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# Simulaite Report

## Pharmacodynamic Simulation of Sphenocentrum jollyanum Mechanism Discovery

*CYP19A1 selectivity · aromatase inhibition · Tongkat Ali mechanism discovery*

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## Executive Summary

Objective: This study tested whether reported Sphenocentrum jollyanum marker compounds can explain the plant's reproductive and aphrodisiac phenotype through specific molecular targets, then benchmarked those findings against target-specific drugs and a Tongkat Ali validation benchmark.

Conclusion: The computational evidence now points away from a Viagra-like PDE5A mechanism, which would act directly on blood-flow signaling, and toward steroid-metabolism targets, which regulate how testosterone and related hormones are made or converted. In structural de-risking, pinnatasterone aligned best with the aromatase/CYP19A1 testosterone pocket, columbamine aligned best with the 5α-reductase/SRD5A2 reference pocket, and pinnatasterone's PDE5A pose scored well in molecular docking but did not match the sildenafil/tadalafil inhibitor subpocket. Short explicit-solvent MD on the PDE5A pose supported the same interpretation: the ligand remained outside the sildenafil-like reference zone over the sampled trajectory.

The Tongkat Ali benchmark gives this interpretation useful context. Run independently, the Tongkat screen matched literature-supported eurycomanone aromatase/phosphodiesterase biology while keeping direct androgen-receptor binding weak versus steroid controls; the cited literature emphasizes aromatase/phosphodiesterase rather than direct androgen-receptor activation [1,2].

The practical takeaway is an assay shortlist, not a product claim: test CYP19A1 and SRD5A2 first (pinnatasterone and columbamine), evaluate PXR/CYP induction early, and treat PDE5A as a low-priority falsification target unless biochemistry surprises.

## Study Objective

Sphenocentrum jollyanum is a West African medicinal plant with reported traditional use in male sexual-performance contexts and published reproductive animal studies [3,4,7]. Existing literature supports phenotype-level effects, including altered testosterone, aphrodisiac behavior, sperm-quality changes, and reproductive toxicity [4,7]. However, the available literature does not appear to resolve which isolated Sphenocentrum compounds interact with

specific endocrine or erectile-function targets.

This study was designed to address that gap by screening reported parent marker compounds against a focused male reproductive pharmacology panel, benchmarking the results against receptor-specific drugs, and applying structural pose de-risking so that binding scores are not interpreted as mechanism proof without reference-pocket alignment.

## Simulation Design

| Study component | Scope | Purpose |
|---|---|---|
| Sphenocentrum mechanism-discovery screen | Reported Sphenocentrum markers plus drug controls docked against AR, CYP19A1, SRD5A2, CYP17A1, PDE5A, and PXR | Identify plausible compound-target mechanisms behind reproductive and aphrodisiac phenotypes. |
| Structural pose de-risking | Co-crystal subpocket centroid distance, anchor-residue contacts, and in-class drug comparators per target | Distinguish reference-aligned poses from partial or off-pocket docking before mechanism claims. |
| PDE5A short MD check | Explicit-solvent MD of docked pinnatasterone versus static PDE5A pose quality | Test whether the docked pose drifts toward the sildenafil reference subpocket under solvation. |
| Target-specific drug comparator panel | Sildenafil, tadalafil, vardenafil, avanafil, finasteride, dutasteride, abiraterone, ketoconazole, exemestane, letrozole, anastrozole, DHT, testosterone, hyperforin, SR12813, and rifampicin | Compare plant marker binding scores and pose class to drugs selected for the relevant target class. |
| Tongkat mechanism benchmark | Tongkat Ali markers docked against aromatase/CYP19A1, PDE4D, and androgen receptor with known controls | Test whether an independent run matches established Tongkat mechanisms and avoids overclaiming direct androgen receptor binding. |

## Compound Panels

The screened Sphenocentrum marker panel included palmatine and columbamine alkaloids [4], columbin and isocolumbin furanoditerpenes [5], and 20-hydroxyecdysone and pinnatasterone ecdysteroids [6,8].

The Tongkat Ali validation panel included eurycomanone, eurycomanol, eurycomalactone, 13,21-dihydroeurycomanone, canthin-6-one, and 9-methoxycanthin-6-one, plus target-relevant controls.

## Methods Summary

Reported marker compounds were evaluated against experimentally derived target pockets. Binding scores were used as ordinal plausibility signals. Lower, more negative scores indicate a more favorable predicted pose within the target pocket.

