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Safety and efficacy of a proprietary *Asparagus racemosus* root extract on ovarian morphology, androgen balance, and insulin resistance in women diagnosed with polycystic ovary syndrome

Sridevi Kondamudi[1], Sravanthi Sadu[1], Sujatha Deva[2], Aishwarya Yalamanchi[3], Amulya Yalamanchi[3]*

[1]Department of Gynecology, Vijaya Sai Hospital, Vijayawada, Krishna, Andhra Pradesh, India; [2]Department of Radiology, Vennela Scan Center and Diagnostics, Vijayawada, Andhra Pradesh, India; [3]Department of General Medicine, Orizin Endocrine Centre, Vijayawada, Andhra Pradesh 520002, India.

Corresponding author: Amulya Yalamanchi, MD, Department of General Medicine, Orizin Endocrine Centre, 7-45, Suryaraopeta, Governor Peta, Vijayawada, Andhra Pradesh 520002, India.

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder characterized by ovarian dysfunction, androgen imbalance, and insulin resistance (IR). Current treatments often target isolated symptoms and may have tolerability limitations, suggesting the need for safe, multi-targeted therapeutic alternatives. *Asparagus racemosus* (Shatavari), which contains steroidal saponins, demonstrates phytoestrogenic and metabolic regulatory activities and may offer potential benefits in PCOS.

Objective: To evaluate the efficacy and safety of CL22205, a standardized *A. racemosus* root extract, on ovarian morphology, reproductive hormones, hyperandrogenic drive, insulin sensitivity, and anthropometric outcomes in women suffering from PCOS.

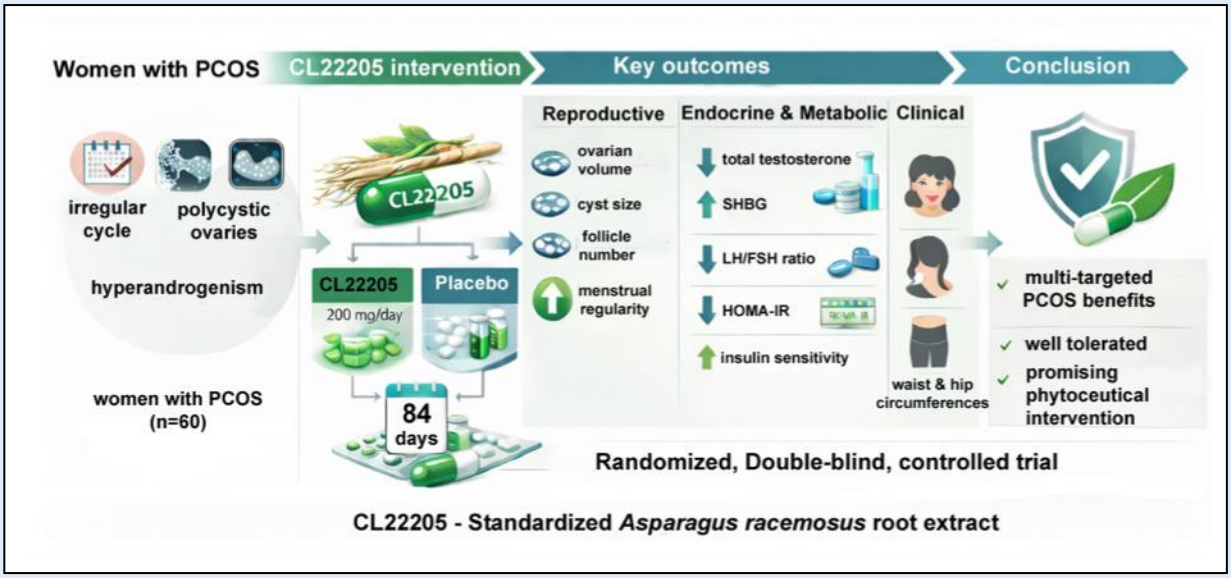
Methods: In a randomized, double-blind, placebo-controlled study, 60 women (age 20–35 years) suffering from PCOS were assigned to receive either CL22205 (200 mg/day) or a placebo over a period of 84 consecutive days. The primary outcome was the change in ovarian volume from baseline. Secondary outcomes included ovarian volume, cyst size, follicle count, and menstrual cycle regularity, hirsutism score, acne severity, serum endocrine factors, insulin resistance,

and anthropometric measurements. Safety was assessed through hematology, serum biochemistry, urinalysis, and monitoring of adverse events.

Results: Fifty-nine participants completed the trial. CL22205 demonstrated significant reductions ($p < 0.05$, vs. baseline) in ovarian volume (18.7%), cyst size (39.0%), and average follicle count (19.7%), and improved menstrual regularity (10.8%) at the end of the study. Hirsutism score (41.8%) and acne severity (40.7%) decreased remarkably. CL22205 significantly increased ($p < 0.05$ vs. baseline) serum levels of sex hormone binding globulin, reduced total testosterone, and lowered the luteinizing hormone: follicle-stimulating hormone ratio. Post-trial, homeostatic model assessment for IR decreased by 13.2% ($p < 0.0001$ vs. baseline), indicating enhanced insulin sensitivity. Reductions in body weight and waist and hip circumferences further supported the metabolic benefits. No major adverse effects were observed.

Conclusion: CL22205 exhibited reproductive, endocrine, and metabolic benefits with excellent tolerability, demonstrating its potential as a phytoceutical intervention for the management of PCOS.

