Computational toxicology

INTRODUCTION

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies and remains a leading cause of cancer-related mortality among men worldwide. Its global burden continues to increase because of population aging, improved diagnostic practices, and lifestyle-related risk factors [1], [2]. While clinical outcomes have been substantially improved by androgen deprivation therapy, androgen receptor (AR) antagonists, chemotherapy, and targeted therapies, disease progression to castration-resistant prostate cancer, as well as the development of drug resistance, are still major therapeutic

challenges [3], [4]. Moreover, currently treatments that are available may be associated with adverse effects, such as fatigue, metabolic disturbances, cardiovascular complications, and reduced quality of life [5], [6]. Therefore, the discovery of safer multi-target therapeutic agents capable of modulating several oncogenic pathways simultaneously remains an important area of prostate cancer research.

Ficus exasperata Vahl (Moraceae), commonly known as the sandpaper tree, is widely employed in African traditional medicine for the management of inflammatory disorders, pain, microbial infections, and several urinary tract conditions [7], [8]. Phytochemical investigations have demonstrated that the plant contains flavonoids, terpenoids, sterols, phenolic compounds, fatty acids, and tannins possessing antioxidant, anti-inflammatory, antiproliferative, and cytoprotective activities [9]. Previous biological studies have demonstrated anticancer activity of *Ficus exasperata* (*F. exasperata*) extracts against prostate cancer cell lines; however, the molecular targets, signaling pathways, and bioactive phytochemicals responsible for these activities remain largely unresolved.

Despite increasing interest in medicinal plants as sources of anticancer agents, relatively few studies have integrated phytochemical profiling, network pharmacology, molecular docking, pharmacokinetic evaluation, and computational toxicology to investigate the molecular basis of the anti-prostate cancer potential of *F. exasperata* [10], [11], [12]. Most previous investigations have focused primarily on experimental bioactivity without systematically identifying the bioactive constituents responsible for target modulation or predicting their pharmacokinetic and safety characteristics [13], [14]. The molecular mechanisms through which *F. exasperata* phytochemicals may regulate AR signaling and other prostate cancer-associated pathways remain poorly understood.

Network pharmacology has emerged as a powerful systems biology approach for investigating the multi-component and multi-target characteristics of medicinal plants by integrating compound–target interactions with disease-associated signaling pathways [15], [16]. Complementary computational techniques, which include molecular docking, predict the ligand-protein binding affinity as well as binding orientation, which facilitate the prioritization of phytochemicals for subsequent experimental evaluation [17], [18], [19]. Together with pharmacokinetic prediction and computational toxicology, these approaches provide a rational framework for identifying promising lead compounds while reducing the cost and time associated with conventional drug discovery [20], [21].

Therefore, the present study employed an integrated computational strategy combining GC-MS phytochemical profiling, pharmacokinetic evaluation, network pharmacology, molecular docking, and computational toxicity prediction to investigate the potential molecular mechanisms through which *F. exasperata* leaves phytochemicals may modulate prostate cancer-associated targets and signaling pathways. This study further prioritizes promising lead compounds for future experimental validation based on their predicted pharmacokinetic characteristics, binding affinity, biological activities, and safety profiles.

MATERIALS AND METHODS

Plant Material Collection and Authentication

Fresh, healthy leaves of *F. exasperata* Vahl were collected in December 2025 from the Botanical Garden, University of Ilorin, Ilorin, Nigeria. Botanical identification and authentication were carried out by Mr. Bolu Ajayi, a taxonomist from the Department of Plant Biology, University of Ilorin, with a voucher specimen (UILH/001/1829/2025) deposited in the institutional herbarium for future reference. After collection, the leaves were washed under running tap water to remove debris, rinsed with distilled water, and air-dried at ambient laboratory temperature (25 °C) with ventilation to reduce the degradation of thermolabile phytochemicals.

Preparation of *F. exasperata* Leaf Extract

The dried leaves were pulverized using a laboratory electric grinder and sieved through a 40-mesh screen to obtain a uniform particle size, and then 100 g of the powdered material was extracted by cold maceration with 500 mL of 70% (v/v) ethanol for 48 h with continuous magnetic stirring. The suspension was filtered through Whatman No. 1, and the filtrate was concentrated under reduced pressure with a rotary evaporator at 40 °C. The concentrated extract was further dried to constant weight in a vacuum desiccator. The dried extract was transferred into a glass bottle and stored at 4 °C until further analysis.

GC-MS Analysis

GC-MS analysis of the ethanol leaf extract was carried out with an Agilent 7890A gas chromatograph coupled with an Agilent 7000 Triple Quadrupole mass spectrometer, equipped with an HP-5MS capillary column (30 m $\times$ 0.25 mm, 0.25 μ m). Helium was the carrier gas at a flow rate of 1 mL/min. The oven temperature was 100 to 260 °C at 4 °C/min, while the injector and desorber temperatures were maintained at 250 and 230 °C, respectively. Phytochemicals were identified through the NIST 2017 mass spectra library [22].

To improve the reliability of compound annotation, each chromatographic peak was evaluated according to its library spectral-match quality. Where multiple library matches were returned for the same chromatographic peak, only the compound with the highest quality-match score was retained for reporting. Compounds with quality-match scores below the predefined acceptance threshold of 70% were excluded from the confirmed phytochemical list and from subsequent computational analyses.

Phytochemical Structure Retrieval and Preparation

The two-dimensional or three-dimensional chemical structures of identified phytochemicals were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) using their reported compound names [23], [24]. Phytochemicals were retrieved using their unique PubChem Compound Identification (CID) numbers were recorded for accurate reference during computational analysis [25], [26]. Duplicate phytochemicals identified at different retention times were removed before downstream analyses to avoid redundancy.

Pharmacokinetic and Drug-Likeness Evaluation Using SwissADME

SwissADME (<http://www.swissadme.ch/>) [27] was employed to evaluate the pharmacokinetic properties and drug-likeness of all the confirmed phytochemicals. Parameters assessed included physicochemical properties, lipophilicity, solubility, GI absorption, CYP inhibition, Lipinski/Ghose/Veber/Egan/Muegge rules, PAINS alerts, and synthetic accessibility. Bioavailability radar and BOILED-Egg plots were generated to visualize oral bioavailability and blood-brain barrier permeability predictions.

