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Integrative Ethnopharmacological and In-Silico Strategy for Identifying Indonesian Jamu to Enhance Athletic Stamina

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Abstrak:

Pendahuluan: Stamina atletik merupakan sifat multifaktorial yang melibatkan interaksi jalur metabolik, endokrin, imun, dan respons stres. Penelitian ini bertujuan mengintegrasikan data etnofarmakologi dan pendekatan *in-silico* untuk mengidentifikasi produk alam Indonesia yang berpotensi meningkatkan stamina. **Metode:** Data jamu kesehatan dari KNApSACK dianalisis menggunakan skor farmakognosi dan analisis korespondensi untuk memprioritaskan tanaman. Senyawa disaring melalui drug-likeness dan ADMET, diikuti prediksi target, penambatan molekuler, serta integrasi hasil dalam Jamu Formulation Score (JFS). **Hasil:** Sebanyak 41 tanaman dan 31 senyawa kandidat diidentifikasi, dengan beberapa menunjukkan afinitas tinggi terhadap target utama seperti oestrone pada ESR1 dan withanolide pada NFKB1. Analisis lebih lanjut mengonfirmasi kesesuaian antara relevansi etnofarmakologi dan plausibilitas molekuler dalam mendukung peningkatan stamina. **Kesimpulan:** Pendekatan integratif ini efektif dalam memprioritaskan kandidat produk alam berbasis bukti untuk peningkatan stamina. Temuan ini memberikan dasar rasional untuk validasi eksperimental dan pengembangan formulasi jamu modern.

Kata kunci: Etnofarmakologi; Fitokimia; Jamu; Penambatan molekuler; Stamina atlet

Abstract:

Introduction: Athletic stamina is a multifactorial trait involving metabolic, endocrine, immune, and stress-response pathways. This study aimed to integrate ethnopharmacological data with in-silico approaches to identify Indonesian natural products with potential stamina-enhancing effects. **Methods:** Health-related jamu formulations from the KNApSACK database were analyzed using pharmacognosy scoring and correspondence analysis to prioritize plants. Compounds were filtered by drug-likeness and ADMET, followed by target prediction, molecular docking, and integration into a Jamu Formulation Score (JFS). **Results:** A total of 41 priority plants and 31 candidate compounds were identified, with several showing strong binding affinities toward key targets such as oestrone with ESR1 and withanolide with NFKB1. The results demonstrated convergence between ethnopharmacological relevance and molecular plausibility in supporting stamina-related activity. **Conclusions:** This integrative approach effectively prioritizes evidence-based natural product candidates for stamina enhancement. The findings provide a rational foundation for future experimental validation and modern jamu formulation development.

Keywords: Athlete stamina; Drug discovery; Ethnopharmacology; Jamu; Molecular docking; Phytochemicals

1. Introduction

Athletic endurance is a multifaceted physiological characteristic that relies on factors beyond mere cardiorespiratory capacity. Sustained performance and effective recovery necessitate the coordinated regulation of skeletal muscle metabolic flexibility, mitochondrial remodeling, oxygen transport, endocrine signaling, immune modulation, and stress-response pathways. Recent exercise-biology research indicates that endurance training elicits molecular adaptations in mitochondrial, metabolic, immune, and stress-response systems, with notable differences in responses between males and females [1]. These results suggest that interventions aimed at enhancing stamina should be assessed using a multi-target physiological framework instead of a singular pathway approach. Ethnobotanical evidence from Indonesian communities indicates that medicinal plants have historically been utilized to enhance stamina, implying that indigenous botanical knowledge may yield pertinent candidates for pharmacological research [2].

A few physiological areas are very important for stamina because they control how much energy is available, how much oxygen is used, how much inflammation stress there is, and how hormones control muscle function. Mitochondrial ATP production is what gives us the energy to keep going for a long time, and pathways that respond to low oxygen levels help keep glycolytic adaptation and oxygen homeostasis in check when the body needs more of them. HIF1A is crucial to this response as it governs cellular metabolic adaptation in hypoxic environments [3]. Exercise-induced inflammation and oxidative stress also affect fatigue, recovery, and training adaptation, which is why immune regulation is an important part of stamina physiology [4]. Endocrine regulation is pertinent, as androgen receptor signaling facilitates muscle adaptation and anabolic responses [5,6], while estrogen receptor signaling enhances mitochondrial function, substrate metabolism, and endurance-related skeletal muscle regulation [7,8].

Although muscle hypertrophy and lactate handling are also relevant to exercise performance, they were not treated as independent target domains in this framework. Muscle hypertrophy is more closely associated with strength and resistance-training adaptation and is partially represented through androgen-related signaling. Lactate handling contributes to fatigue and recovery, but it is closely integrated with broader skeletal-muscle energy metabolism, including glycolytic ATP production and oxidative phosphorylation [9]. Therefore, this study prioritized broader stamina-related domains, including energy metabolism, hypoxia adaptation, immune regulation, endocrine signaling, and muscle endurance.

Natural products are attractive candidates for stamina-related applications because plant-derived phytochemicals may influence oxidative balance, inflammatory signaling, substrate utilization, and post-exercise recovery. Interest in botanical ergogenic aids has increased, especially for polyphenol-rich supplements used by athletes and physically active individuals. However, current evidence remains heterogeneous, with reported benefits depending on compound type, dosage, duration of use, and exercise context [10]. This uncertainty highlights the need for rational prioritization strategies that can distinguish traditionally valued plants from compounds with stronger pharmacological plausibility.

Indonesia's rich plant life and long history of using jamu make it a great place to look for natural products that can help with stamina. Jamu is a multicomponent herbal medical system that is still widely used to keep people healthy. However, many of the benefits it claims to have are still better supported by real-world use than by pharmacological evidence based on mechanisms [11]. The KNApSACK Jamu Database and the KNApSACK Core Database are two digital resources that let you connect formulation names, claimed effects, ingredient plants, and metabolite information in a way that you can search. In this research, jamu "sehat" products were classified into male-specific, female-specific, and general-health claim categories to facilitate a claim-oriented analysis of botanicals and phytochemicals pertinent to stamina enhancement.

Previous research has examined aspects of this issue but has not completely amalgamated them into a cohesive prioritization workflow. Ethnobotanical studies have recorded medicinal plants utilized for stamina preservation; however, they typically do not evaluate whether the identified plants possess orally bioavailable, pharmacologically active, or therapeutically relevant compounds [2]. Computational studies have investigated target prediction in jamu formulas and illustrated the significance of correlating jamu composition with prospective molecular targets [12,13]. Nonetheless, claim-specific ethnopharmacological patterns, plant-part distribution, compound filtering, target prediction, molecular docking, and formulation-level prioritization have not been adequately amalgamated within a singular analytical framework.

This gap is significant because ethnopharmacological prominence does not inherently signify molecular plausibility. Plants that are often used in traditional formulations may not always have compounds that work well as drugs or are relevant to the target, while plants that are not often used may still have phytochemicals with strong biological potential. Combining ethnopharmacological data with in-silico methods like ADMET filtering, target prediction, and molecular docking is a smart way to choose which biologically plausible compounds and targets to focus on. These computational methods are advantageous for preliminary screening; however, their results are still hypothesis-generating and necessitate experimental confirmation [14,15].