Keywords: *Asparagus racemosus*, Clinical trial, Hyperandrogenism, Insulin resistance, Phytoceutical, Polycystic ovary syndrome, Selective estrogen receptor modulator



Graphical abstract: Safety and efficacy of a proprietary *Asparagus racemosus* root extract on ovarian morphology, androgen balance, and insulin resistance in women diagnosed with polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is recognized as one of the most consequential endocrine disorders affecting women during their reproductive years. Estimates suggest that 5–15% of women of reproductive age are diagnosed with PCOS, emphasizing its broad clinical and social impact [1-2]. The syndrome accounts for up to 70–75% of anovulatory infertility cases, making it a leading contributor to infertility worldwide. PCOS imposes a growing global health burden. The global prevalence of

PCOS-associated infertility reached 315.8 per 100,000 women in 2021, representing 124.7 million cases, a sharp rise of 34.2% since 1990 [3]. This trend highlights a persistent need for therapeutic strategies that address the diverse manifestations of this disorder.

PCOS presents as a set of interconnected endocrine, metabolic, and reproductive dysfunction rather than a single-pathway condition. Central to its pathophysiology is excess androgen levels, which interfere with follicular growth, disrupt the regular menstrual cycle, and contribute to hirsutism and acne [2, 4]. Insulin resistance, frequently observed across PCOS phenotypes, amplifies androgen excess via hyperinsulinemia and promotes adiposity, chronic inflammation, and metabolic dysfunctions [5-6]. Parallel disruption of the hypothalamic–pituitary–ovarian (HPO) axis, often reflected as an elevated luteinizing hormone (LH): follicle-stimulating hormone (FSH) ratio, impairs folliculogenesis and ovulation, thereby reinforcing the anovulatory state [7-8]. These interacting mechanisms yield a heterogeneous clinical profile encompassing menstrual irregularities, infertility, hyperandrogenic symptoms, and metabolic disturbances, each of which can profoundly affect psychological well-being and quality of life [9].

Although pharmacological treatments such as combined oral contraceptive pills, insulin sensitizers (e.g., metformin), anti-androgens, and ovulation-inducing agents are routinely prescribed, these therapies primarily target specific symptom domains rather than the multisystem nature of PCOS. Their long-term effectiveness and safety remain uncertain, with notable adverse effects—including gastrointestinal intolerance, mood changes, and cardiometabolic concerns—limiting adherence [9-10]. The limitations of symptom-targeted therapy have prompted growing interest in holistic, plant-based alternatives capable of influencing multiple physiological pathways relevant to PCOS [11-13].

In this context, Shatavari (*Asparagus racemosus* Willd.), a traditionally valued herb in Ayurvedic medicine for supporting female reproductive health, has gained increasing scientific and clinical attention. Shatavari contains a diverse array of bioactive constituents, including steroidal saponins (Shatavarins I–IV), polysaccharides, alkaloids, and isoflavones, that collectively exhibit antioxidant, adaptogenic, metabolic, and reproductive health-promoting properties. In addition to its broad-spectrum safety profile, these benefits position Shatavari as a promising candidate for development as a phytotherapeutic intervention [14]. Experimental and emerging clinical findings demonstrate that Shatavari supports follicular maturation, alleviates hormonal imbalance, mitigates oxidative stress and vasomotor symptoms, and promotes menstrual regularity [15-16]. These attributes align with therapeutic requirements in PCOS, where abnormalities in ovarian steroidogenesis, systemic inflammation, and metabolic imbalance converge.

CL22205, a standardized extract of *A. racemosus* root (containing at least 6% total Shatavarins), is a modern, quality-controlled formulation designed to harness these traditional phytotherapeutic properties. In a recent controlled study involving perimenopausal women, CL22205 supplementation led to reductions in FSH and LH and increases in anti-mullerian hormone (AMH) and 17β-estradiol (E2), indicating improved ovarian endocrine dynamics [14]. Although these findings orginate from a population distinct from women with PCOS, the observed hormonal shifts mirror key dysregulations seen in PCOS, thereby providing a scientific rationale for extending the investigation of CL22205 in the management of PCOS.

The phytochemical profile and preliminary clinical evidence on CL22205 may offer a multi-targeted approach that addresses both metabolic and reproductive components of PCOS. We conducted a

randomized, double-blind, placebo-controlled clinical trial over 84 days in sixty women (age: 20–35 years) diagnosed with PCOS according to the Rotterdam criteria [17]. This study evaluated changes in ovarian morphology, follicular parameters, menstrual cyclicity, androgenic symptoms, anthropometric measures, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and reproductive hormonal biomarkers, including FSH, LH, sex hormone binding globulin (SHBG), and total testosterone (TT), along with comprehensive safety assessments.

MATERIALS AND METHODS

Study design and ethics approval: This prospective, randomized, double-blind, placebo-controlled trial was designed to evaluate the effects of CL22205, a standardized *Asparagus racemosus* extract, on reproductive, metabolic, and hormonal parameters in women diagnosed with polycystic ovary syndrome (PCOS). The study was conducted from November 21, 2023, to June 11, 2024, following the ethical principles outlined in the International Council for Harmonization – Good Clinical Practice (ICH-GCP) guidelines, as well as the Indian Council of Medical Research ICMR) and the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) guidelines, Government of India. The intervention period was 84 consecutive days, during which participants received either CL22205 or an identical placebo capsule daily. All clinical procedures adhered to ethical principles consistent with the Declaration of Helsinki and Good Clinical Practice guidelines. The Institutional Ethics Committee of Yalamanchi Hospital, Vijayawada, Andhra Pradesh, India (ECR/564/Inst/AP/2014/RR-20) approved the study protocol. This trial was registered (CTRI/2023/11/059457) with the Clinical Trials Registry–India (CTRI), New Delhi, India. All participants understood the risks and benefits of the study and provided written informed consent before enrollment.