Compounds selected satisfied the following criteria and were prioritized for further analysis: ≤ 1 Lipinski violation; high gastrointestinal absorption; and zero PAINS alerts.

Network Pharmacology Analysis

The compounds that passed the preliminary pharmacokinetic and drug-likeness screening were subjected to target prediction and network pharmacology analysis. Putative protein targets associated with the selected phytochemicals were retrieved using SwissTargetPrediction (>0) and standardized to *Homo sapiens* gene/protein identifiers using UniProt. Prostate cancer-associated targets were compiled from Open Targets, GeneCards, and DisGeNET. The original analysis used database-specific thresholds of ≥ 0.5 for Open Targets, ≥ 5 for GeneCards, and ≥ 0.70 for DisGeNET. The database-specific thresholds were selected to restrict the disease-associated target datasets to relatively stronger associations and to reduce the inclusion of weak or poorly supported disease–gene relationships. The phytochemical-associated targets and prostate cancer-associated targets were compared using Venn 2.1 to identify common targets. Duplicate identifiers were removed before intersection analysis.

Protein–Protein Interaction and Functional Enrichment Analysis

The common phytochemical–prostate cancer targets were submitted to the STRING database (version 12.0) for protein–protein interaction (PPI) analysis using a high-confidence interaction threshold of ≥ 0.70 . The resulting network was visualized and analyzed using Cytoscape version 3.10.4, with NetworkAnalyzer used to evaluate network topology and identify highly connected nodes.

Functional enrichment analysis was performed to characterize the biological processes and molecular functions associated with the common targets. Gene Ontology (GO) enrichment was conducted using ShinyGO version 0.85.1, while Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment was performed using DAVID. Pathways and GO terms with $p/\text{FDR} < 0.05$ were considered statistically enriched. The resulting enrichment data were visualized using R/ggplot2, and target–pathway relationships were represented using Cytoscape.

Molecular Docking Studies

1 Target Selection and Structural Preparation

The AR (PDB ID: 2AX6) was selected because it represents the principal therapeutic target in androgen-dependent prostate cancer and contains a co-crystallized ligand suitable for docking validation. The receptor structure was prepared using the Protein Preparation Wizard in Schrödinger Maestro 2023-4. The preparation procedure included bond-order assignment, addition of hydrogen atoms, optimization of hydrogen-bonding interactions, treatment of appropriate side-chain conformations using Prime, removal of water molecules located more than 5 Å from the relevant binding region, and energy minimization using the OPLS4 force field.

2 Ligand Preparation

Structures of the prioritized *F. exasperata* phytochemicals were prepared using LigPrep in Schrödinger Maestro 2023-4. Three-dimensional conformations were generated, and protonation/ionization states were considered using Epik at pH 7.0±2.0. Up to 32 stereoisomeric forms were permitted where applicable, and energetically favorable conformations were retained for docking.

3 Receptor Grid Generation and Docking

The receptor grid was generated around the binding site of the co-crystallized ligand using a grid dimension of 20×20×20Å. Molecular docking was initially performed using Glide Standard Precision (SP), followed by Glide Extra Precision (XP) docking for compounds showing favorable SP docking characteristics. Enzalutamide was included as the reference drug for comparative analysis.

The docking results were evaluated using Glide docking scores together with predicted ligand–receptor interactions. The lowest-energy poses were examined for hydrogen-bonding, hydrophobic, π -related, and other non-covalent interactions using BIOVIA Discovery Studio 2021.

4 MM-GBSA Rescoring

MM-GBSA binding free-energy calculations were used as a complementary post-docking assessment of the predicted ligand–AR complexes. The MM-GBSA values were interpreted as relative computational estimates of binding favorability and were not treated as experimental measurements of binding affinity.

Importantly, Glide XP scores and MM-GBSA values were not considered interchangeable. Glide XP scores were used to assess the relative quality of predicted docking poses, whereas MM-GBSA was used as a complementary energetic rescoring approach.

This distinction is particularly important because the submitted results show that hexadecanoic acid ethyl ester had the most favorable XP MM-GBSA value, whereas enzalutamide had a more favorable XP Glide score.

5 Prediction of Biological Activities

The biological activity profiles of the prioritized phytochemicals were evaluated using PASS Online. PASS predicts the probability of biological activity (Pa) and inactivity (Pi) based on structural features and a Bayesian approach.

Activities for which Pa>Pi were considered computationally predicted activities. Consistent with the original study design, activities with Pa>0.50 were regarded as stronger predictions, whereas activities below this threshold were interpreted cautiously as exploratory computational signals rather than established biological activities.

6 Computational Toxicity Prediction

Potential toxicity profiles were evaluated using StopTox and ProTox-3.0. StopTox was used to predict selected toxicity endpoints, including hepatotoxicity, mutagenicity, carcinogenicity, and cytotoxicity, whereas ProTox-3.0 was used to estimate acute toxicity, predicted LD₅₀, and toxicity classification together with selected toxicity endpoints.

The toxicity predictions were used for lead prioritization rather than definitive safety assessment. Predicted toxicity classes and endpoint alerts were interpreted comparatively and were not considered substitutes for experimental toxicological testing.

RESULTS AND DISCUSSION

Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

The total ion chromatogram (TIC) of the ethanol leaf extract of *F. exasperata* showed well-resolved chromatographic signals within the reported retention-time range of approximately 4–21 min, with prominent peaks occurring at 12.374, 12.586, 12.746, 13.501, 13.679, 14.433/14.463, and 14.640 min. The most abundant reported peak occurred at 12.374 min. Compound assignments were obtained by comparison with the NIST 2017 mass spectral library, as shown in Figure 1 and Table 1.

To improve the reliability of compound annotation, the highest-quality library match was retained for each chromatographic peak, while library matches with quality scores below 70% were excluded from the confirmed compound list. On this basis, the reported GC-MS data provides high-confidence assignments for eight chromatographic peaks, whereas four peaks did not meet the $\geq 70\%$ spectral-match criterion.