Therefore, this study employed an integrative ethnopharmacological and in-silico strategy to identify 65 Indonesian natural products with potential stamina-enhancing effects. Ethnopharmacological data from the 66 KNAPSAcK Jamu Database were used to prioritize species according to frequency and claim specificity, after which 67 phytochemicals from selected plants were screened for drug-likeness and ADMET properties, matched to stamina-related targets, evaluated through molecular docking, and integrated into a Jamu Formulation Score. By linking 69 traditional claim categories with physiologically relevant domains, this study aims to move from empirical jamu use toward evidence-based prioritization of candidate plants and compounds for future pharmacological validation.

2. Materials and Methods

2.1. Ethnopharmacology Data Collection and Cleaning

Ethnopharmacological data were obtained from the KNAPSAcK Jamu Database (<https://www.knapsackfamily.com/jamu/top.php>) [16]. Jamu products containing the keyword “sehat” were extracted from the full catalog. These products were classified into three claim-based categories according to the keywords in their product names: male-specific, female-specific, and general health. For each product, constituent botanicals were retrieved from the same platform, including scientific name, Indonesian vernacular name, plant part, and manufacturer. Scientific names retrieved from KNAPSAcK Jamu Database were curated by removing synonyms, nonstandard nomenclature, and authorship citations. Botanical names were then standardized using the GBIF Species Match tool (kingdom = Plantae; strict = False).

2.2. Pharmacognosy Scoring and Correspondence Analysis

Pharmacognosy scoring was performed on aggregated botanical frequencies mapped to accepted species and claim categories. The total frequency of producers for each plant was the sum of the producers listing the plant under male specific, female specific and general health categories. Each plant was then classified into a claim group based on a Venn-diagram classification: multi-claim (more than one category), male-specific, female-specific or general health. Plants with multiple claims were given a penalty weight of 0.7 to reflect the lower specificity of the claim, while plants with exclusive claims were given a weight of 1.0. A final score was computed as:

$$\text{final_score} = \text{total_freq} \times \text{weight}$$

Priority plants for downstream compound screening were identified using a statistical cut-off. To avoid taxonomic over-representation, a maximum of three plants per family could be chosen.

Correspondence analysis was conducted to look into the multivariate relationships between plant species (or parts of plants) and jamu claim categories. The analyses are done with the FactoMineR package in RStudio version 2026.01.1+403. The input contingency matrix had rows and columns for filtered plants and claim categories. In each cell, you could see how many producers had that plant in that claim category. We kept the first two dimensions for visualization because they showed 61.3% (Dim 1) and 38.7% (Dim 2) of the total inertia. The arrows pointed to the column coordinates (Male, Female, Neutral). The color of the node showed which plant family it belonged to (the top eight families by total frequency), and the size of the node was based on how many producers there were in total. CA coordinates were exported as a .csv file to use as positional seeds in network visualization. The ggrepel package was used to make labels repel each other. We did separate correspondence analysis for how people used plant parts. This used an input matrix that combined standardized plant parts with claim categories to see if some organs were more likely to be linked to certain types of jamu claims.

2.3. Compound Retrieval and Filtering

Phytochemical compounds from the priority plants were retrieved from the KNApSACk Core Database (https://www.knapsackfamily.com/knapsack_core/top.php), providing KNApSACk ID, CAS number, and compound name. Canonical SMILES and basic molecular properties were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), while additional descriptors (logP, H-bond donors/acceptors, TPSA, rotatable bonds, logS, PAINS alerts, and predicted GI absorption) were computed from SMILES using RDKit. All processing was performed in a Python 3.14.2 workflow within Visual Studio Code version 1.112.0 (<https://github.com/tmatthewv/jamu-integrated-filtering.git>).

Filtering began with SMILES-based deduplication, followed by drug-likeness screening using Lipinski, Veber, and Muegge thresholds ($MW \leq 500$ Da, $\log P \leq 5$, H-bond donors ≤ 5 , H-bond acceptors ≤ 10 , $TPSA \leq 140 \text{ \AA}^2$, rotatable bonds ≤ 10). ADMET filtering required no PAINS alerts, high predicted GI absorption, and $\log S \geq -6$. Further filtering was conducted through target prediction using structural similarity searches in ChEMBL with a Tanimoto threshold of 60%. For each matched analogue with a reported pChEMBL value, UniProt accessions of associated targets were extracted and compared against six predefined proteins relevant to athletic performance and recovery, identified from GeneCards (<https://www.genecards.org/>) queries on “immune modulation”, “androgen signaling”, “estrogen signaling”, “ATP production”, and “muscle endurance” [17]. Androgen receptor and estrogen receptor were added manually, whereas IL-6 receptor and IGF-1 receptor were excluded due to no matching hits. The relationship between the selected proteins and athletic performance and recovery was validated using Reactome pathway enrichment implemented in STRING [18]. Compound–target pairs were retained when pChEMBL ≥ 5.0 and at least one of the six targets was matched.

2.4 Molecular Docking

2.4.1. Protein Preparation

We got the three-dimensional structures of the four target proteins from the AlphaFold Server (<https://alphafoldserver.com/>) by using sequences from the UniProt database (<https://www.uniprot.org/>) [12,13]. The per-residue confidence score (pLDDT) in the B-factor field of each PDB file was used to check the quality of the model. Residues with pLDDT < 70 were taken out to get rid of low-confidence or naturally disordered areas that could cause false docking interactions.

We used both the graphical interface and the command-line mode in UCSF ChimeraX version 1.11 to prepare the protein [14]. The workflow involved taking out water molecules, solvent atoms, and small ligands that had crystallized together, trimming low-confidence areas, adding hydrogens, giving partial charges, and saving the cleaned structures as PDB files. Then, a custom Python script changed the PDB files into PDBQT format. This script assigned AutoDock atom types and partial charges, and it merged non-polar hydrogens into their parent heavy atoms according to AutoDock rules.

2.4.2. Binding Site and Grid Box Identification

A multi-method approach was used to find the binding sites to make sure they were correct and reliable. Using a native co-crystallized-ligand approach, we checked the binding-site coordinates for ANDR, ESR1, and NFKB1. We used ChimeraX structural alignment (matchmaker command) to superimpose the crystal structures (PDB: 2AM9 for ANDR, 1GWR for ESR1, and 8TQD for NFKB1) onto the corresponding AlphaFold models. We then used the native ligand coordinates from the superimposed crystal structures to set the docking-grid centers in the AlphaFold coordinate frame. For HIF1A, we used CB-Dock2 to predict the coordinates of the binding site using 1,4-DPCA. This made sure that energetically favorable pockets (binding score < -6.0 kcal/mol) were kept [15]. **Table 1** shows the validated grid centers and box sizes for all targets.

Table 1. Binding site coordinates and grid box parameters for each target protein.