Subject recruitment: Women were recruited from the outpatient gynecology departments of Vijaya Sai Hospitals and Orizin Endocrine Centre, both located in Vijayawada (Andhra Pradesh, India), and screened for participation based on inclusion and exclusion criteria (Table 1). Eligible subjects were 20–35 years of age, with a body mass index (BMI) between 22 and 29 kg/m² and were not receiving any hormonal therapy at the time of screening. They were in their premenopausal stage and had a confirmed diagnosis of PCOS according to the Rotterdam criteria, which require the presence of at least two of the following features: (i) clinical and/or biochemical hyperandrogenism, (ii) oligo- or anovulation, and (iii) polycystic ovarian morphology using transvaginal ultrasonography.

Table 1: Inclusion-exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Women aged 20–35 years with a body mass index between 22 and 29 kg/m².	• History or presence of clinically significant cardiovascular, hepatic, renal, or endocrine disorders; active gallbladder disease; or gynecological or breast surgery within the preceding 6 months.
• Diagnosis of polycystic ovary syndrome according to the Rotterdam diagnostic criteria.	• Use of hormonal therapies, insulin-sensitizing agents (e.g., metformin), or herbal/nutraceutical supplements within 3 months before screening.
• Evidence of oligo- or anovulation during the previous year, with baseline follicle-stimulating hormone levels between 1–10 U/L and normal serum estradiol concentrations.	• Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg) or fasting plasma glucose >125 mg/dL.

Inclusion Criteria	Exclusion Criteria
• Polycystic ovarian morphology on ultrasonography, defined as ovarian volume ≥10 cm^3 and/or ≥20 follicles per ovary.	• Current or prior diagnosis of breast, endometrial, or gynecological malignancy, or any other cancer within the past 5 years.
• Willingness and ability to provide written informed consent and adhere to all study procedures.	• Pregnancy, breastfeeding, or known hypersensitivity to the investigational product or its components.
• Sexually active and practicing non-hormonal methods of contraception during the study period.	• Positive screening tests for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or syphilis.
• Normal findings on screening assessments, including vital signs, electrocardiogram (ECG), and standard laboratory investigations.	• Excessive alcohol consumption (>2 standard drinks/day), recreational drug use, or history of substance or psychiatric drug dependence.
	• Participation in another interventional clinical study within 30 days prior to enrolment.

Randomization and blinding: An independent statistician generated a computerized randomization sequence using SAS PROC PLAN with a block design to assign participants in a 1:1 ratio to receive either CL22205 or a placebo. Treatment codes were marked on pre-labelled containers that were indistinguishable in color, weight, capsule size, and packaging. Neither participants nor investigators involved in assessments or data analysis were aware of group assignments throughout the trial.

Intervention: CL22205 is a patent-pending botanical formulation derived from *Asparagus racemosus* (Shatavari) tuberous roots. The *A. racemosus* tuberous roots used for the formulation were wild-harvested in Morena, Madhya Pradesh, India. Botanical identity was confirmed by a certified taxonomist and verified against authenticated reference material. A voucher specimen (Accession No. 6243) is preserved in the herbarium archive of the Chemiloids Life Sciences Research & Development Center (Aswaraopet, Andhra Pradesh, India). CL22205 is standardized by high-performance liquid chromatography (HPLC) to contain not less than 6.0% total shatavarins, ensuring batch-to-batch consistency. CL22205 is produced in a Current Good Manufacturing Practices (cGMP) facility of Laila Nutra Private Limited, Vijayawada, India.This study employed a batch of CL22205 (no. LPP23090186), manufactured in September 2023 and certified with a shelf life of two years.

Both CL22205 and placebo (a 1:1 blend of brown dextrin and rice maltodextrin) were encapsulated in identical-size “one” hard gelatine capsules, matched for appearance—including color, weight, and dimensions, and packaged in white high-density polyethylene (HDPE) bottles to maintain blinding. Products were stored under controlled ambient conditions (cool, dry, and protected from light).

Dose regimen: Participants received either a placebo or CL22205 at baseline and at the scheduled follow-up visit on day 42. They were instructed to consume one capsule daily, either 200 mg of CL22205 or a placebo, after breakfast with sufficient water, for 84 consecutive days.

Study visits and follow-up: Participants attended four scheduled visits: Visit 1 – Screening: verification of eligibility and baseline assessments; Visit 2 – Day 1: randomization and initiation of supplementation; Visit 3 – Day 42 of Treatment: midpoint evaluation; and Visit 4 – Day 84 of Treatment: final assessment (Figure 1). Compliance was monitored through capsule counts and participant diaries documenting daily capsule intake and any adverse events.