A second structural layer classified each docked marker against the co-crystal reference ligand on that target: ligand centroid distance to the reference subpocket (<=6 Å with required anchor contacts = reference-aligned), intermediate contact with offset centroid (partial), or weak/off-pocket placement. This step is essential for large phytoactive scaffolds, which often achieve favorable docking scores without matching the binding mode of the target-class drug.

For PDE5A, docked pinnatasterone underwent short explicit-solvent MD with pocket and ligand restraints. Analysis asked whether the ligand centroid approached the sildenafil (VIA) reference subpocket over the sampled trajectory; this was a consistency check on the static pose, not long-timescale potency validation.

All conclusions should be interpreted as computational prioritization, not biochemical confirmation. The goal was to identify which target hypotheses deserve experimental follow-up first.

## Sphenocentrum Drug-Comparator Results (Docking)

| Target | Best Sphenocentrum marker (docking score) | Target-specific drug benchmark | Relative interpretation |
|---|---|---|---|
| PDE5A | pinnatasterone, -10.53 kcal/mol | tadalafil, -11.07; avanafil, -10.22; sildenafil, -9.959; vardenafil, -9.881 | Strong docking score, but structural de-risking does not support inhibitor-subpocket alignment (see below). |
| SRD5A2 | isocolumbin, -11.04 kcal/mol | dutasteride, -13.0; finasteride, -11.5 | Strong docking score; columbamine is the best reference-aligned Sphenocentrum marker on this target. |
| CYP17A1 | pinnatasterone, -9.687 kcal/mol | abiraterone, -10.48; ketoconazole, -10.36 | Favorable docking score, but poses are off the abiraterone reference pocket; treat as unreliable until re-docked. |
| Aromatase/CYP19A1 | 20-hydroxyecdysone, -9.678 kcal/mol | exemestane, -10.72; letrozole, -7.69; anastrozole, -7.125 | Moderate docking score; pinnatasterone is reference-aligned in static de-risking. |
| Androgen receptor | columbin, -9.454 kcal/mol | DHT, -11.05; testosterone, -10.93 | Direct androgen receptor binding is not the primary mechanism suggested by the model. |

| Target | Best Sphenocentrum marker (docking score) | Target-specific drug benchmark | Relative interpretation |
|---|---|---|---|
| PXR | isocolumbin, -9.997 kcal/mol | hyperforin, -9.325; SR12813, -8.587 | Safety-liability signal. PXR activation and herb-drug interaction potential should be tested early. |