The high-confidence assignments included neophytadiene, 1-hexadecyne, n-hexadecanoic acid, hexadecanoic acid ethyl ester, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, stigmasta-4,22-diene, 9,12,15-octadecatrienoic acid ethyl ester, and octadecanoic acid ethyl ester. The corresponding spectral-match scores ranged from 70 to 99% [13], [28].

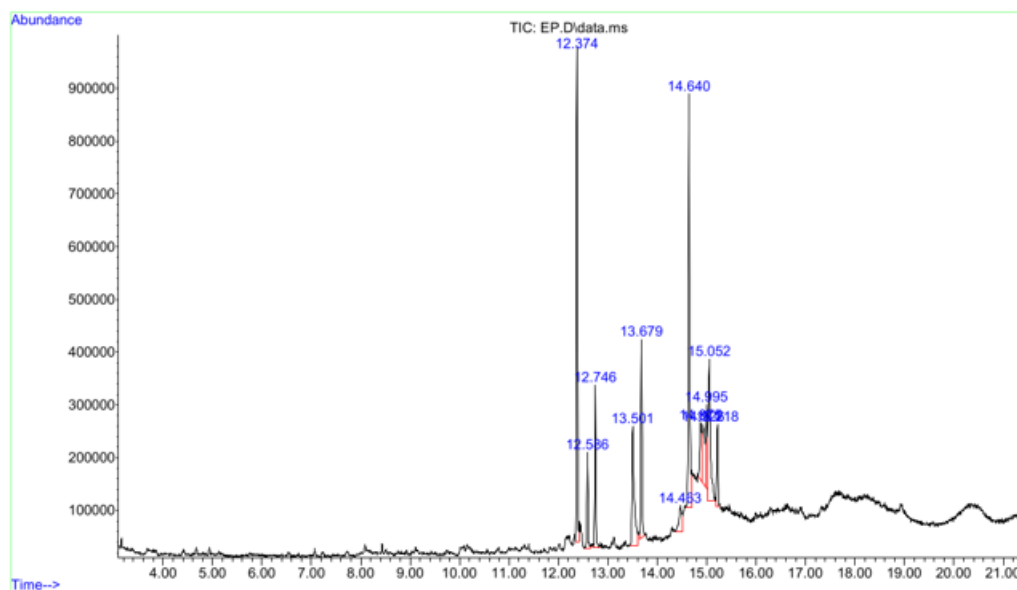


Figure 1. Total ion chromatogram (TIC) of the ethanol leaf extract of *F. exasperata*

Pharmacokinetic and Drug likeness Evaluation

The confirmed GC-MS compounds were subjected to SwissADME analysis to evaluate their physicochemical properties, predicted gastrointestinal absorption, drug-likeness, and medicinal-chemistry characteristics. The revised analysis was restricted to compounds supported by a GC-MS library quality score of $\geq 70\%$, thereby avoiding propagation of low-confidence compound assignments into downstream computational analyses.

Compounds were considered eligible for further computational prioritization when they exhibited no more than one Lipinski violation, high predicted gastrointestinal absorption, and no PAINS alerts (Table 2) [27]. The final number of compounds fulfilling these criteria was determined after removal of duplicate structures and correction of the GC-MS compound list.

Table 1. GC-MS phytochemical constituents of *F. exasperata* ethanol leaf extract based on the highest-quality library match for each chromatographic peak

No.	Peak	RT (min)	Area (%)	Selected compound	Quality (%)	Molecular Formula	Molecular Weight (g/mol)
1	1	12.374	18.16	Neophytadiene	99	C ₂₀ H ₃₈	278.5
2	3	12.746	6.68	1-Hexadecyne	86	C ₁₆ H ₃₀	222.41
3	4	13.501	9.74	n-Hexadecanoic acid	99	C ₁₆ H ₃₂ O ₂	256.42
4	5	13.679	8.83	Hexadecanoic acid, ethyl ester	99	C ₁₈ H ₃₆ O ₂	284.5
5	7	14.640	20.51	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	90	C ₂₀ H ₄₀ O	296.5
6	9	14.926	5.79	Stigmasta-4,22-diene	70	C ₂₉ H ₄₈	396.7
7	11	15.052	11.56	9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z)-	96	C ₂₀ H ₄₈ O ₂	306.5
8	12	15.218	3.53	Octadecanoic acid, ethyl ester	99	C ₂₀ H ₄₀ O ₂	312.5

Table 2. Pharmacokinetic and drug likeness evaluation of *F. exasperata* phytoconstituents using SwissADME

No.	Compound Name	Mol. Formula	Lipinski Violations	GI Absorption	PAINS Alerts	Status
1	Neophytadiene	C ₂₀ H ₃₈	1 (MLOGP)	Low	0	Fail
2	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	C ₂₀ H ₄₀ O	1 (MLOGP)	Low	0	Fail
3	1-Hexadecyne	C ₁₆ H ₃₀	1 (MLOGP)	Low	0	Fail
4	n-Hexadecanoic acid	C ₁₆ H ₃₂ O ₂	1 (MLOGP)	High	0	Pass
5	Hexadecanoic acid, ethyl ester	C ₁₈ H ₃₆ O ₂	1 (MLOGP)	High	0	Pass
6	Stigmasta-4,22-diene	C H	1 (MLOGP)	Low	0	Fail
7	9,12,15-Octadecatrienoic acid, ethyl ester (Z,Z,Z)-	C H O	1 (MLOGP)	Low	0	Fail
8	Octadecanoic acid, ethyl ester	C ₂₀ H ₄₀ O ₂	1 (MLOGP)	Low	0	Fail

Network Pharmacology

SwissTargetPrediction identified 174 putative molecular targets associated with the prioritized *F. exasperata* phytochemicals. In parallel, 3,388 prostate cancer-associated genes were compiled from Open Targets, GeneCards, and DisGeNET using the predefined database-specific selection criteria. Intersection analysis of the phytochemical-associated targets with the prostate cancer-associated genes identified 97 common targets (Figure 2). These overlapping targets represent potential molecular nodes through which the phytochemicals of *F. exasperata* may influence prostate cancer-associated biological processes.