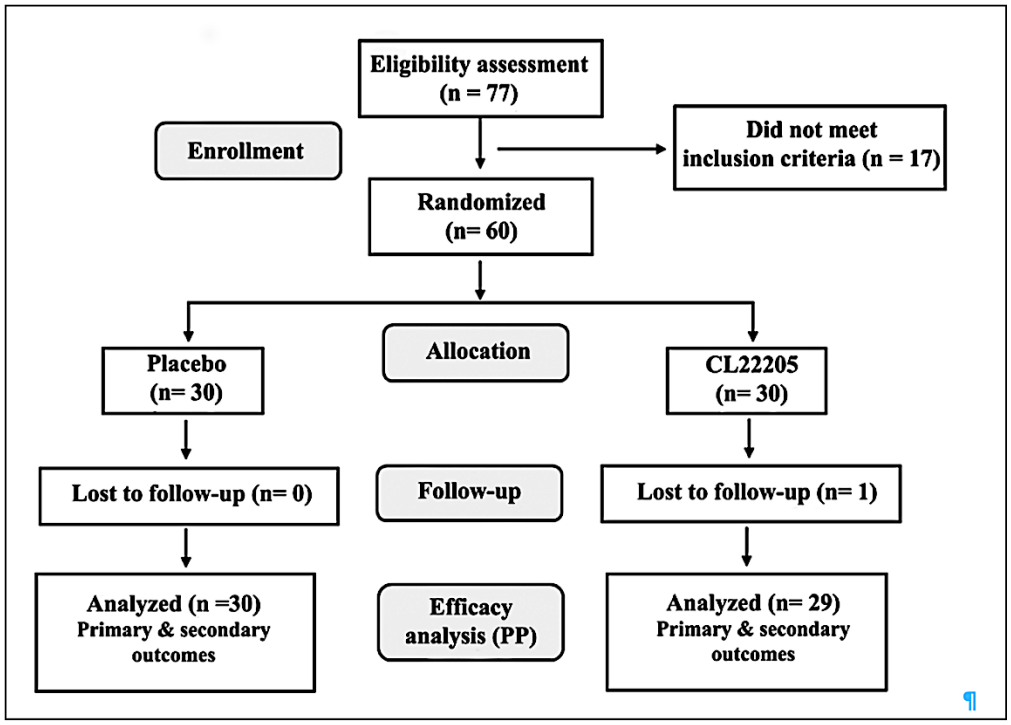


Figure 1: A flow diagram illustrates the sequential flow of participants from initial screening and enrolment through randomization, intervention allocation, follow-up assessments, and study completion, in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Outcome measures

Ovarian morphology assessments: Ovarian morphology was evaluated using high-resolution transvaginal ultrasonography (GE Voluson E8, United States; Philips Epic 7G, Netherlands), equipped with an 8-MHz transducer. All scans were performed in a dedicated clinical setting. To maximize imaging clarity, the probe was positioned to align with the utero-ovarian ligament, allowing consistent visualization of each ovary. Both sagittal and transverse planes were systematically examined to capture the full ovarian outline from the medial to lateral borders. The following parameters were documented: (i) ovarian volume, calculated in cm^3 using the prolate ellipsoid formula (length × width × height × 0.523); (ii) the total number of antral follicles; and (iii) the diameter of the largest visible cyst, in millimeters [18]. All ultrasound assessments were performed by a trained sonographer who adhered to standardized imaging protocols for the evaluation of polycystic ovarian morphology. To minimize variability, all scans were performed during the early follicular phase (cycle days 3–5), when feasible.

Menstrual cycle regularity assessment: Menstrual cycle regularity was evaluated by tracking the intermenstrual interval, defined as the number of days between two successive menstrual episodes. Throughout the intervention, participants documented the onset of each menstrual period in their study diaries. These entries were reviewed during every scheduled follow-up visit, enabling investigators to monitor changes in cycle patterns, identify improvements in regularity, and detect any episodes of prolonged cycle length or amenorrhea.

Assessment of hirsutism and acne scores: Hirsutism was assessed using the Modified Ferriman–Gallwey (mFG) scoring system, which quantifies terminal hair growth across nine anatomical sites: upper lip, chin, chest, upper and lower abdomen, upper and lower back, thighs, and upper arms [19]. Each site was scored on a scale from 0

(absence of terminal hair) to 4 (marked terminal hair growth), and the total number represented the participant's overall hirsutism score. Scores of 5 or higher were considered indicative of hirsutism.

Acne severity was evaluated using the Global Acne Grading System (GAGS), which assesses six body regions: the forehead, left and right cheeks, nose, chin, and chest/back [20]. Each region is assigned a weighting factor that reflects its surface area and density of sebaceous glands. Lesion types, including comedones, papules, pustules, and nodules, were recorded and multiplied by the regional factor to calculate a composite GAGS score. Severity categories were defined as mild (1–18), moderate (19–30), severe (31–38), and very severe (> 38).

Anthropometric measurements: Body weight was assessed using a digital weighing scale (Tanita Corporation, Tokyo, Japan), with participants dressed in light clothing and barefoot to minimize measurement variability. Waist circumference was obtained using a non-stretchable measuring tape, positioned at the anatomical midpoint between the lower border of the last palpable rib and the superior margin of the iliac crest, ensuring consistent tape tension with the aid of an insertion buckle. Hip circumference was measured at the level of greatest gluteal protrusion, just inferior to the iliac crest. All waist and hip measurements were recorded to the nearest even millimeter, and the average values were used for analysis to reduce measurement error.