No	Protein Name (Gene)	Center X (Å)	Center Y (Å)	Center Z (Å)	Box Size (Å)
1	Androgen receptor (ANDR)	26.78	2.36	4.61	22×22×22
2	Estrogen receptor (ESR1)	-12.83	11.25	-8.94	
3	Hypoxia-inducible factor 1-alpha (HIF1A)	-3.00	-11.00	-11.00	
4	Nuclear factor NF-kappa-B p105 subunit (NFKB1)	-1.96	14.65	-30.24	

2.4.3. Ligand Preparation

RDKit (rdkit-pypi) was used to make three-dimensional shapes of the 30 filtered compounds (Section 2.3). Chem.MolFromSmiles was used to build molecular graphs, and Chem. was used to add hydrogen.AddHs(), 3D coordinate embedding with the ETKDgv3 algorithm (AllChem).EmbedMolecule, seed=42, and AllChem's MMFF94 energy minimization.MMFFOptimizeMolecule can run up to 2,000 times. Using meeko version 0.5.0, the 3D SDF files were then changed into PDBQT format, which works with AutoDock.

2.4.4. Docking Simulation

We used AutoDock Vina version 1.2.5 [13] to do all of the molecular docking calculations. The docking parameters were: exhaustiveness: 8; output poses: 9; energy range: 3 kcal/mol; grid spacing: 0.375 Å (default); scoring function: Vina (empirical); random seed: auto (stochastic). A custom Python automation pipeline was created (<https://github.com/tmatthewv/jamu-molecular-docking.git>) to make it easier to systematically dock 31 compounds against 4 receptor proteins. The pipeline did the following steps in order: (1) prepared receptor PDBQT from ChimeraX-prepped PDB files; (2) prepared SMILES-to-PDBQT ligands using RDKit and meeko; (3) created a Vina configuration file with validated binding site parameters; (4) ran Vina docking calculations in parallel; and (5) automatically parsed docking score tables and made consolidated comma-separated value (CSV) result files.

Re-docking experiments were conducted with the respective native ligands to validate the docking protocol and ensure that the specified binding site coordinates accurately identified the known binding pocket of each target protein. The native ligands employed for validation included Testosterone (CID: 6013) for ANDR, Estradiol (CID: 5757) for ESR1, 1,4-diaminopropane-carboxylic acid (1,4-DPCA; CID: 459803) for HIF1A, and parthenolide (CID: 6473881) for NFKB1.

2.4.5. Interaction Analysis and Visualization

We used UCSF ChimeraX version 1.11 for 3D inspection and LigPlot+ version 2.3.1 for 2D diagrams to do interaction analysis and visualization [14,17]. The hbonds command in ChimeraX, with interSubmodel enabled, was used to find hydrogen bonds between receptors and ligands. The standard geometric criteria were: donor-acceptor distance ≤ 3.5 Å (tolerance 0.4 Å) and donor-H-acceptor angle ≥ 120° (tolerance 20°). Using the clashes command with an overlap tolerance of 0.6 Å and an H-bond overlap reduction of 0.4 Å, we found hydrophobic contacts. We used LigPlot+ version 2.2 to make secondary 2D interaction diagrams. We sent receptor-ligand complex PDB files

(MODEL 1) to LigPlot+ so that it could automatically find hydrogen bonds and hydrophobic contacts with a cutoff of 3.9 Å. We used LigPlot+ outputs to make 2D interaction maps and ChimeraX outputs to make 3D interaction maps.

2.5. Jamu Formulation Scoring

A multi-criteria scoring framework was developed to rank medicinal plants for stamina-related jamu formulations by integrating ethnopharmacological usage frequencies, experimental bioactivity (pChEMBL), and molecular docking affinities. Tendency Score (TS) quantifies the ethnopharmacological specificity of plant *p* for category *c* as the proportion of its producer frequency attributed to that category:

$$TS(p,c) = \frac{FREQ_c(p)}{\sum_c FREQ_c(p)}$$

Bioactivity Score (BAS) was computed at the compound level by combining normalized pChEMBL ($\hat{Q}$) and normalized docking affinity ($\hat{D}$), weighted by a Target Relevance Score (TRS) reflecting the biological importance of each protein target for category *c*:

$$BAS(i,t,c) = \frac{\hat{Q}(i) + \hat{D}(i)}{2} \times TRS_{t,c}$$

Both $\hat{Q}$ and $\hat{D}$ were rescaled to [0,1] prior to integration. TRS were assigned based on justification in **Table 2** and value given in Table 2. BAS was then aggregated to the plant level by summing across all compounds and targets derived from plant *p*:

$$BAS_{plant}(p,c) = \sum_{i \in C(p)} \sum_{t \in T(i)} BAS(i,t,c)$$

Jamu Formulation Score (JFS) integrates all components, additionally weighted by normalized ethnopharmacological prominence ($\hat{f}_s$):

$$JFS(p,c) = TS(p,c) \times BAS_{plant}(p,c) \times \hat{f}_s(p)$$

where $\hat{f}_s(p) = \frac{final_score(p)}{\max(final_score)}$. Plants without compound data received a penalty factor of 0.3. Plants were then ranked by JFS per category and selected under a maximum of two plants per botanical family to ensure phytochemical diversity.

Table 2. Target Relevance Score (TRS) value

Protein	TRS _{male}	TRS _{female}	TRS _{general}
ANDR	1.00	0.10	0.40
ESR1	0.10	1.00	0.40
HIF1A	0.70	0.70	1.00
NFKB1	0.80	0.70	0.90

2.6. Statistical Analysis

Selection of the 41 priority plants was based on a non-parametric threshold using the Tukey upper fence ($Q1 + 1.5 \times IQR$) applied to the distribution of final scores. Given the strongly right-skewed distribution (median = 5.6; threshold = 5.5), this method provided a robust cutoff without imposing distributional assumptions. Docking affinities for the 31 ligand–protein pairs were validated against the affinities of their respective reference ligand–protein complexes (testosterone–ANDR: –6.30; estradiol–ESR1: –8.16; 1,4-DPCA–HIF1A: –6.21; parthenolide–NFKB1: –4.42).

Distributional differences in JFS across formulation categories were assessed using the Wilcoxon rank-sum test for pairwise comparisons and the Kruskal–Wallis’s test for overall group differences. The statistical significance of top-ranked plants was evaluated by permutation testing (10,000 iterations), where observed JFS sums were compared against a null distribution generated by random sampling. Convergence between experimental and

computational evidence was evaluated using Spearman's rank correlation between BAS derived from pChEMBL alone and BAS integrating docking affinity, providing a measure of consistency and cross-validation between the two data sources.

3. Results

3.1. Compound Acquisition

The KNApSack Jamu Database contains 5310 formulation involving 550 medicinal plants curated from more than 7000 commercial jamu products in Indonesia [9]. From this collection, 368 products included the keyword “sehat” or “healthy”, indicating formulations marketed for health maintenance, physical well-being, or stamina enhancement. Within this subset, 103 products contained male-specific keywords (e.g. “lelaki”, “pria”, “Jantan”, “perkasa”), 62 contained female-specific keywords (e.g. “wanita” and “perempuan”), and 202 contained general health keywords (e.g. “raga”, “badan”, “bugar”). Product name-based selection allowed rapid inference of claimed benefits and consumer targeting in actual market in Indonesia. Screening process successfully identified 41 priority plants from 26 families that associated with 2246 curated KNApSack compounds. Druglikeness and ADMET filtering, followed by similitary-based filtering, further depleted the list to 30 candidate compounds. The overall compound acquisition process is shown in **Figure 1**.