The identification of 97 common targets suggests a multi-target pharmacological profile for the prioritized *F. exasperata* phytochemicals rather than interaction with a single molecular target. The shared targets were therefore subjected to protein-protein interaction (PPI) and functional enrichment analyses to characterize their biological relationships and identify signaling pathways potentially relevant to prostate cancer progression.

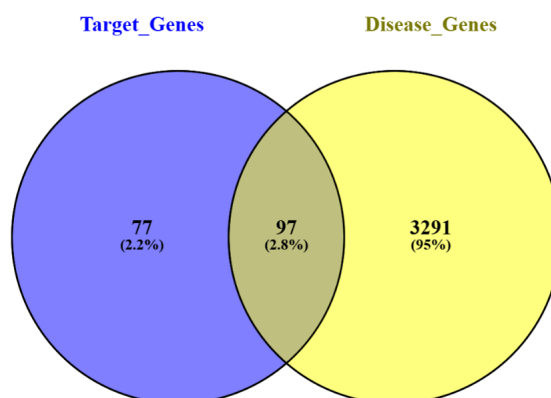


Figure 2. Venn diagram illustrates the intersection between *F. exasperata* phytochemical-associated molecular targets and prostate cancer-associated genes. A total of 174 putative phytochemical targets and 3,388 prostate cancer-associated genes were analyzed, yielding 97 common targets for subsequent network pharmacology analyses

Network Pharmacology and Pathway Enrichment Analyses The 97 common targets identified from the intersection of *F. exasperata* phytochemical-associated targets and prostate cancer-associated genes were subjected to PPI and KEGG pathway enrichment analysis, and KEGG prostate cancer signaling pathway showed the mapped target genes (Figure 3).

1 Protein-protein interaction/network analysis

The PPI network demonstrated interconnected relationships among the common targets, with several highly connected nodes forming prominent interaction clusters (Figure 3a). These interactions suggest that the identified targets may function cooperatively within interconnected molecular processes rather than acting independently.

2 KEGG pathway enrichment analysis

KEGG analysis revealed enrichment of several biologically relevant pathways. Steroid hormone biosynthesis showed the highest fold enrichment, followed by ovarian steroidogenesis, arachidonic acid metabolism, AGE-RAGE signaling, prolactin signaling, PPAR signaling, chemical carcinogenesis, insulin resistance, inflammatory mediator regulation of TRP channels, and HIF-1 signaling (Figure 3b). Importantly, pathways in cancer were also significantly enriched, supporting the potential relevance of the identified targets to cancer-associated molecular processes.

3 KEGG prostate cancer signaling pathway showing the mapped target genes

The prostate cancer pathway map demonstrated that the common targets are distributed across multiple interconnected signaling processes, including AR, PI3K-Akt, MAPK, mTOR, p53, cell-cycle, apoptosis, and steroid hormone biosynthesis pathways (Figure 3c). Several highlighted targets, including AR, SRD5A2, GSK3, NF- κ B, BCL2, GSTP1 and PSMA, occupy positions within pathways associated with tumor-cell proliferation, survival, apoptosis, invasion and hormonal regulation.

Integrated PPI Network and Gene Ontology Enrichment Analysis

Figure 4 presents the systems-level analysis of the common targets associated with *F. exasperata* and prostate cancer. (a) The PPI network shows extensive interconnections among the common targets, with a densely connected central network indicating potential functional relationships among multiple molecular targets. (b) Cellular component enrichment was dominated by membrane-associated and nuclear compartments, including membrane rafts, caveolae, nuclear chromatin, transcription-factor complexes, and plasma membranes. (c) Molecular-function enrichment highlighted steroid hormone receptor activity, nuclear receptor activity, ligand-activated transcription, DNA-binding transcription-factor activity, and protein kinase activity. (d) Biological-process enrichment was predominantly associated with regulation of transcription, signal transduction, inflammatory and apoptotic responses, cell proliferation, cellular stress responses, angiogenesis, and

oxidative-stress responses. Collectively, these findings indicate that the common targets are functionally involved in hormonal regulation, transcriptional control, inflammation, cell survival/proliferation, and cancer-related signaling, providing a mechanistic basis for further investigation of the predicted anti-prostate cancer potential of *F. exasperata*.