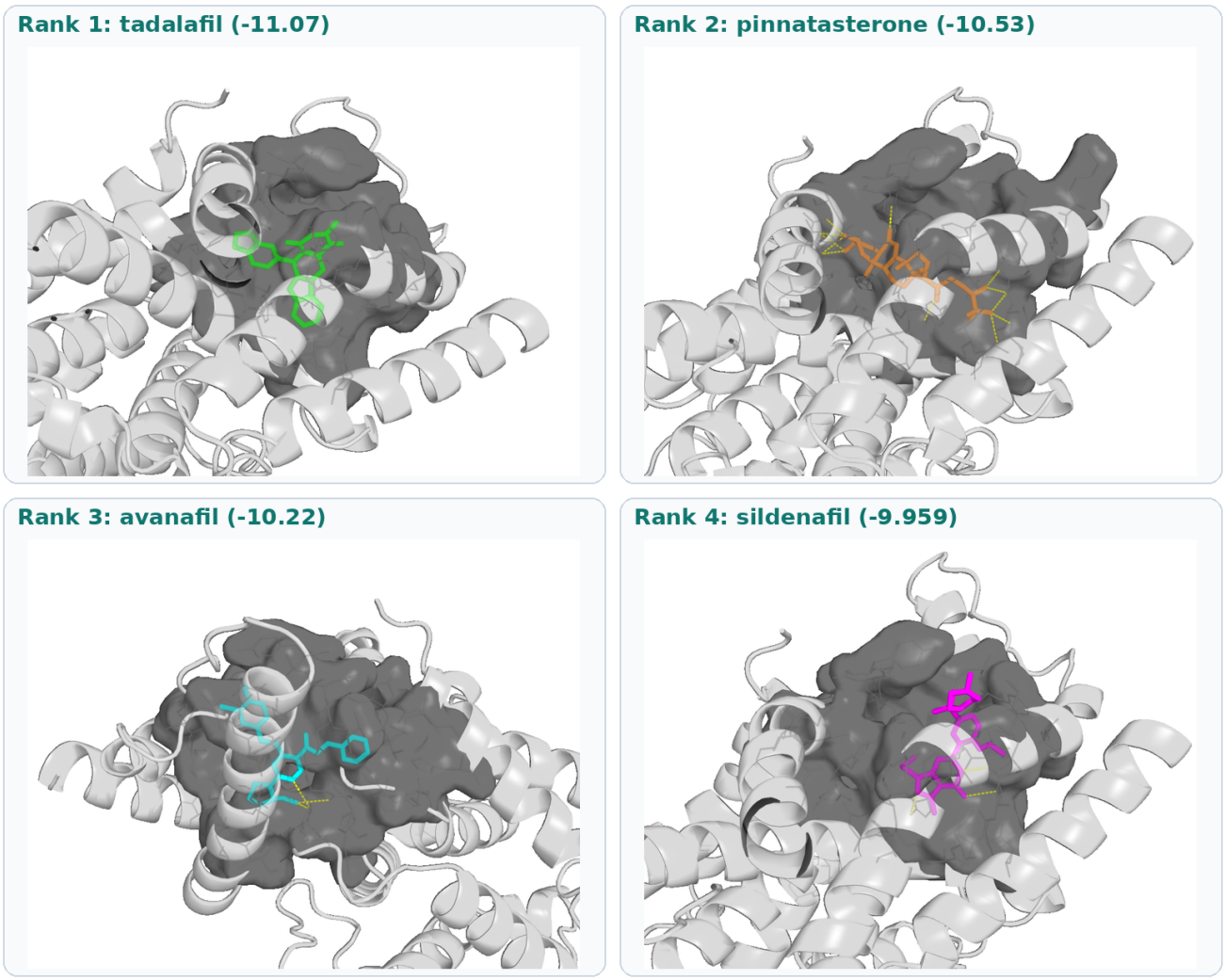
## Structural Pose De-risking

Docking scores alone can overstate herbal mechanisms when large polycyclic markers fill hydrophobic enzyme pockets without matching the co-crystal drug pose. The table below summarizes static pharmacophore de-risking for Sphenocentrum markers on the six-target panel (reference ligand: TES on AR and CYP19A1, NDX/finasteride on SRD5A2, abiraterone on CYP17A1, VIA/sildenafil on PDE5A, SR12813 on PXR).

| Target | Marker | Docking score (kcal/mol) | Distance to reference subpocket (Å) | Pose class | Assay priority |
|---|---|---|---|---|---|
| CYP19A1 | pinnatasterone | -8.969 | 2.77 | Reference-aligned | High |
| CYP19A1 | 20-hydroxyecdysone | -9.678 | 2.30 | Reference-aligned | High |
| CYP19A1 | isocolumbin | -9.423 | 2.27 | Reference-aligned | High |
| SRD5A2 | columbamine | -9.233 | 4.95 | Reference-aligned | High |
| SRD5A2 | isocolumbin | -11.04 | 6.57 | Partial | Medium (docking-led; pose caveat) |
| SRD5A2 | pinnatasterone | -10.67 | 6.47 | Partial | Medium |
| PDE5A | tadalafil (control) | -11.07 | 4.00 | Inhibitor-like | Benchmark |
| PDE5A | pinnatasterone | -10.53 | 6.22 | Partial | Low (falsification only) |
| AR | columbin | -9.454 | 0.69 | Reference-aligned | Context / secondary |
| AR | pinnatasterone | -6.701 | 2.42 | Pocket contact only | Low |
| PXR | 20-hydroxyecdysone | -9.614 | 0.55 | Reference-aligned | Safety context |
| PXR | isocolumbin | -9.997 | 3.78 | Pocket contact only | Safety |
| CYP17A1 | pinnatasterone | -9.687 | 28.8 | Partial (off-pocket) | Omit until re-docked |

Interpretation rule used in this report: reference-aligned poses support target-specific assay planning; partial poses (~6 Å from reference with some anchor contacts) support weak ordinal hypotheses only; CYP17A1 placements with very large centroid offsets are treated as docking failures, not biology.