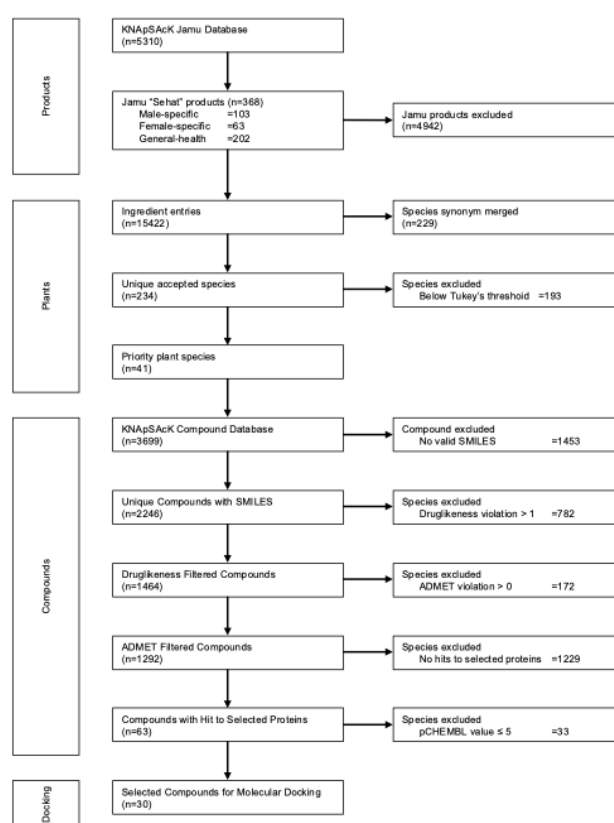


Figure 1. Compound acquisition workflow

pChEMBL-based compound-protein matching critically defined ligands and molecular targets for molecular docking. This step led to the exclusion of IL6R and IGF1R, despite being initially identified as shared targets through GeneCards (**Figure 2**), due to the absence of matching compounds in the curated dataset. In contrast, ANDR and ESR1, which were manually included, resulted in multiple compound matches. This outcome supports the effectiveness of compound acquisition in capturing sex-specific, stamina-related compounds. This interpretation is further supported by pathway enrichment analysis, which corroborated key stamina and endurance biological

pathways, including SUMOylation of intracellular receptors, nuclear receptor transcription pathways, transcriptional regulation by VENTX, deubiquitination processes, and cellular responses to stress (**Figure 3**). Collectively, these findings confirm that the selected targets are mechanistically relevant to the biological roles of human stamina as summarized in Table 3.

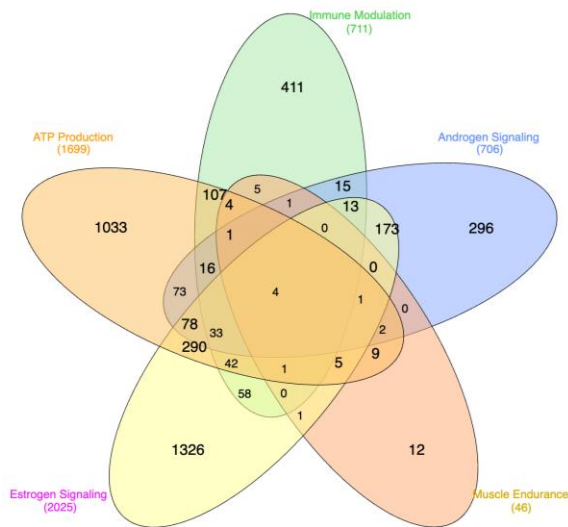


Figure 2. Venn diagram of shared stamina-related target proteins.

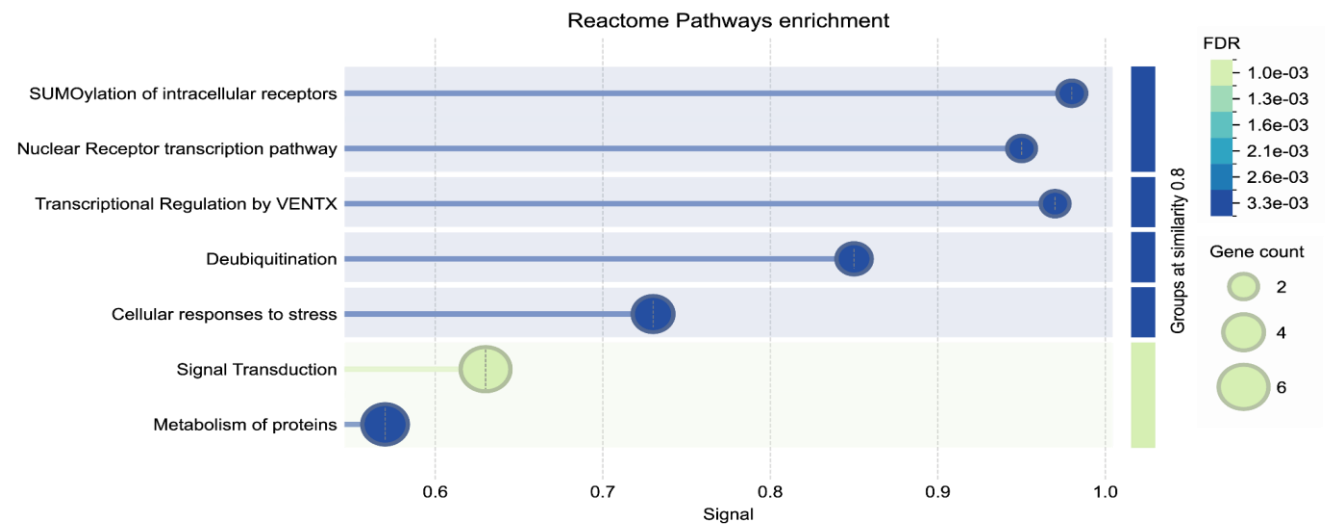


Figure 3. Reactome pathway enrichment of shared stamina-related target proteins.

Table 3. Shared stamina-related target proteins.

No	Protein Name (Gene)	UniProt Entry	Justification
1	Androgen receptor (ANDR)	P10275	Included manually because it is associated with stamina in males [23] and was matched to at least one ligand in the compound set.
2	Estrogen receptor (ESR1)	P03372	Included manually because it is associated with stamina in females [24] and was matched to at least one ligand in the compound set.
3	Hypoxia-inducible factor 1-alpha (HIF1A)	Q16665	Identified as a shared protein through GeneCards, involved in regulating metabolic pathways related to energy production and expenditure [3].
4	Nuclear factor NF-kappa-B p105 subunit (NFKB1)	P19838	Identified as a shared protein through GeneCards, involved in controlling the balance between glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) [25].
5	Interleukin-6 receptor subunit alpha (IL6RA)	P08887	Identified as a shared protein through GeneCards but excluded because it had no ligand matches from the compound list.
6	Insulin-like growth factor 1 receptor (IGF1R)	P08069	Identified as a shared protein through GeneCards but excluded because it had no ligand matches from the compound list.