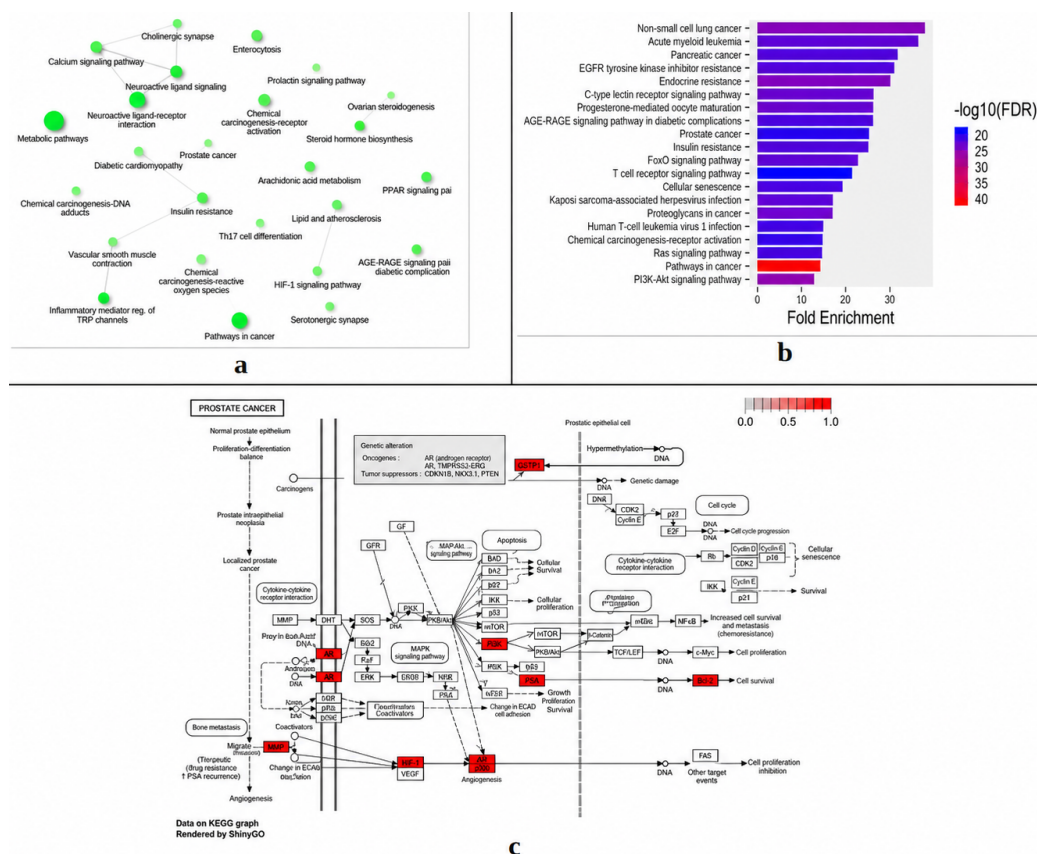


Figure 3. Network pharmacology and pathway enrichment analyses. (a) Protein-protein interaction/network analysis; (b) KEGG pathway enrichment analysis; and (c) KEGG prostate cancer signaling pathway showing the mapped target genes

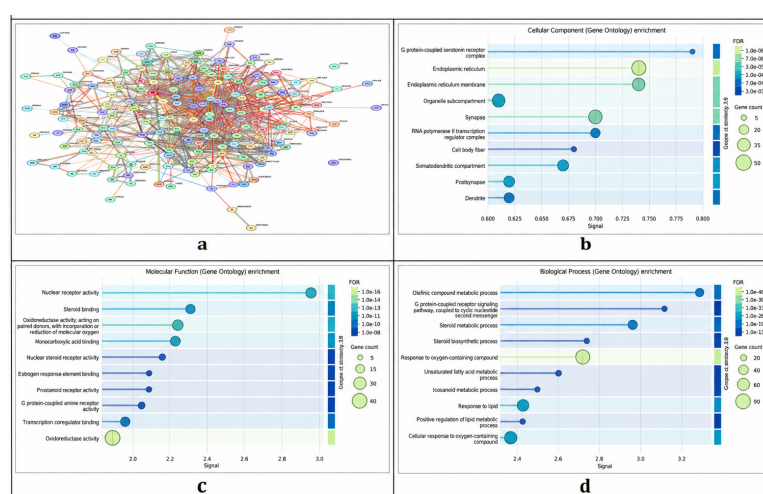


Figure 4. Integrated PPI network and gene ontology enrichment analysis of *F. exasperata*/Prostate cancer common targets

The present network profile supports the multi-target and multi-pathway nature expected for medicinal-plant-derived phytochemicals. Similar network-pharmacology studies of other medicinal plants against prostate cancer have reported interconnected targets involving signaling, proliferation, apoptosis and cancer-associated pathways. For example, *Hedyotis diffusa* analysis identified a network involving MAPK8, IL6, VEGFA, STAT3, JUN, MMP9 and RELA, highlighting inflammatory, proliferative and transcriptional signaling as important components of its predicted anti-prostate-cancer mechanism [29]. Likewise, studies of *Pyrrosiae folium* used intersecting phytochemical and prostate-cancer targets followed by GO/KEGG and PPI analyses, supporting the usefulness of this integrated approach for identifying multi-target mechanisms [30].

The present findings are particularly notable for the strong enrichment of steroid hormone receptor and nuclear receptor activities, together with steroid hormone biosynthesis in the pathway analysis. This provides a biologically coherent connection between the identified *F. exasperata* targets and androgen-dependent prostate-cancer biology. Recent work on *Ficus hispida* has similarly focused on phytochemical interactions with the AR, although that study proceeded primarily through docking, ADMET/PASS prediction, and molecular-dynamics analysis rather than the broader network framework used here [31].

Importantly, the present results should be regarded as computationally generated mechanistic hypotheses rather than evidence of therapeutic efficacy. The enrichment of AR-related functions, apoptosis, inflammatory signaling, proliferation and oxidative-stress responses provides a rational basis for subsequent docking and experimental validation but does not by itself demonstrate that *F. exasperata* modulates these pathways in prostate cancer cells. This cautious interpretation is consistent with recent prostate-cancer network-pharmacology studies that have combined computational predictions with experimental validation to establish biological relevance [32].

Molecular Docking Results

Molecular docking against the AR showed distinct binding profiles among the evaluated compounds. Enzalutamide, used as the reference inhibitor, produced an SP score of -2.957 kcal/mol and an SP MM-GBSA value of -38.97 kcal/mol, while its XP score and XP MM-GBSA value were -2.609 and -31.99 kcal/mol, respectively [33].

Among the *F. exasperata*-associated compounds, Hexadecanoic acid, ethyl ester showed the most favorable XP score and MM-GBSA estimate (-1.866 and -38.29 kcal/mol, respectively). n-Hexadecanoic acid showed comparatively weaker performance, with an XP score of -1.625 kcal/mol and an XP MM-GBSA of -2.22 kcal/mol. Overall, the integrated ranking was enzalutamide > Hexadecanoic acid, ethyl ester > n-Hexadecanoic acid.

The results are broadly consistent with previous computational studies showing that fatty-acid-derived phytochemicals can establish favorable protein interactions, although their docking scores are highly target- and binding-site-dependent. For example, ethyl linolenate has previously demonstrated favorable docking against other protein targets, including a reported docking score of -6.76 kcal/mol against a muscarinic receptor and -4.88 kcal/mol against GlcN-6-P synthase [34]. However, these values were obtained against different proteins and docking protocols and therefore cannot be directly compared numerically with the present AR results.