Endocrine and metabolic biomarkers assessment: Fasting venous blood samples were obtained by trained phlebotomists following standard clinical procedures on menstrual cycle days 3–5 at baseline and post-intervention. Following centrifugation of clotted blood samples at 3000 rpm for 15 minutes at 4°C, clear serum was separated, aliquoted, and stored at –80°C until analysis. Hormonal assessments—including follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), and sex hormone-binding globulin (SHBG)—were conducted using a Cobas 6000 biochemistry analyzer (Roche Healthcare, Basel, Switzerland). Each analyte was quantified using Roche electrochemiluminescence immunoassay kits: LH (Elecsys Ref# 11732234122), FSH (Elecsys FSH Ref# 11775863122), TT (Elecsys Testosterone II Ref# 05200067190), and SHBG (Elecsys SHBG Ref# 03052001190), following the manufacturer's validated protocols. The assays had lower detection limits of 0.100 mIU/mL for LH and FSH, 0.025 ng/mL for TT, and 0.350 nmol/L for SHBG. To assess insulin resistance, fasting glucose and insulin levels were obtained and used to calculate HOMA-IR according to the formula [21]:

$$\text{HOMA-IR} = [\text{Glucose (mg/dL)} \times \text{Insulin (mIU/L)}] \div 405$$

Safety Evaluation: Comprehensive safety assessments were conducted at the screening visit and on day 84 of the intervention period to monitor participant well-being and detect any treatment-related adverse events. Evaluations were performed in accordance with Good Clinical Practice (GCP) standards and included measurement of vital signs, hematological parameters, fasting serum biochemistry, urinalysis, and documentation of any systemic adverse events. The hematology panel included red blood cell (RBC) count, hemoglobin concentration, platelet count, total and differential leukocyte counts, and the erythrocyte sedimentation rate (ESR). A broad serum biochemistry profile was used to assess metabolic, hepatic, renal, electrolyte, and cardiovascular-muscular status. Urinalysis evaluated sample pH, appearance, specific gravity, and screened for protein, glucose, and RBC.

Power calculation and data analysis: A total of 60 women participated in the study, with 30 per arm recruited, and a projected 5% dropout rate (approximately 1 participant per group). The sample size

calculation was based on a two-sided t-test with a significance level of 0.05 and 90% power, assuming a mean difference of 2.2 units in ovarian volume change and an expected standard deviation of 2.5, as reported in previous studies [22].

Efficacy outcomes were analyzed in the per-protocol (PP) population, and results are presented as mean ± standard deviation (SD). Descriptive statistics were used to summarize demographic variables, baseline characteristics, clinical findings, laboratory measurements, and vital signs with paired t-tests applied for within-group assessments, while comparisons between the treatment and placebo groups for primary and secondary endpoints employed analysis of covariance (ANCOVA), incorporating the corresponding baseline value as a covariate. All statistical procedures were performed using SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline demographics and participant compliance: A total of 60 women, aged 20–35 years with a BMI of 22–29 kg/m², were enrolled in the study after meeting the clinical criteria for PCOS. Participants were randomly assigned to receive either CL22205 (200 mg) or a matching placebo capsule, once daily for 84 consecutive days. Baseline demographic characteristics were comparable between the groups (Table 2). One participant in the CL22205 arm was lost to follow-up, leaving 59 women included in the per-protocol (PP) analysis. The mean compliance rates were 98.56% and 98.42% in the placebo and CL22205 groups, respectively.

Table 2: Baseline demographics.

Parameter/Group	Mean ± SD	p-value (vs. placebo)	95% CI (vs. placebo)
Age (Years)			
Placebo (n=30)	27.2 ± 4.3	-	-
CL22205 (n=30)	27.4 ± 3.9	0.8754	-1.92, 2.32
Body Mass Index (BMI, kg/m²)			
Placebo (n=30)	26.9 ± 1.5	-	-
CL22205 (n=30)	26.6 ± 1.8	0.5230	-0.56, 1.16
Height (m)			
Placebo (n=30)	1.5 ± 0.0	-	-
CL22205 (n=30)	1.5 ± 0.0	0.8202	0.00, 0.00
Body weight (kg)			
Placebo (n=30)	63.5 ± 4.7	-	-
CL22205 (n=30)	63.0 ± 4.6	0.6604	-1.90, 2.90

Between-group comparison was analyzed using ANCOVA.

Effect of CL22205 supplementation on ovarian volume: Participants receiving CL22205 demonstrated a progressive reduction in ovarian volume as compared with those in the placebo group (Table 3). Significant decreases ($p < 0.0001$) were observed in the right ovary, 10.7% on day 42 and 17.4% on day 84, whereas the placebo group showed only modest reductions of 5.4% ($p = 0.0183$) and 3.4% ($p = 0.0422$), respectively. A similar pattern was observed in the left ovary, where CL22205 resulted in substantial reductions of 17.6% and 20.2% on days 42 and 84 of supplementation, respectively ($p < 0.0001$). In contrast, the placebo group demonstrated minimal increases (not significant) of 3.3% and 0.5% at the identical time points of the study. When averaged

across both ovaries, mean ovarian volume declined by 14.0% and 18.7% on days 42 and 84, respectively, in the CL22205 group ($p < 0.0001$ vs. baseline), compared with negligible decreases of 1.2% and 1.5% in the placebo group. Between-group analyses confirmed that the reductions in mean ovarian volume with CL22205 were significantly greater than those with placebo at both follow-up visits (Table 3).

Table 3: Assessment of ovarian volume.