3.2. Distribution of Plant Parts and Species Across Stamina-Related Claims Jamu

3.2.1. Distribution of Plant Parts Used

Distribution of plant parts from 272 entries exhibited nine plant parts used in stamina-related jamu. Leaves, fruits, roots, and rhizomes representing the largest number of species. Distribution of plant parts is shown in **Figure 4**.

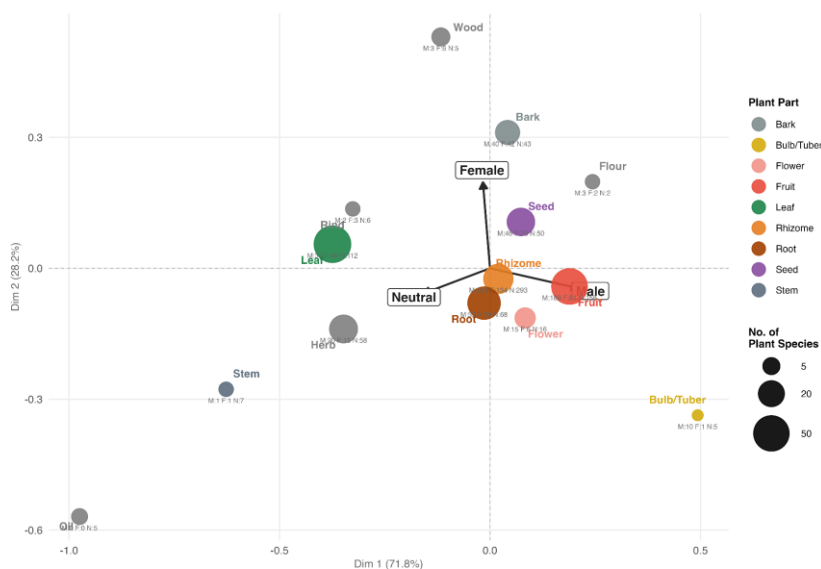


Figure 4. Correspondence analysis plot of plant parts used across stamina-related claims jamu.

3.2.2. Distribution of Plant Species Used

The species distribution of 234 unique plant species indicated several usage patterns. Species from the Zingiberaceae family occurred in general health jamu and extended to the male-specific category. In contrast, species from the Piperaceae family appeared at both the male- and female-specific extremes, indicating that certain plant families cannot be claimed based on specific empirical usage. These patterns highlight the need for molecular screening to obtain more accurate evidence of usage of specific species or families. The distribution of species is shown in **Figure 5**.

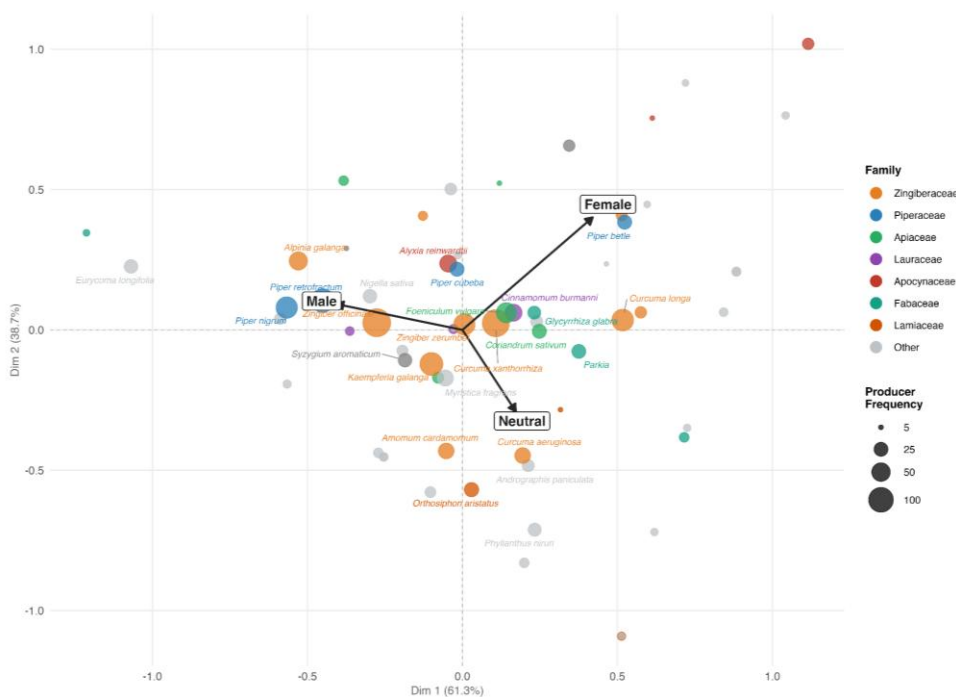


Figure 5. Correspondence analysis plot of plant species and families used across stamina-related claims jamu.

3.3. Core Species and Core Compounds

Compound acquisition and filtering resulting in 30 bioactive compounds with potential activity against four stamina-associated protein targets. These compounds were derived from 10 different plant species and families,

highlighting the distribution of diverse plants with distinct phytochemical profiles. A detailed relationship between compounds and corresponding plant species and families is presented in **Figure 6**.

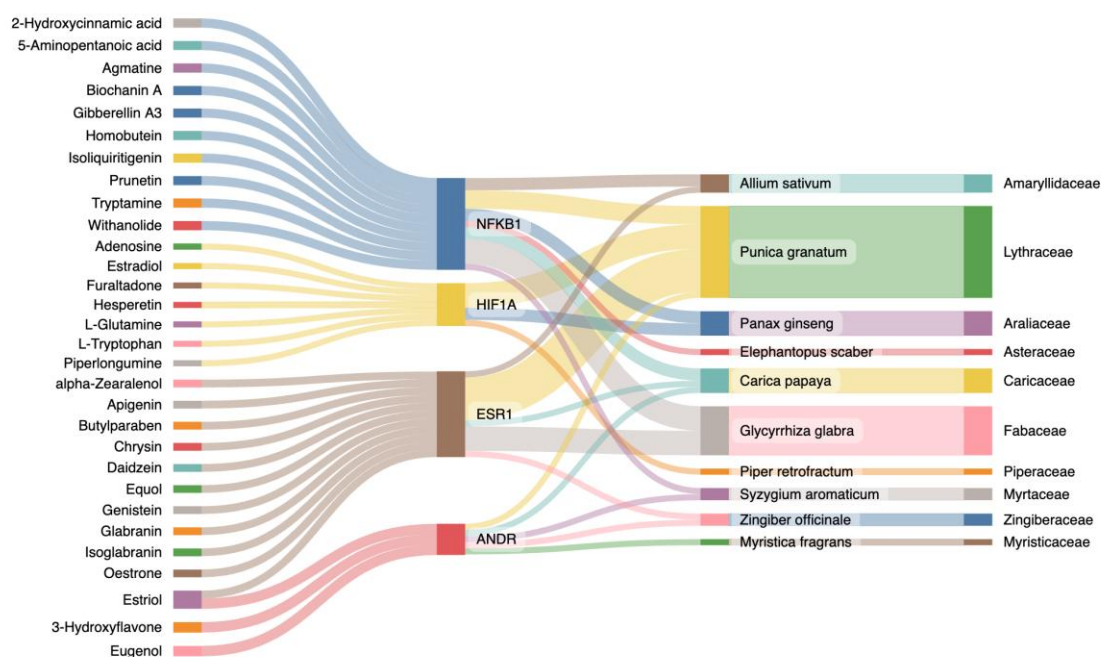


Figure 6. Relationship between core compounds, protein targets, source species and families.