Importantly, previous experimental work on *F. exasperata* has demonstrated anti-proliferative and pro-apoptotic effects in PC-3 prostate cancer cells, providing biological context for investigating its phytochemicals in prostate cancer [12], [35]. Nevertheless, those findings do not establish AR binding by the individual compounds identified in the present study. Similarly, previous phytochemical investigations of *F. exasperata* have identified diverse phenolic and other secondary metabolites, supporting the chemical complexity of the plant but also highlighting that GC-MS captures only a subset of its phytochemical composition [36], [37].

Binding Interaction Analysis

The 2D and 3D interaction analyses (Figure 5a and 5b) indicated that both hexadecanoic acid, ethyl ester and the reference antiandrogen enzalutamide were accommodated within the AR binding pocket, although their interaction patterns differed. Hexadecanoic acid, ethyl ester was stabilized predominantly by hydrophobic contacts involving residues such as Val684, Val685, Val715, Trp718, Leu744, Met745, Ala748, Trp751, Pro801, Phe804, and Leu805, with an additional hydrogen-bond interaction involving Trp751. Its long aliphatic chain showed strong hydrophobic complementarity with the receptor cavity, suggesting that non-polar interactions were the major contributors to binding stabilization.

Table 3. Molecular docking scores and MM-GBSA binding energy estimates

Compound	Glide (kcal/mol)	Score SP	MMGBSA (kcal/mol)	XP (kcal/mol)	Score XP	MM-GBSA Glide SP
Enzalutamide (reference drug)	-2.957		-38.97	-2.609		-31.99
Hexadecanoic acid, ethyl ester	0.725		-32.33	-1.866		-38.29
n-Hexadecanoic acid	0.869		-9.75	-1.625		-2.22

In comparison, enzalutamide (Figure 5c and 5d) exhibited a more structurally diverse interaction profile, combining extensive hydrophobic contacts with polar and hydrogen-bonding interactions involving residues such as Gln711, Gln723, Thr877, His804, and surrounding hydrophobic amino acids including Leu701, Leu704, Leu708, Leu873, Ala874, Phe876, Phe797, and Cys805. The 3D hydrophobicity surfaces further confirmed favorable positioning of the non-polar regions of both ligands within hydrophobic portions of the receptor pocket, while their polar functional groups were oriented toward more hydrophilic regions. The broader interaction network displayed by enzalutamide is consistent with its established AR-binding characteristics, whereas the favorable accommodation of hexadecanoic acid, ethyl ester suggests a plausible contribution to the predicted anti-prostate cancer activity of *F. exasperata*. Nevertheless, these docking-derived interactions represent computational predictions and require further validation through molecular dynamics simulations and experimental AR assays.

The present observation is consistent with previous computational studies showing that Hexadecanoic acid, ethyl ester can interact favorably with protein binding pockets through extensive hydrophobic and van der Waals contacts. For example, Hexadecanoic acid, ethyl ester has previously shown a docking affinity of approximately -6.5 kcal/mol against matrix metalloproteinase-9 (MMP-9), illustrating the capacity of this class of unsaturated fatty-acid derivatives to occupy hydrophobic ligand-binding cavities [38].

Importantly, previous investigations of *F. exasperata* have demonstrated considerable phytochemical diversity, including phenolic compounds and other secondary metabolites, but the reported chemical profiles depend strongly on extraction and analytical methodology [36], [39]. More recent *F. exasperata* in silico studies have likewise used molecular docking to explore interactions between identified phytochemicals and disease-relevant protein targets [39], [40]. The present analysis extends this computational evidence by examining the interaction of a GC-MS-identified fatty-acid ester with AR in the context of prostate cancer.

The figure demonstrates plausible structural accommodation of hexadecanoic acid ethyl ester within the AR binding pocket, but the visualization alone does not establish receptor antagonism or therapeutic activity. The observed interactions should therefore be regarded as a computational hypothesis requiring confirmation through additional approaches, such as molecular dynamics and experimental AR-binding or functional assays.

PASS Predicted Biological Activity

The combined PASS analysis indicates a marked difference between Hexadecanoic acid, ethyl ester and the reference drug enzalutamide in terms of prostate-cancer-specific predictions. Enzalutamide exhibited strong predicted activities for prostate cancer treatment (Pa = 0.854), androgen antagonism (Pa = 0.801), prostate disorders treatment (Pa = 0.737), benign prostatic hyperplasia treatment (Pa = 0.658), and antineoplastic activity (Pa = 0.616). In contrast, hexadecanoic acid, ethyl ester showed prominent predictions for testosterone 17 β -dehydrogenase inhibition (Pa = 0.781), TP53 expression enhancement (Pa = 0.719), alpha-methylacyl-CoA racemase inhibition (Pa = 0.665), anti-inflammatory activity (Pa = 0.600), caspase-8 stimulation (Pa = 0.495), and MMP9 expression inhibition (Pa = 0.427). These findings suggest that, while enzalutamide displays a more direct AR- and prostate cancer-related activity profile, hexadecanoic acid, ethyl ester may exert potential anti-prostate cancer effects through modulation of androgen metabolism, tumor-suppressor signaling, apoptosis, inflammation, and metastatic pathways.