## PDE5A Pose Comparison




*Ranked PDE5A docked-pose comparison for tadalafil, pinnatasterone, avanafil, and sildenafil.*

Molecular docking ranked pinnatasterone competitively on PDE5A, but static pharmacophore analysis placed it ~6.2 Å from the sildenafil (VIA) co-crystal centroid while retaining Gln817 and Phe820 contacts. Tadalafil met the inhibitor-subpocket criteria (~4.0 Å). Short explicit-solvent MD on docked pinnatasterone was consistent with the static result: the ligand centroid remained outside the <=6 Å VIA overlap zone over the sampled trajectory and did not show rapid entry into the reference inhibitor subpocket. PDE5A should therefore not headline the Sphenocentrum mechanism story; optional PDE5A biochemical testing remains useful only to falsify the erectile-target hypothesis.

## Primary Mechanistic Interpretation

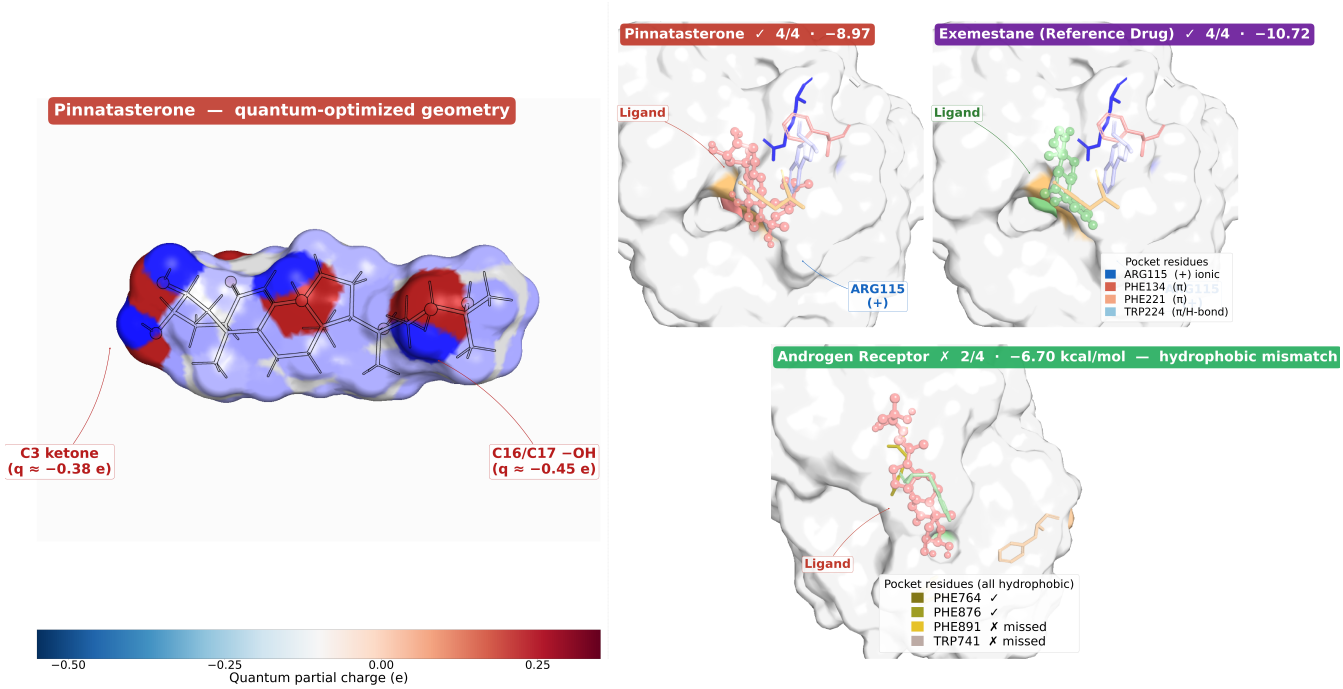
The most compelling Sphenocentrum hypothesis after de-risking is combined steroid-metabolism and endocrine-

enzyme modulation rather than direct androgen receptor agonism or PDE5A-driven erectile pharmacology.

Aromatase/CYP19A1 is the cleanest structural efficacy hypothesis for pinnatasterone. It is reference-pocket aligned (~2.8 Å from the testosterone co-crystal subpocket) with favorable anchor contacts. 20-hydroxyecdysone and isocolumbin also align on CYP19A1. This fits a testosterone-to-estrogen conversion axis upstream of receptor activation and parallels the aromatase emphasis in the Tongkat literature [1,2].

