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NETWORK PHARMACOLOGY OF CYPERUS ROTUNDUS ESSENTIAL OIL: MECHANISTIC BASIS OF ITS EFFECT ON THE ANDROGEN SIGNALING AXIS

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ABSTRACT

Cyperus rotundus L. (Cyperaceae) rhizome essential oil is a sesquiterpene-rich natural product with a long history of traditional use against unwanted, androgen-driven hair growth. This article synthesizes published network pharmacology, molecular docking, and phytochemical evidence to explain the mechanistic basis of the oil's action on the androgen signaling axis. Note on terminology: the literature supports an anti-androgenic action — primarily 5α-reductase inhibition — rather than an androgen-boosting one; "androgenic effect" is used throughout to mean the oil's interaction with, and dampening influence on, this signaling pathway. Compound-target network construction, protein-protein interaction (PPI) mapping, and docking studies converge on 5α-reductase (SRD5A1/SRD5A2) as the primary hub target, with sesquiterpene constituents such as cyperene, α-humulene, and β-selinene showing favorable predicted binding. Secondary, inflammation-linked hub proteins (IL-6, TNF, PTGS2, STAT3) suggest an additional indirect route of action. The evidence base remains largely computational and preclinical, and clinical validation is still needed.

1. INTRODUCTION

Cyperus rotundus L., known commonly as nutgrass or purple nutsedge, is among the most extensively studied medicinal plants worldwide, with documented use in Ayurveda, Traditional Chinese Medicine, and Unani practice for gynecological complaints, digestive disorders, inflammation, and unwanted hair growth. Its rhizome yields an essential oil dominated by sesquiterpenes and monoterpenes, a chemical profile underlying a strikingly broad pharmacological footprint: antibacterial, anti-inflammatory, antioxidant, anticancer, antidiabetic, neuroprotective, and anti-androgenic activities have all been reported for extracts or the oil itself.

Among these, the anti-androgenic property carries particular clinical relevance. Excess androgen signaling — whether from elevated circulating hormone or heightened tissue sensitivity mediated by the androgen receptor (AR) and 5α-reductase-driven dihydrotestosterone (DHT) production — underlies conditions including hirsutism, androgenetic alopecia, acne, and benign prostatic hyperplasia. Network pharmacology, a systems-level approach integrating compound-target prediction, PPI network construction, and pathway enrichment, offers a way to reconstruct how a multi-component oil such as *C. rotundus* essential oil (CREO) might act on this axis — a mechanistic layer that classical single-target pharmacology cannot provide alone.

Objective: This article aims to (i) summarize the phytochemical basis of CREO's reported anti-androgenic activity, (ii) describe the network pharmacology and docking methodology used to investigate this activity, (iii) present the resulting target and pathway findings, and (iv) critically discuss their mechanistic and translational implications.

2. METHODS

2.1 Literature and Data Sources

Relevant studies were identified through the biomedical and phytochemical literature (PubMed, ScienceDirect, Springer, ResearchGate, and related sources), covering GC-MS profiling of CREO, network pharmacology analyses of *C. rotundus* extracts, and molecular docking studies targeting 5α-reductase and related enzymes.

2.2 Compound Identification

Constituents of CREO were catalogued from gas chromatography and GC-MS profiling studies conducted across multiple geographic sources (India, China, Tunisia, Algeria,

Nigeria, Egypt), which vary in relative composition but consistently identify a sesquiterpenoid-dominant oil.

2.3 Compound-Target Network Construction

The reported network pharmacology pipeline for this plant follows these steps:

- ADME / drug-likeness screening — filtering the constituent list using absorption, distribution, metabolism, and excretion criteria (typically via SwissADME) to retain compounds likely to be bioactive when applied topically or taken orally.
- Target prediction — mapping each retained compound to probable protein targets using SwissTargetPrediction, the Similarity Ensemble Approach (SEA), STITCH, or PharmMapper.
- Disease/pathway target collection — retrieving androgen-pathway-relevant genes from GeneCards, DisGeNET, or OMIM, covering AR signaling and the 5α-reductase isoenzymes (SRD5A1/SRD5A2).
- Network construction — building compound–target and protein–protein interaction (PPI) networks using STRING and Cytoscape, then ranking hub proteins by degree, betweenness, and closeness centrality.
- Enrichment analysis — GO and KEGG pathway enrichment to contextualize hub targets within broader signaling networks.

2.4 Molecular Docking

Top-ranked compounds were docked against hub protein crystal/model structures — principally 5α-reductase type 2 and, in comparator studies on related plants, the AR ligand-binding domain — using tools such as AutoDock/PyRx, with binding free energies (kcal/mol) used as the primary comparison metric against reference inhibitors (e.g., finasteride, dutasteride). Selected studies extended this with molecular dynamics simulation (root-mean-square deviation/fluctuation analysis) to assess complex stability over time.