Parameter/Group	Time of Evaluation	Mean ± SD	Change from baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo)
Right ovarian volume (cm^3)						
Placebo (n=30)	Baseline	11.83 ± 1.66	-	-	-	-
	Day 42	11.19 ± 1.88	-0.64 ± 2.19	0.0183	-	-
	Day 84	11.43 ± 1.61	-0.40 ± 1.16	0.0422	-	-
CL22205 200 mg (n=29)	Base line	11.98 ± 1.80	-	-	0.7344	-0.75, 1.05
	Day 42	10.71 ± 1.55	-1.28 ± 1.40	< 0.0001	0.1586	-0.42, 1.38
	Day 84	9.91 ± 1.48	-2.08 ± 1.46	< 0.0001	< 0.0001	0.71, 2.33
Left ovarian volume (cm^3)						
Placebo (n=30)	Baseline	11.01 ± 1.84	-	-	-	-
	Day 42	11.37 ± 1.76	0.36 ± 0.84	0.1538	-	-
	Day 84	11.07 ± 1.79	0.06 ± 1.63	0.9564	-	-
CL22205 200 mg (n=29)	Base line	11.28 ± 1.53	-	-	0.5878	-0.61, 1.15
	Day 42	9.30 ± 1.97	-1.98 ± 1.45	< 0.0001	< 0.0001	1.09, 3.04
	Day 84	9.00 ± 1.79	-2.28± 1.89	< 0.0001	< 0.0001	1.14, 3.00
Mean ovarian volume (both ovaries) (cm^3)						
Placebo (n=30)	Baseline	11.42 ± 1.38	-	-	-	-
	Day 42	11.28 ± 1.78	-0.14 ± 1.17	0.4389	-	-
	Day 84	11.25 ± 1.38	-0.17 ± 1.11	0.2860	-	-
CL22205 200 mg (n=29)	Baseline	11.63 ± 1.25	-	-	0.5638	-0.48, 0.89
	Day 42	10.01 ± 1.41	-1.63 ± 0.93	< 0.0001	< 0.0001	0.43, 2.11
	Day 84	9.45 ± 1.26	-2.18 ± 1.25	< 0.0001	< 0.0001	1.11, 2.49

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

Effect of CL22205 supplementation on ovarian cyst size and follicle count: CL22205-supplemented participants showed marked improvements in ovarian morphology as compared with the placebo group (Table 4). Mean ovarian cyst size decreased progressively in the CL22205 group, with significant reductions ($p < 0.0001$) of 12.0% on day 42 and 39.0% on day 84 of treatment.

Similarly, the average follicle count (per ovary) declined substantially ($p < 0.0001$) with CL22205, by 14.4% and 19.7% on day 42 and 84, respectively, vs. baseline. In contrast, the placebo group showed no significant change in ovarian cyst size from baseline. Between-group comparisons at both follow-up visits consistently reduced ($p < 0.0001$ vs. placebo) the cyst size and follicular count in the CL22205 group (Table 4).

Table 4: Assessment of mean ovarian cyst size and number of ovarian follicles.

Parameter/Group	Time of Evaluation	Mean ± SD	Change vs. baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo)
Mean ovarian cyst size (both ovaries) (mm)						
Placebo (n=30)	Baseline	6.62 ± 0.99	-	-	-	-
	Day 42	6.40 ± 1.08	-0.23 ± 0.78	0.1702	-	-
	Day 84	6.42 ± 1.08	-0.21 ± 0.81	0.3823	-	-
CL22205 200 mg (n=29)	Baseline	6.44 ± 0.98	-	-	0.4627	-0.33, 0.69
	Day 42	5.68 ± 1.03	-0.77 ± 0.58	< 0.0001	0.0078	0.17, 1.27
	Day 84	3.93 ± 1.35	-2.51 ± 1.25	< 0.0001	< 0.0001	1.85, 3.13
Mean number of follicles (both ovaries)						
Placebo (n=30)	Baseline	19.02 ± 2.96	-	-	-	-
	Day 42	18.52 ± 2.84	-0.50 ± 1.50	0.1385	-	-
	Day 84	17.90 ± 3.03	-1.12 ± 2.10	0.0039	-	-
CL22205 200 mg (n=29)	Baseline	19.33 ± 1.98	-	-	0.6524	-1.01, 1.63
	Day 42	16.53 ± 2.25	-2.79 ± 2.46	< 0.0001	< 0.0001	0.65, 3.33
	Day 84	15.52 ± 2.19	-3.81 ± 2.46	< 0.0001	< 0.0001	0.99, 3.76

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

CL22205 supplementation improves menstrual cycle regularity: Evaluation of menstrual cycle patterns showed a trend toward improved cycle regularity in participants receiving CL22205 (Table 5). At baseline, the interval between consecutive menstrual episodes was comparable between groups. On day 84, the CL22205 group exhibited a notable reduction of 10.8% in intermenstrual interval (–5.28 ± 6.41 days; $p < 0.0001$). Although the placebo group demonstrated a substantial decrease of 6.1% (–2.77 ± 3.65 days; $p = 0.0031$) on day 84, the magnitude of improvement was smaller than that with CL22205. However, between-group comparisons did not reach statistical significance at the end of the study (Table 5).

Table 5: Assessment of menstrual cycle regularity.

Group	Time of Evaluation	Duration between two subsequent bleedings (days)	Change vs. baseline	p-value (vs. baseline)	p-value (vs. Placebo)	95% CI (vs. placebo)
Placebo (n=30)	Baseline	45.73 ± 8.41	-	-	-	-
	Day 42	48.60 ± 5.16	2.87 ± 11.71	0.5845	-	-
	Day 84	42.97 ± 8.56	-2.77 ± 3.65	0.0031	-	-
CL22205 200 mg (n=29)	Baseline	49.03 ± 4.92	-	-	0.0623	-0.31, 6.91
	Day 42	48.10 ± 2.90	-0.93 ± 6.18	0.4634	0.8935	-1.69, 2.69
	Day 84	43.76 ± 7.72	-5.28 ± 6.41	< 0.0001	0.2576	-3.46, 5.04

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

CL22205 reduces androgen-related clinical symptoms: CL22205 supplementation led to significant improvements in androgen-related symptoms in the participants. The mFG score for hirsutism declined by 16.9% on day 42 and 41.8% on day 84, both highly significant ($p < 0.0001$), whereas the placebo group showed only minor changes at the end of the study (not significant) (Table 6).