The figure below shows the quantum-computed electrostatic basis for this selectivity. Pinnatasterone carries electron-rich oxygen groups with computed partial charges of approximately −0.38 to −0.45 e. These groups are geometrically and electrostatically complementary to ARG115, the positively charged guanidinium residue in the CYP19A1 binding pocket, forming the same four anchor contacts (ARG115, PHE134, PHE221, TRP224) as the approved aromatase inhibitor exemestane. The androgen receptor, by contrast, presents an entirely hydrophobic binding core (PHE764, PHE876, PHE891, TRP741) with no ionic partner for the electron-rich oxygens, explaining the weaker predicted binding (2/4 contacts, −6.70 kcal/mol vs −8.97 kcal/mol on CYP19A1).

**Electrostatic Selectivity: Pinnatasterone favours CYP19A1 over Androgen Receptor**




*Electrostatic selectivity panel: pinnatasterone quantum-optimized geometry with partial-charge surface (left), compared to its binding pose in CYP19A1 alongside exemestane reference drug (top right) and the androgen receptor (bottom right).*

SRD5A2 provides the second mechanistic route. SRD5A2 controls conversion of testosterone to dihydrotestosterone. Isocolumbin achieved the strongest docking score on SRD5A2, but static de-risking classifies it as partial (~6.6 Å from the finasteride reference subpocket). Columbamine is the best reference-aligned Sphenocentrum marker on SRD5A2 (~4.9 Å). Assay planning should prioritize columbamine for structural plausibility and include isocolumbin as a docking-led follow-up with explicit pose uncertainty.

The PDE5A signal is a cautionary example of score-versus-mode divergence. Pinnatasterone scored below tadalafil

but above several approved PDE5 drugs in molecular docking, yet it does not reproduce the inhibitor pharmacophore/subpocket geometry that tadalafil and the co-crystal ligand satisfy. That pattern is common when large phytoactive scaffolds dock in the broader catalytic pocket without matching the drug binding mode. Erectile-function claims should not rest on this target unless biochemistry contradicts the structural result.

CYP17A1 showed favorable docking scores for pinnatasterone but reference-centroid distances near ~29 Å, indicating off-pocket or unreliable poses under the current binding-site setup. Androgen-biosynthesis interpretation from CYP17A1 should wait on pose repair or orthogonal modeling.

The androgen receptor remains a secondary context. Columbin and several alkaloids show reference-aligned or near-aligned poses in the testosterone pocket, but steroid controls still dominate molecular docking. Direct AR agonism is not the primary story.

The PXR signal is best interpreted as a safety finding. PXR activation can induce drug-metabolizing enzymes and transporters. Strong docking by isocolumbin and related markers, together with mixed static alignment on PXR, indicates that a standardized, high-bioavailability extract concept would need CYP induction and drug-interaction evaluation before any product-facing claims.

## Recommended Experimental Follow-up

| Priority | Target | Marker(s) | Rationale |
|---|---|---|---|
| 1 | CYP19A1 | pinnatasterone; 20-hydroxyecdysone | Reference-aligned docking; central to steroid-conversion narrative. |
| 2 | SRD5A2 | columbamine; isocolumbin | Columbamine best pose class; isocolumbin best docking score with partial pose caveat. |
| 3 | PXR / CYP3A4 induction | isocolumbin; palmatine | Safety and herb-drug interaction screening. |
| 4 | PDE5A | pinnatasterone | Optional IC50 to falsify erectile mechanism; not recommended as lead hypothesis. |
| Hold | CYP17A1 | pinnatasterone | Re-dock or revise pocket before assays. |

## Novelty Assessment

| Evidence layer | Published status | Contribution of this screen |
|---|---|---|