3. RESULTS

3.1 Phytochemical Composition

Across the sources reviewed, CREO is consistently dominated by the compound classes summarized in Table 1.

Table 1. Major chemical classes and representative constituents of C. rotundus essential oil.

Class	Representative Compounds
Sesquiterpene hydrocarbons	cyperene, α-copaene, β-selinene, δ-selinene, α-humulene, γ-murolene
Oxygenated sesquiterpenes	α-cyperone, cyperotundone, cubenol, isocyperol, nootkatone, valencene, khusinol, agarospirol
Monoterpenes	α-pinene, campholenic aldehyde, α-terpineol, trans-pinocarveol

Chemical structures. Several key constituents are illustrated below with authentic structure images sourced from PubChem/NIST references.

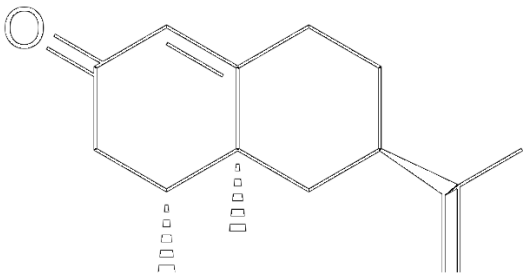

Figure 1. α-Cyperone — 2D structural depiction (source: NIST/PubChem reference image), the principal oxygenated sesquiterpenone constituent of C. rotundus rhizome oil and a compound of primary interest in its anti-androgenic activity.

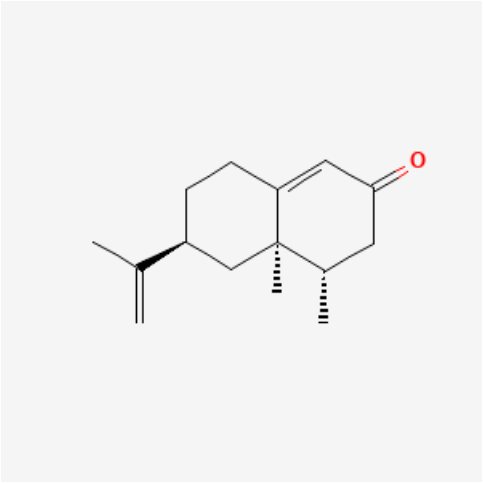

Figure 2. α-Cyperone — alternative structural rendering (PubChem), shown for cross-reference against Figure 1.

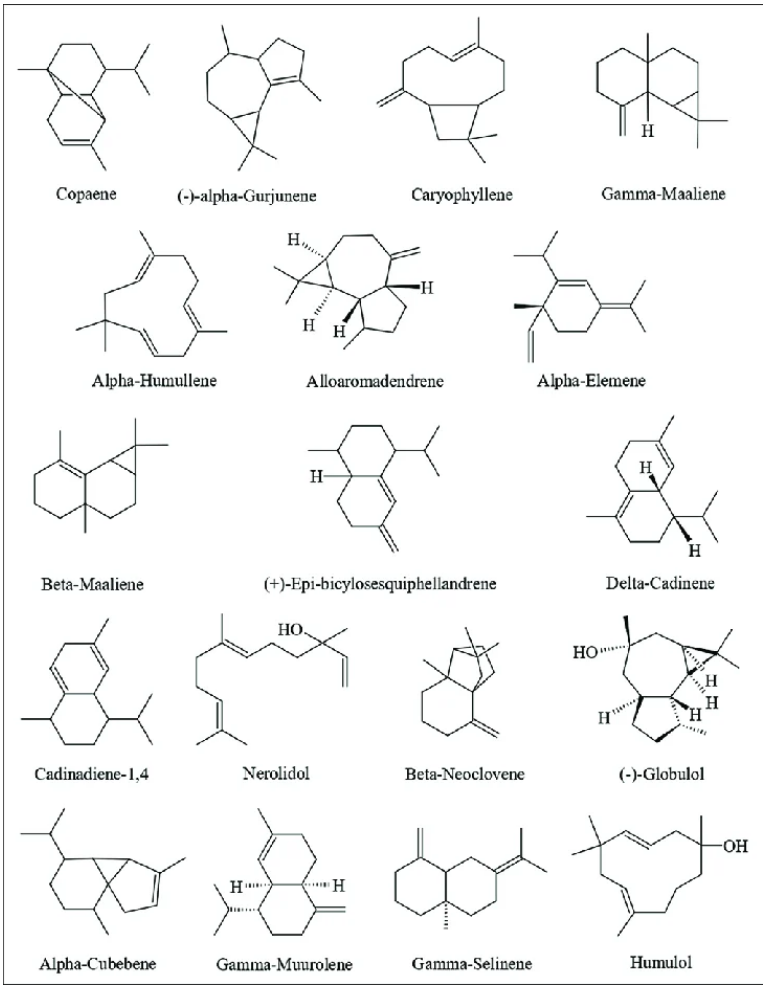

Figure 3. Structural diversity among sesquiterpene hydrocarbons and alcohols reported across plant essential oils. α-Humulene (top row, center-left), one of the sesquiterpene hydrocarbons also identified in C. rotundus oil, is shown here alongside structurally related sesquiterpenes from the broader chemical family, illustrating the skeletal diversity typical of this compound class.