Acne severity (GAGS score) showed a similar pattern during the intervention, decreasing by 20.2% and 40.7% on days 42 and 84, respectively, in the CL22205 group, with minimal improvements observed in the placebo arm (Table 6).

At the end of the study, between-group comparisons confirmed significantly greater reductions ($p < 0.0001$) in mFG and GAGS scores in the CL22205 group, indicating meaningful improvement in clinical signs of androgenic drive (Table 6).

Table 6: Assessment of androgen-related clinical symptoms.

Parameter/Group	Time of Evaluation	Mean ± SD	Change vs. baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo)
Modified Ferriman-Gallwey Questionnaire for Hirsutism (mFG) score						
Placebo (n=30)	Baseline	6.97 ± 1.35	-	-	-	-
	Day 42	6.47 ± 1.41	-0.50 ± 1.80	0.0427	-	-
	Day 84	6.60 ± 1.38	-0.37 ± 1.16	0.1106	-	-
CL22205 200 mg (n=29)	Baseline	6.93 ± 1.53	-	-	0.9271	-0.71, 0.79
	Day 42	5.76 ± 1.70	-1.17 ± 1.44	< 0.0001	0.0482	-0.10, 1.52
	Day 84	4.03 ± 1.70	-2.90 ± 1.61	< 0.0001	<0.0001	1.76, 3.38
Global Acne Grading System (GAGS) score						
Placebo (n=30)	Baseline	8.93 ± 2.97	-	-	-	-

Parameter/Group	Time of Evaluation	Mean ± SD	Change vs. baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo)
	Day 42	8.43 ± 3.28	-0.50 ± 1.50	0.0584	-	-
	Day 84	8.27 ± 3.60	-0.67 ± 2.23	0.0218	-	-
CL22205 200 mg (n=29)	Baseline	9.07 ± 1.67	-	-	0.8322	-1.12, 1.40
	Day 42	7.24 ± 2.03	-1.83 ± 1.85	< 0.0001	0.0012	-0.24, 2.62
	Day 84	5.38 ± 1.18	-3.69 ± 1.37	< 0.0001	<0.0001	1.48, 4.29

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

CL22205 supplementation improves anthropometric measures: Participants receiving CL22205 demonstrated significant reductions in anthropometric measures (Table 7).

Body weight decreased significantly in the CL22205 group by 0.9% (p = 0.0007) on day 42 and continued to decline through day 84 (2.8%, p < 0.0001), with a significant difference vs. placebo (p < 0.0001) at the end of the study (Table 7).

Waist circumference showed a similar pattern, with significant reductions from baseline on both day 42 (0.7%, p = 0.0014) and day 84 (2.1%, p < 0.0001), and a substantial between-group difference at day 84 (p < 0.0001) vs. placebo (Table 7).

Hip circumference also declined significantly in the CL22205 group on day 42 (0.5%, p = 0.0190) and day 84 (1.6%, p < 0.0001), with the reduction on day 84 being significantly greater than that of the placebo group (p < 0.0001) (Table 7).

Table 7: Assessment of anthropometric measures.

Parameter/Group	Time of Evaluation	Mean ± SD	Change from baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo
Body weight (kg)						
Placebo (n=30)	Baseline	63.53 ± 4.72	-	-	-	-
	Day 42	63.32 ± 4.54	-0.21 ± 0.71	0.1875	-	-
	Day 84	63.29 ± 4.56	-0.24 ± 0.67	0.1554	-	-
CL22205 200 mg (n=29)	Baseline	63.10 ± 4.65	-	-	0.7625	-2.01, 2.87
	Day 42	62.53 ± 4.83	-0.57 ± 0.89	0.0007	0.1185	-1.65, 3.23
	Day 84	61.36 ± 4.60	-1.74 ± 0.52	< 0.0001	< 0.0001	-0.46, 4.32
Waist circumference (cm)						
Placebo (n=30)	Baseline	78.61 ± 5.64	-	-	-	-
	Day 42	78.43 ± 5.67	-0.18 ± 0.75	0.2507	-	-
	Day 84	78.38 ± 5.68	-0.23 ± 0.63	0.0733	-	-

Parameter/Group	Time of Evaluation	Mean ± SD	Change from baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo
CL22205 200 mg (n=29)	Baseline	79.26 ± 4.83	-	-	0.6218	-2.09, 3.39
	Day 42	78.72 ± 4.87	-0.53 ± 0.91	0.0014	0.1279	-2.47, 3.05
	Day 84	77.58 ± 4.83	-1.68 ± 0.56	< 0.0001	< 0.0001	-1.95, 3.55
Hip circumference (cm)						
Placebo (n=30)	Baseline	97.03 ± 5.67	-	-	-	-
	Day 42	96.92 ± 5.72	-0.11 ± 1.07	0.5537	-	-
	Day 84	96.88 ± 5.54	-0.15 ± 1.45	0.4909	-	-
CL22205 200 mg (n=29)	Baseline	97.14 ± 3.86	-	-	0.9376	-2.43, 2.65
	Day 42	96.67 ± 4.04	-0.47 ± 1.10	0.0190	0.2009	-2.34, 2.84
	Day 84	95.62 ± 3.92	-1.52 ± 1.30	< 0.0001	< 0.0001	-1.25, 3.77

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

CL22205 supplementation alters serum endocrine factors and improves insulin sensitivity: CL22205 supplementation produced beneficial changes in key reproductive and metabolic biomarkers in participants over the intervention period (Table 8). Post-trial, participants receiving CL22205 exhibited a significant increase in serum FSH levels as compared with baseline (p = 0.0264). In contrast, LH levels remained relatively unchanged across both time points and did not differ significantly from the placebo group. Notably, the LH: FSH ratio demonstrated a significant reduction in the CL22205 group at day 84 of treatment (p = 0.0076), and this improvement was also significantly greater than that observed in the placebo group (p = 0.0336) (Table 8).