| Evidence layer | Published status | Contribution of this screen |
|---|---|---|
| Traditional aphrodisiac use | Reported in ethnomedicinal literature and reviews [3,7] | Provides historical context but is not novel. |
| Testosterone and fertility phenotype | Animal studies report testosterone changes, sexual-behavior effects, sperm-quality changes, and testicular degeneration [4,7] | Confirms the biological rationale for mechanism deconvolution. |
| Reported chemistry | Literature describes palmatine and columbamine alkaloids [4], columbin, isocolumbin, and fibleucin furanoditerpenes [5], and ecdysteroids including pinnatasterone, polypodine B, 20-hydroxyecdysone, and atrotosterone A [6,8] | Defines the parent-marker input panel. |
| CYP19A1 / aromatase binding | No direct Sphenocentrum compound-target evidence was found in the reviewed sources | Novel, high-priority efficacy hypothesis (pinnatasterone reference-aligned). |
| SRD5A2 binding | No direct Sphenocentrum compound-target evidence was found in the reviewed sources | Novel reproductive-axis hypothesis (columbamine / isocolumbin). |
| PDE5A binding | No direct Sphenocentrum compound-target evidence was found in the reviewed sources | Docking-positive but structurally weak as PDE5 inhibitor mimic; deprioritized after de-risking. |
| CYP17A1 binding | No direct Sphenocentrum compound-target evidence was found in the reviewed sources | Docking poses unreliable in current setup; not actionable without re-docking. |
| PXR binding | No direct Sphenocentrum PXR evidence was found in the reviewed sources | Novel safety-liability hypothesis. |

## Tongkat Ali Benchmark Validation

Tongkat Ali was used as a validation comparator because it has a better-established reproductive mechanism literature. Published work on eurycomanone reports increased testosterone production in Leydig-cell models, inhibition of aromatase-mediated testosterone-to-estrogen conversion, and possible phosphodiesterase involvement at higher concentration [1]. Clinical literature on standardized Eurycoma longifolia extract supports testosterone-related effects in ageing men and summarizes eurycomanone-associated aromatase/phosphodiesterase mechanisms [2]. These sources emphasize aromatase/phosphodiesterase biology rather than direct androgen-receptor activation.

| Literature-supported mechanism | Simulation result | Validation interpretation |
|---|---|---|
| Eurycomanone-family Tongkat markers are linked to aromatase inhibition and testosterone-to-estrogen conversion biology [1,2] | On CYP19A1, eurycomanol scored -9.893, 13,21-dihydroeurycomanone -9.690, and eurycomanone -9.553, near steroid substrate controls and below exemestane at -10.68 | Positive benchmark. The independent result matched the expected aromatase target space. |

| Literature-supported mechanism | Simulation result | Validation interpretation |
|---|---|---|
| Eurycomanone may involve phosphodiesterase inhibition [1,2] | On PDE4D, eurycomanone scored -9.344, 13,21-dihydroeurycomanone -9.119, and 9-methoxycanthin-6-one -8.685, all above the included PDE controls rolipram -7.821 and IBMX -6.817 | Directional benchmark. The independent result matched phosphodiesterase plausibility, though isoform specificity requires experimental confirmation. |
| Tongkat effects are not primarily explained by direct androgen receptor binding [1,2] | In the AR benchmark, steroid controls dominated: stanozolol -11.57, DHT -11.09, testosterone -10.93, and nandrolone -10.45. Tongkat markers were weaker, with 9-methoxycanthin-6-one at -8.543 and eurycomanone at -6.355 | Negative-control validation. The model did not overstate Tongkat as a direct AR ligand. |

## Interpretation Across Both Botanicals

| Question | Tongkat Ali | Sphenocentrum jollyanum |
|---|---|---|
| Existing phenotype evidence | Extensive testosterone and male-vitality literature | Aphrodisiac and reproductive-toxicity literature exists, but with less target resolution |
| Known compound-target mechanism | Partly known; eurycomanone aromatase and phosphodiesterase involvement are published | Direct target mechanisms were not found in the reviewed sources |
| Primary simulation signal | Aromatase and phosphodiesterase validation; weak direct AR | CYP19A1 and SRD5A2 after pose de-risking; PXR safety; weak direct AR |
| Best report role | Accuracy benchmark for the screening approach | Novel discovery case study with explicit score-versus-pose discipline |

## Limitations

This is an ordinal structural screen supplemented by static pharmacophore de-risking and a short PDE5A MD consistency check. It can prioritize hypotheses but cannot determine enzyme potency, receptor activation, tissue exposure, selectivity, metabolism, or clinical effect. The screened marker panel is representative rather than exhaustive, and additional reported Sphenocentrum constituents should be evaluated as follow-up candidates. CYP17A1 results in this report are limited by off-pocket docking placements. PDE5A MD used restraints and a short sampled trajectory; it supports pose-class consistency only, not long-timescale binding stability or clinical efficacy.

## Literature References

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## R&D Disclaimer

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