Table 4. Comparison of Ethnobotanical Prominence and Core-Compound Richness.

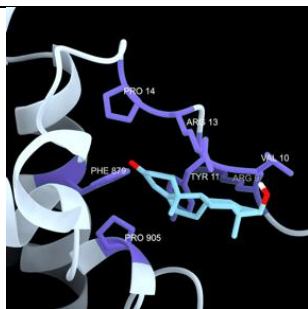
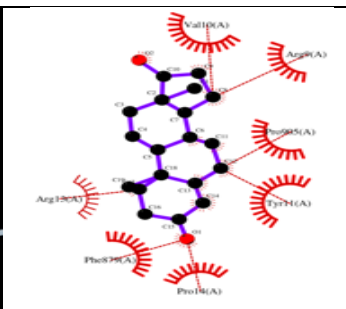
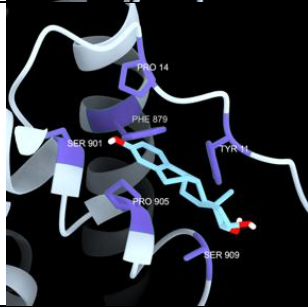
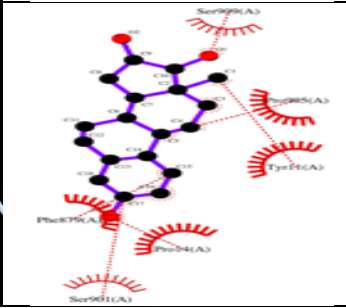
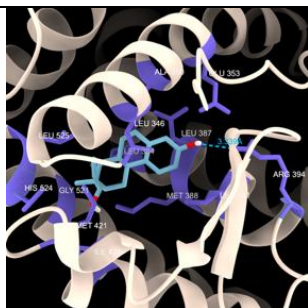
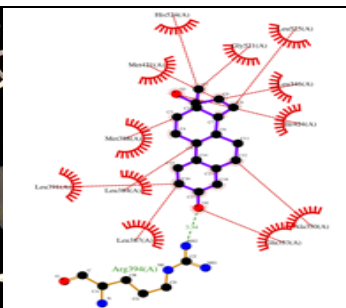
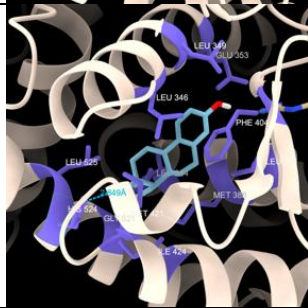
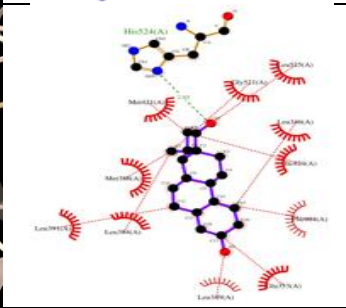
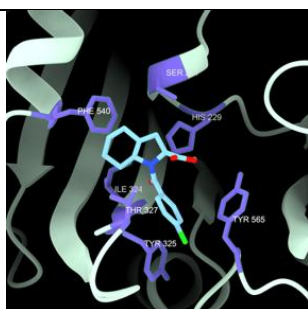
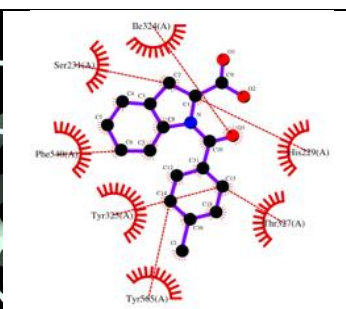
Plant Name	Final Score	Number of Compounds	Plant Name
<i>Zingiber officinale</i> *	93.1	15	<i>Punica granatum</i>
<i>Curcuma xanthorrhiza</i>	86.8	8	<i>Glycyrrhiza glabra</i>
<i>Piper retrofractum</i> *	63.0	4	<i>Carica papaya</i>
<i>Kaempferia galanga</i>	58.8	4	<i>Panax ginseng</i>
<i>Piper nigrum</i>	50.0	3	<i>Allium sativum</i>
<i>Foeniculum vulgare</i>	43.3	2	<i>Syzygium aromaticum</i>
<i>Alyxia reinwardtii</i>	29.0	2	<i>Zingiber officinale</i> *
<i>Cinnamomum burmanni</i>	28.7	1	<i>Myristica fragrans</i> *
<i>Myristica fragrans</i> *	26.4	1	<i>Piper retrofractum</i> *
<i>Orthosiphon aristatus</i>	19.2	1	<i>Elephantopus scaber</i>

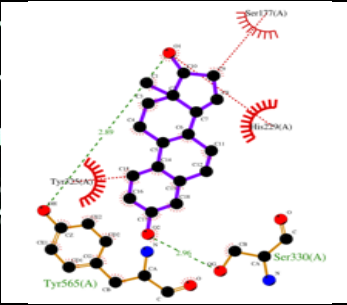
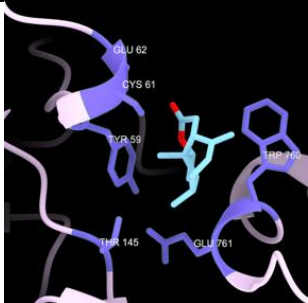
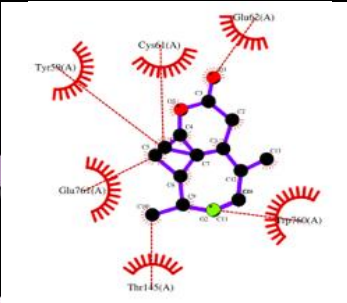
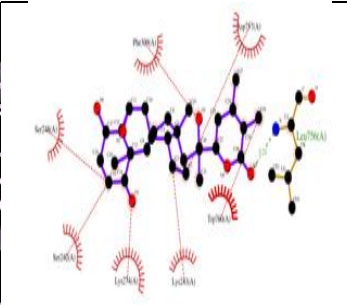
* Plants appear in both the frequency-based ranking and the core-compound ranking.

3.4. Molecular Docking Analysis

Molecular docking was performed on 31 pairs of compounds and protein targets. Multi-ligand multi-target docking exhibits binding poses consistent with the respective reference ligand, indicating potential similarity of molecular activity dynamics. The detailed results are reported in **Table 5** and **Table S1**.

Table 5. Docking Poses and Binding Affinities of Top-Scoring and Reference Compounds.