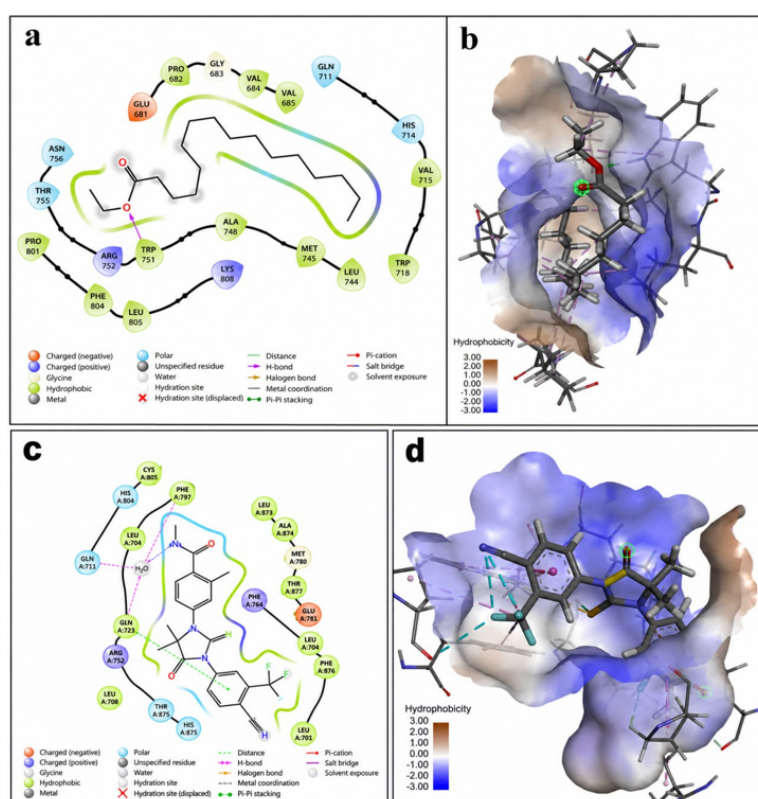


Figure 5. Comparative 2D Ligand Interaction and 3D Hydrophobicity Profiles of Hexadecanoic acid, ethyl ester and Enzalutamide within the AR Binding Pocket. (a) 2D ligand interaction of Hexadecanoic acid, ethyl ester; (b) 3D hydrophobicity representation of Hexadecanoic acid, ethyl ester; (c) 2D ligand interaction of enzalutamide; (d) 3D hydrophobicity representation of enzalutamide.

Table 4. Comparison of PASS-predicted biological activities of Hexadecanoic acid, ethyl ester and Enzalutamide

Biological activity	Hexadecanoic acid, ethyl ester (Pa/Pi)	Enzalutamide (Pa/Pi)
Prostate cancer treatment	—	0.854/0.003
Androgen antagonist	—	0.801/0.003
Prostate disorders treatment	0.198/0.160	0.737/0.005
Prostatic (benign) hyperplasia treatment	—	0.658/0.004
Antineoplastic	0.455/0.061	0.616/0.042
Testosterone 17 β -dehydrogenase inhibitor	0.781/0.030	—
Alpha-methylacyl-CoA racemase inhibitor	0.665/0.004	—
TP53 expression enhancer	0.719/0.022	—
Anti-inflammatory	0.600/0.004	—
Caspase-8 stimulant	0.495/0.018	—
MMP9 expression inhibitor	0.427/0.043	—

ProTox-3.0 and StopTox-predicted Acute Toxicity

The computational toxicity assessment indicated a comparatively favorable predicted acute-toxicity profile for Hexadecanoic acid, ethyl ester relative to enzalutamide. The fatty-acid ethyl ester showed a predicted LD₅₀ of 5,000 mg/kg (toxicity class 5), compared with 650 mg/kg (class 4) for enzalutamide (Table 5). It was predicted as non-toxic for acute oral, inhalation and dermal toxicity, although it

was classified as a skin sensitizer. In contrast, enzalutamide was predicted to be toxic following oral exposure and for eye irritation/corrosion, while remaining non-toxic for acute inhalation and dermal toxicity and non-sensitizing in the StopTox model.

The relatively favorable computational profile of the fatty-acid ester is broadly consistent with available chemical-safety information for ethyl palmitate, which is not classified as a major acute hazard in PubChem; however, available safety information does indicate the possibility of skin irritation, emphasizing that a favorable computational prediction does not imply absence of hazard [41]. Conversely, previous clinical literature indicates that enzalutamide is generally tolerated but is associated with adverse effects including fatigue, diarrhoea, musculoskeletal symptoms, headache and hypertension, providing biological context for its less favorable computational toxicity profile [42].

Collectively, ProTox-3.0 and StopTox predicted a comparatively favorable acute-toxicity profile for hexadecanoic acid, ethyl ester relative to enzalutamide, although its predicted skin-sensitization liability highlights the need for experimental safety assessment before further pharmacological development.

Table 5. ProTox 3.0 and StopTox predicted acute toxicity parameters for Hexadecanoic acid, ethyl ester and Enzalutamide

	Hexadecanoic acid, ethyl ester	Enzalutamide
Predicted LD ₅₀ (mg/kg)	5,000	650
Predicted Toxicity Class	5	4
Acute Inhalation Toxicity	Non-toxic	Non-toxic
Acute Oral Toxicity	Non-toxic	Toxic
Acute Dermal Toxicity	Non-toxic	Non-toxic
Eye Irritation and Corrosion	Non-toxic	Toxic
Skin Sensitization	Sensitizer	Non-sensitizer
Skin Irritation and Corrosion	Negative	Negative

The integrated network-pharmacology findings provide a system-level rationale for investigating *F. exasperata* phytochemicals in prostate cancer. The identification of 97 common targets linking the predicted phytochemical targets with prostate cancer-associated genes suggests that the extract may influence multiple molecular nodes rather than a single therapeutic target. This multi-target pattern is consistent with the pharmacological behavior commonly proposed for plant-derived bioactive mixtures, in which several constituents may act on interconnected signaling pathways rather than producing a single-target response. However, target overlap from network pharmacology represents a computational association and should not be interpreted as evidence of actual target modulation.

The enrichment of PI3K-Akt, Ras, and prostate-cancer-associated signaling, together with steroid hormone-related processes, is particularly relevant to prostate cancer biology. The AR remains a central regulator of prostate-cancer-cell proliferation and survival, while extensive reciprocal crosstalk exists between AR and the PI3K/AKT/mTOR axis. Disruption of one pathway can promote compensatory activation of the other, contributing to disease progression and therapeutic resistance [43], [44]. Thus, the convergence of AR-associated signaling with PI3K-Akt-related pathways in the present network provides a biologically plausible framework for the observed computational activity of *F. exasperata* constituents.