Table 2 lists exact PubChem identifiers for compounds discussed in this article, allowing independent verification of the structures shown above and of additional constituents.

Table 2. PubChem identifiers for key C. rotundus oil constituents.

Compound	Formula	PubChem CID	Direct Link
α-Pinene	C10H16	6654 (racemic); 440968 ((–)-form)	pubchem.ncbi.nlm.nih.gov/compound/6654
Cyperene	C15H24	99856	pubchem.ncbi.nlm.nih.gov/compound/99856
β-Selinene	C15H24	442393	pubchem.ncbi.nlm.nih.gov/compound/442393
α-Humulene	C15H24	5281520	pubchem.ncbi.nlm.nih.gov/compound/5281520
α-Cyperone	C15H22O	6452086	pubchem.ncbi.nlm.nih.gov/compound/6452086
Nootkatone	C15H22O	1268142	pubchem.ncbi.nlm.nih.gov/compound/1268142

3.2 Predicted Targets and Network Hubs

Compound-target network construction for *C. rotundus* extracts (across inflammation, cancer, diabetes, and androgen-related studies) consistently identifies a recurring set of hub proteins. For the androgen axis specifically, the central hub is 5α-reductase (SRD5A1/SRD5A2); secondary hub proteins drawn from broader anti-inflammatory network studies on the same plant include IL-6, TNF, PTGS2 (COX-2), STAT3, PI3K, AKT, and MAPK1.

3.3 Molecular Docking Findings

Docking of CREO sesquiterpene and monoterpene constituents — including cyperene, α-humulene, β-selinene, campholenic aldehyde, and α-pinene — against the 5α-reductase enzyme structure has been reported to yield favorable binding energies, interpreted by the original authors as consistent with competitive active-site inhibition. Comparator docking studies on related sesquiterpene-bearing plants extend similar analysis to the androgen receptor ligand-binding domain, testing whether terpenoid constituents can occupy or destabilize the receptor's binding pocket.

3.4 Experimental/Translational Findings

- Topical application of CREO has been reported to reduce hair growth in tested models, attributed by study authors to 5α-reductase inhibition.
- Comparator plant-derived 5α-reductase inhibitors, such as sesquiterpene-enriched *Curcuma aeruginosa* extract, have shown efficacy against axillary hair growth in a randomized, placebo-controlled trial — supporting sesquiterpenes as a chemotype of interest for topical anti-androgenic use more broadly.

4. DISCUSSION

The convergence of network pharmacology, molecular docking, and phytochemical evidence supports a plausible anti-androgenic mechanism for *C. rotundus* essential oil centered on 5α-reductase inhibition by its sesquiterpene constituents. This mechanistic picture is consistent with, and helps rationalize, the plant's long ethnobotanical use for hirsutism and unwanted androgenic hair growth.

The secondary hub proteins identified in broader network analyses (IL-6, TNF, COX-2, STAT3) point to a second, less-explored possibility: that some of the oil's anti-androgenic phenotype in vivo may be indirect, working through reduction of local inflammation and oxidative stress in the pilosebaceous unit — both of which are known to heighten follicular sensitivity to DHT — rather than through direct enzyme inhibition alone.

Limitations. Several caveats temper these conclusions:

- Compositional variability across geographic sources means a network built from one regional oil's constituent profile may not generalize to all commercial CREO products.
- The in silico–to–in vivo gap: favorable docking scores indicate binding potential, not confirmed physiological inhibition; few studies progress to cell-free enzymatic assays or controlled clinical trials.
- Database-dependent target prediction: tools such as SwissTargetPrediction and SEA can misassign compound-target relationships in either direction.
- Polypharmacology complicates causal attribution: with dozens of terpenoids acting on multiple hub pathways simultaneously, isolating the specific contribution of 5α-reductase inhibition from anti-inflammatory or antioxidant effects requires fractionation studies that are largely still lacking.

CONCLUSION

Network pharmacology evidence to date is consistent with an anti-androgenic mechanism for *C. rotundus* oil built around 5α-reductase inhibition, with a plausible secondary anti-inflammatory contribution. However, the evidence base remains predominantly computational and preclinical. Enzymatic validation, standardized topical formulations, and controlled clinical trials are needed before this oil can be considered a validated alternative to established anti-androgens such as finasteride or spironolactone.

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