Compound	pChEMBL	Affinity	Hydrogen Bond(s) Non-Bonded Contact(s)	2D Pose	3D Pose
Androgen Receptor (ANDR)					
Testosterone*	N/A	-6.30	N/A PRO 905, PHE 879, PRO 14, ARG 13, TYR 11, VAL 10, ARG 9		
Estriol	9.32	-6.63	N/A SER 909, PRO 905, SER 901, PHE 879, PRO 14, TYR 11		
Estrogen Receptor (ESR1)					
Estradiol*	N/A	-8.16	ARG 394 LEU 525, HIS 524, GLY 521, ILE 424, MET 421, LEU 391, MET 388, LEU 387, LEU 384, GLU 353, ALA 350, LEU 346		
Oestrone	9.15	-9.45	HIS 524 LEU 525, HIS 524, GLY 521, ILE 424, MET 421, PHE 404, LEU 391, MET 388, LEU 384, GLU 353, LEU 349, LEU 346		
Hypoxia-inducible factor 1-alpha (HIF1A)					
1,4-DPCA*	N/A	-6.21	N/A TYR 565, PHE 540, THR 327, TYR 325, ILE 324, SER 231, HIS 229		
Estradiol	5.80	-7.39	TYR 565, SER 330		

			TYR 565, SER 330, TYR 325, HIS 229, SER 177		
Nuclear factor NF-kappa-B p105 subunit (NFKB1)					
			N/A		
Parthenolide*	N/A	-4.42	GLU 761, TRP 760, THR 145, GLU 62, CYS 61, TYR 59		
			LEU 756		
Withanolide	7.44	-7.66	TRP 760, ASP 757, LEU 756, PHE 309, LYS 274, SER 248, LYS 243, SER 242		

* : Reference ligand
N/A : Not applicable

3.5. Jamu Formulation Score

The Jamu Formulation Score (JFS) demonstrated significant discriminatory ability in evaluating plant candidates for male-specific, female-specific, and general health applications, yielding distinctly differentiated top-ranking profiles (Table 4). Statistical analyses substantiated the framework's robustness and biological significance. The absence of a statistically significant difference between male and female JFS distributions ($p = 0.108$) suggests considerable functional overlap, aligning with the common adaptogenic characteristics of numerous phytochemicals. In contrast, the general health category was markedly different from both male ($p = 0.0016$) and female ($p < 0.001$) groups, with the Kruskal–Wallis test validating overall separation ($p < 0.001$), indicating that generalized formulations represent a unique bioactivity landscape. Permutation testing further substantiated that the prioritization was not influenced by random variation, as all top-ranked plants significantly surpassed null expectations ($p < 0.001$). Also, the strong and statistically significant correlation between bioactivity-only scores and integrated scores ($p = 0.900$, $p = 0.037$) shows that docking-derived metrics are very consistent with experimental data and also make it easier to tell the difference between them. All of these results together show that JFS is a strong, biologically based framework for the rational design of herbal formulations.

Table 4. Jamu Formulation Score (JFS) segregates plant candidates according to their potential as ingredients for male-specific, female-specific, and general health claims in jamu formulations.

Rank	Male-specific		Female-specific		General Health	
	Plant	Score	Plant	Score	Plant	Score
1	<i>Zingiber officinale</i>	0.228	<i>Punica granatum</i>	0.126	<i>Piper retrofractum</i>	0.035
2	<i>Piper retrofractum</i>	0.162	<i>Curcuma xanthorrhiza</i>	0.072	<i>Kaempferia galanga</i>	0.024
3	<i>Piper nigrum</i>	0.132	<i>Glycyrrhiza glabra</i>	0.064	<i>Curcuma xanthorrhiza</i>	0.018
4	<i>Alpinia galanga</i>	0.120	<i>Foeniculum vulgare</i>	0.060	<i>Piper nigrum</i>	0.018
5	<i>Foeniculum vulgare</i>	0.078	<i>Curcuma domestica</i>	0.054	<i>Andrographis paniculata</i>	0.000

4. Discussion

The ethnobotanical patterns in **Figures 4** and **5** show that traditional jamu formulations have different plant-part and species preferences for claims about men's health, women's health, and general health. Formulations associated with males were primarily connected to the fruits and flowers of aromatic species, which are typically abundant in volatile compounds, alkaloids, and essential oils. These components may facilitate traditional applications pertaining to vitality, alertness, and energy regulation [2,22]. In contrast, formulations associated with females were more closely linked to seeds and bark, which are often rich in phenolics, phytoestrogens, and other metabolite-dense compounds related to hormonal and anti-inflammatory activities [23–26]. General-health formulations exhibited diminished plant-part specificity, aligning with the extensive utilization of leaves and rhizomes as versatile remedies [27–31]. These patterns indicate that conventional plant selection is not random. The correspondence analysis seems to show a real difference between plant organs with different phytochemical profiles instead. The compound–target–species network in **Figure 6** supports this interpretation by showing that flavonoid and phenolic compounds are strongly linked to ESR1 and NFKB1. These targets pertain to estrogen signaling and inflammatory regulation, respectively [7,8,32–35], indicating that plant-part differentiation may align with specific molecular functions. On the other hand, compounds from more general plant sources had more interactions with targets but were less specific. This is in line with their role in general health formulations.

The choice of target proteins was based on an analysis of the overlap of pathways related to stamina (**Figure 2**). IL6RA, IGF1R, HIF1A, and NFKB1 were first found to be proteins that are common to important physiological areas. IL6RA and IGF1R were not included because there were no ligand matches in the filtered compound dataset, which meant they couldn't be used for docking analysis. ANDR and ESR1 were subsequently incorporated to signify sex-related hormonal regulation [19,20], culminating in four definitive docking targets: HIF1A, NFKB1, ANDR, and ESR1. Reactome pathway enrichment (**Figure 3**) backed up this choice by showing that it was enriched in pathways for nuclear receptor transcription, intracellular receptor regulation, cellular stress response, and protein regulation [18]. These findings collectively substantiate the biological significance of the chosen targets for stamina-related mechanisms [3,19–21]. We used docking analysis to make these target–compound relationships better. To avoid relying too much on docking score alone, docking affinity was looked at along with pChEMBL values. This is important because strong docking doesn't always mean biological activity, and pChEMBL gives more support from known bioactivity data [14,15,36].

Of the four targets, ESR1 had the strongest and most stable interaction profile. Oestrone exhibited a greater binding affinity compared to the reference ligand estradiol (–9.45 vs –8.16 kcal/mol). Furthermore, additional ESR1-associated compounds listed in Supplementary Table 1 indicated a more extensive phytoestrogen-like interaction pattern. Several of these compounds interacted with critical ESR1 binding-site residues, including ARG394 and GLU353, indicating their compatibility with the standard estrogen receptor binding environment. ESR1 plays a role in mitochondrial function, substrate utilization, fatty acid oxidation, and protection against oxidative stress. Interactions related to ESR1 may enhance metabolic efficiency and resistance to fatigue [7,8,32,33]. Nonetheless, these findings must be regarded as indicative of structural plausibility rather than direct evidence of estrogenic activity [14,15,36]. ANDR exhibited a more constrained interaction profile. Estriol was the primary compound meeting both potency and docking criteria, exhibiting a binding affinity marginally superior to that of the testosterone reference ligand (–6.63 vs –6.30 kcal/mol), whereas other ANDR-associated compounds demonstrated

inferior binding. This indicates that androgen-mediated anabolic pathways may play a role in the overall mechanism, but they are unlikely to be the primary factor driving the anticipated stamina-related activity [5,6,37].