The molecular-docking results further supported the possibility of interaction between selected phytochemicals and AR. Hexadecanoic acid, ethyl ester produced the most favorable XP Glide score among the investigated phytochemicals (-1.866 kcal/mol), compared with -2.609 kcal/mol for enzalutamide. Nevertheless, its XP MM-GBSA estimate (-38.29 kcal/mol) was more favorable than that of enzalutamide (-31.99 kcal/mol). This discrepancy is important because Glide docking scores and MM-GBSA estimates reflect different computational characteristics and should not be interpreted as equivalent measures of experimental affinity. Consequently, the more favorable XP score of the fatty-acid ester does not demonstrate superior AR binding to enzalutamide. Rather, it indicates that the compound can adopt a plausible orientation within the AR binding pocket and warrants further investigation.

The predicted interaction pattern of hexadecanoic acid, ethyl ester is also biologically plausible from a structural perspective. Its long unsaturated hydrocarbon chain is expected to favor hydrophobic accommodation within the receptor cavity, whereas the ester group may contribute polar interac-

tions that help orient the ligand. Such an interaction mode differs from the more chemically diverse interaction network expected for enzalutamide and may partly explain the differences between the docking and MM-GBSA results. Importantly, because fatty-acid esters are not established AR antagonists, the docking result should be regarded as a binding hypothesis rather than evidence of AR antagonism.

The PASS analysis provides additional, although indirect, biological context. For hexadecanoic acid, ethyl ester, relatively strong predicted activities included testosterone 17 β -dehydrogenase inhibitor (Pa = 0.781), TP53 expression enhancement (Pa = 0.719), and alpha-methylacyl-CoA racemase inhibitor (Pa = 0.665). These predictions are mechanistically relevant because 17 β -dehydrogenase inhibitor, TP53-dependent responses, and alpha-methylacyl-CoA racemase inhibitor are important determinants of prostate-cancer-cell survival and progression. Nevertheless, the compound did not receive a direct PASS prediction for prostate-cancer treatment or androgen antagonism, and its antineoplastic (Pa = 0.455) and prostate disorders treatment (Pa = 0.198) were below the predefined 0.50 threshold. Therefore, these results should be described as potential cancer-associated mechanisms rather than evidence of prostate-cancer efficacy.

The biological interpretation is strengthened by previous experimental observations on *F. exasperata*. Earlier work has reported antiproliferative and pro-apoptotic effects of *F. exasperata* preparations in prostate-cancer-related experimental models, providing some biological context for the computational predictions obtained in the present study. More broadly, phytochemicals are increasingly investigated because their potential anticancer effects can involve simultaneous modulation of proliferation, apoptosis, inflammation and signaling pathways rather than a single molecular mechanism. Such multi-target behavior is particularly relevant to prostate cancer, where reciprocal signaling between AR and PI3K/AKT/mTOR contributes to tumor progression and resistance to androgen-directed therapy [43], [44].

The computational toxicity results also provide useful preliminary information. Hexadecanoic acid, ethyl ester had a predicted LD₅₀ of 5,000 mg/kg and toxicity class 5, compared with 650 mg/kg and class 4 for enzalutamide. It was predicted as non-toxic for acute oral, inhalation, and dermal exposure, although skin sensitization was predicted. These findings suggest a comparatively favorable predicted acute-toxicity profile, but they should not be interpreted as evidence that the phytochemical is clinically safer than enzalutamide. Computational toxicity models are predictive and can differ from experimental toxicological outcomes.

Herbal extracts generally exert biological activity through the collective action of multiple constituents rather than a single dominant compound [45]. The network pharmacology results support this concept by demonstrating simultaneous modulation of several interconnected signaling pathways [46]. Consequently, the observed computational effects may reflect additive or synergistic interactions among terpenoids, fatty acids, sterols, and other phytochemicals present in *F. exasperata* [47]. Although such synergistic interactions cannot be confirmed computationally, they provide a plausible explanation for the broad pathway enrichment observed in this study and warrant future experimental investigation using fractionated extracts and combination assays.

CONCLUSION

The integrated computational analyses suggest that phytochemicals from *F. exasperata* leaves may exert multi-target effects relevant to prostate cancer, particularly through AR-associated and PI3K–Akt signaling pathways. Hexadecanoic acid, ethyl ester, demonstrated a favorable predicted interaction profile with the AR and exhibited several cancer-associated PASS activities, alongside a comparatively favorable predicted acute toxicity profile. However, these findings represent computational predictions rather than experimental confirmation of therapeutic efficacy or safety. Therefore, further molecular dynamics simulations, as well as in vitro and in vivo studies, are required to validate the predicted molecular interactions, biological activities, and toxicological characteristics of the identified phytochemicals. This study has several limitations. First, all findings are based on computational analyses and thus require validation using appropriate in vitro and in vivo prostate cancer models. Second, GC-MS primarily detects volatile and semi-volatile constituents and may not identify highly polar phytochemicals that could also contribute to biological activity. Third, molecular docking and MM-GBSA provide useful predictions of ligand–protein interactions but cannot fully account for protein flexibility, solvent effects, or long-timescale conformational changes. Although this study incorporates MM-GBSA rescoring to enhance docking interpretation, future investigations should include molecular dynamics simulations and experimental binding assays to confirm ligand stability and biological activity.

SUPPLEMENTARY MATERIAL

None.

AUTHOR CONTRIBUTIONS

Mutiu A. Alabi: Conceptualization, Methodology, Investigation, Supervision and Writing - original draft. Habeebullah A. Jamiu: Methodology, Investigation and Software. Dauda S. Adebara: Methodology, Investigation and Software. Akeem O. Salawu: Methodology, Investigation, and Software. AbdulJeleel A. Yusuph: Methodology, Investigation, and Software. Abdulhameed O. Alli: Methodology, Investigation, and Software. Fatai A. Kareem: Methodology, Investigation, and Software. Emmanuel O. Ajani: Formal analysis, Visualization, and Supervision.

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are included within the article. All computational data, including phytochemical, pharmacokinetic, network pharmacology, molecular docking, and toxicity prediction results, are available from the corresponding author upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF GENERATIVE AI USE

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, model GPT-5.6) for language editing and text improvement. After using this tool, the authors thoroughly reviewed and revised the generated content, taking full responsibility for the accuracy and integrity of the final manuscript.

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