Estradiol and hesperetin exhibited the most pertinent docking profiles for HIF1A, with affinities that are comparable to or exceed the reference ligand 1,4-DPCA (−7.39 and −6.28 vs −6.21 kcal/mol). HIF1A is involved in sensing low oxygen levels, controlling glycolysis, forming new blood vessels, and keeping oxygen levels stable. These interactions may help the body adapt its metabolism during long periods of physical activity [3,38–40]. HIF1A seems to be a supportive target rather than the main axis in the predicted mechanism. NFKB1 exhibited a unique interaction profile, with withanolide demonstrating superior binding affinity compared to the reference ligand parthenolide (−7.66 vs −4.42 kcal/mol). Gibberellin A3, homobutein, and isoliquiritigenin were some of the other compounds that had moderate interactions. NFKB1-related compounds may enhance stamina by modulating inflammatory signaling, oxidative stress responses, and recovery processes associated with exercise-induced inflammation and post-exertional recovery [4,34,35,41,42]. This mechanism enhances the metabolic functions of ESR1 and HIF1A.

The patterns of interaction at the residue level further support target-specific binding behavior (**Table 5**). ESR1 interactions were defined by polar anchoring residues like ARG394 and GLU353, which is in line with an estrogen-like binding orientation. ANDR seemed to rely more on hydrophobic and steric compatibility. This was especially true for PRO905, PHE879, PRO14, and TYR11, which made non-bonded contacts with each other over and over again. This may be why fewer compounds showed strong binding to this target. HIF1A had both polar and aromatic contacts, especially around TYR565, TYR325, and HIS229. This is in line with a binding environment that can hold structurally different ligands that are involved in regulating hypoxia. NFKB1 had a more flexible interaction landscape, with contacts spread out around residues like TRP760, GLU761, LEU756, ASP757, and SER242. This made it possible for structurally complex compounds like withanolide to bind well. These patterns show that docking affinity alone should not be used to rank compounds. Instead, the structure of the ligand and the characteristics of the binding site should also be taken into account.

These molecular patterns elucidate the necessity for plant prioritization to incorporate both traditional prominence and compound-level representation. **Table 4** compares plants with high ethnobotanical final scores to plants with high numbers of core compounds. This shows whether traditional frequency matches phytochemical richness. Some plants, like *Zingiber officinale*, *Myristica fragrans*, and *Piper retrofractum*, did well on both the final score and the compound count. This means that the ethnobotanical importance and the phytochemical representation were in agreement. *Curcuma xanthorrhiza* and *Kaempferia galanga*, on the other hand, had high final scores but lower core-compound representation. This means that just because a plant is used a lot in traditional medicine doesn't mean it has a lot of different chemicals. On the other hand, *Punica granatum* had a lot of different compounds, even though it wasn't used as much in traditional medicine. This shows that it has a lot of potential for mechanistic use, even when it isn't as well-known in culture. These results demonstrate that traditional use and phytochemical richness reflect distinct yet complementary facets of candidate prioritization [14,15].

The Jamu Formulation Score (JFS) combines ethnopharmacological specificity, compound-level bioactivity, docking affinity, and plant-level prominence into one system for ranking things. The ranking pattern in **Table 7** shows that this framework can tell the difference between male-specific, female-specific, and general-health formulation candidates. The non-significant difference between male- and female-specific JFS distributions indicates a partial overlap in the phytochemical foundation of sex-targeted formulations, aligning with the dual-use characteristics of numerous anti-inflammatory, adaptogenic, and hormone-modulating compounds [4,7,8,32,33,35]. Conversely, the notable distinction of general-health formulations from both male- and female-specific categories indicates that general stamina assertions are underpinned by a more extensive and less sex-specific phytochemical profile. The statistical validation bolsters this interpretation. Permutation testing demonstrated that the highest-ranked plants were improbable to occur by chance. Additionally, the robust correlation between BAS derived from pChEMBL alone and BAS integrating docking affinity suggests a concordance between bioactivity and docking-based evidence. These results support the idea that JFS is better as an integrative prioritization tool than as a simple ranking based on frequency. Overall, the results support a multi-level model of stamina enhancement. In this model, traditional jamu use finds culturally relevant plant candidates, compound filtering finds drug-like phytochemicals, docking gives structural support for target engagement, and JFS combines

these levels into formulation-level prioritization. The most robust predicted mechanistic signals indicate ESR1-mediated metabolic regulation, HIF1A-associated hypoxia adaptation, and NFKB1-related inflammation control, with ANDR having a more restricted function.

The comparison of the JFS ranking with the Final Score and core-compound richness in **Tables 4** and **6** shows that the prioritization layers were somewhat similar but not the same. The highest JFS-ranked plants in the male-specific category were also among the top plants based on Final Score, which means that *Zingiber officinale*, *Piper retrofractum*, *Piper nigrum*, and *Foeniculum vulgare* were all in agreement with the Final Score ranking. The same thing happened in the general health category, where *Piper retrofractum*, *Kaempferia galanga*, *Curcuma xanthorrhiza*, and *Piper nigrum* were all on both the JFS ranking and the upper Final Score list. This overlap indicates that, for male-specific and general health claims, prioritization at the formulation level was generally aligned with prioritization at the plant level. But this relationship wasn't always the same in every category. In the female-specific category, *Punica granatum* and *Glycyrrhiza glabra* were highly ranked in JFS and were included among the core-compound-associated plants. However, they were not among the plants with the highest Final Score. This pattern suggests that they put more weight on the relevance of the formulation at the compound level and for each claim than on the overall frequency of ethnobotany. Consequently, JFS ought not to be construed as a direct replication of either the Final Score ranking or the core-compound ranking. Instead, it picks up a formulation-level signal that combines claim specificity, formulation context, plant occurrence, and compound relevance. The observed pattern is best understood as partial concordance rather than complete consistency: the rankings generally align when high-JFS plants also have strong Final Scores, but differences occur because each scoring layer represents a different level of evidence.

These results must be understood in light of the constraints inherent in an in-silico study. Docking analysis substantiates structural compatibility yet fails to validate receptor activation, biological efficacy, or modulation of downstream pathways [14,15,36]. Target prediction and pChEMBL-based filtering rely on accessible database annotations, whereas static docking models inadequately represent protein flexibility, metabolism, bioavailability, or in vivo pharmacological responses. Consequently, the identified compounds and plant candidates remain theoretical and necessitate experimental validation; however, they offer a logical foundation for the selection of Indonesian jamu candidates for forthcoming pharmacological and formulation studies.

5. Conclusions

This study presents a robust integrative pipeline that combines ethnopharmacological evidence with computational pharmacology to systematically identify candidate natural products for athletic stamina enhancement. By leveraging large-scale jamu data, pharmacognostic scoring, and multivariate correspondence analysis, the study successfully prioritized plant species with both high traditional relevance and claim specificity. Subsequent in-silico filtering, target prediction, and molecular docking refined these candidates to a focused set of bioactive compounds with favorable drug-like properties and meaningful interactions with key physiological targets. Based on the JFS rankings, *Zingiber officinale* (male-specific) and *Punica granatum* (female-specific) are prioritized for immediate in vivo endurance model validation, with *Piper retrofractum* recommended for general health models. These findings provide a rational foundation for future experimental validation and modern jamu formulation development.

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