A notable rise in serum SHBG level was observed with CL22205 supplementation (+5.65 ± 11.72 nmol/L; p = 0.0256), whereas SHBG level declined in the placebo group; the between-group comparison showed a significant increase in the CL22205 group (p = 0.0064) (Table 8).

Table 8: Serum endocrine factors and Homeostatic Model Assessment for Insulin Resistance.

Parameter/Group	Time of Evaluation	Mean ± SD	Change vs. baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo
Follicle-stimulating hormone (mIU/mL)						
Placebo (n=30)	Baseline	6.43 ± 1.83	-	-	-	-
	Day 84	6.82 ± 2.87	0.38 ± 2.45	0.5136	-	-
CL22205 200 mg (n=29)	Baseline	6.01 ± 1.62	-	-	0.3769	-0.48, 1.32
	Day 84	7.46 ± 3.14	1.45 ± 2.66	0.0264	0.2543	-0.93, 2.21
Luteinizing hormone (mIU/mL)						

Parameter/Group	Time of Evaluation	Mean ± SD	Change vs. baseline	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo
Placebo (n=30)	Baseline	12.13 ± 5.19	-	-	-	-
	Day 84	12.53 ± 5.95	0.40 ± 5.29	0.2898	-	-
CL22205 200 mg (n=29)	Baseline	10.18 ± 3.31	-	-	0.0734	-0.33, 4.23
	Day 84	11.05 ± 3.69	0.87 ± 3.26	0.5556	0.7456	-1.11, 4.07
LH to FSH ratio						
Placebo (n=30)	Baseline	1.85 ± 0.42	-	-	-	-
	Day 84	1.83 ± 0.45	-0.02 ± 0.54	0.7531	-	-
CL22205 200 mg (n=29)	Baseline	1.71 ± 0.40	-	-	0.2095	-0.07, 0.35
	Day 84	1.55 ± 0.40	-0.16 ± 0.26	0.0076	0.0336	0.06, 0.50
Sex hormone binding globulin (nmol/L)						
Placebo (n=30)	Baseline	35.52 ± 13.12	-	-	-	-
	Day 84	31.69 ± 11.32	-3.83 ± 14.68	0.0958	-	-
CL22205 200 mg (n=29)	Baseline	33.07 ± 12.16	-	-	0.4874	-4.15, 9.05
	Day 84	38.72 ± 9.34	5.65 ± 11.72	0.0256	0.0064	1.61, 12.45
Total Testosterone (ng/mL)						
Placebo (n=30)	Baseline	0.64 ± 0.46	-	-	-	-
	Day 84	0.65 ± 0.43	0.01 ± 0.22	0.9280	-	-
CL22205 200 mg (n=29)	Baseline	0.69 ± 0.56	-	-	0.6944	-0.22, 0.32
	Day 84	0.44 ± 0.33	-0.25 ± 0.35	< 0.0001	0.0003	0.01, 0.41
Homeostatic Model Assessment for Insulin Resistance score						
Placebo (n=30)	Baseline	3.19 ± 0.41	-	-	-	-
	Day 42	3.33 ± 0.52	0.15 ± 0.63	0.3683	-	-
	Day 84	3.28 ± 0.54	0.09 ± 0.65	0.8140	-	-
CL22205 200mg (n=29)	Baseline	3.34 ± 0.43	-	-	0.1557	-0.07, 0.37
	Day 42	3.05 ± 0.38	-0.29 ± 0.50	0.0075	0.0119	0.04, 0.52
	Day 84	2.90 ± 0.33	-0.44 ± 0.45	< 0.0001	0.0009	0.15, 0.61

Data is presented as mean ± SD. A p-value < 0.05 indicates significance in the intragroup (vs. baseline) or intergroup (CL22205 vs. placebo) comparison, analyzed using ANCOVA.

Correspondingly, total testosterone decreased substantially in the CL22205 group (−0.25 ± 0.35 ng/mL; $p < 0.0001$), with a significant difference compared to placebo ($p = 0.0003$), reflecting improved androgen status (Table 8).

Metabolic assessment via HOMA-IR showed a significant reduction on day 42 (−0.29 ± 0.50; $p = 0.0075$) and further reduced on day 84 of treatment (−0.44 ± 0.45; $p < 0.0001$), with both time points demonstrating significantly greater improvements (day 42: $p = 0.0119$; day 84: $p = 0.0009$) than placebo (Table 8).

Safety Assessments and Adverse Events: CL22205 was generally well tolerated, with no clinically meaningful alterations observed in hematological indices or serum biochemistry, including liver enzymes, renal function markers, cardiovascular parameters, lipid profile, or complete blood counts (Table 9). Adverse events were few and mild. In the placebo group, three participants reported transient symptoms, including headache, nasal congestion, or sore throat. In the CL22205 group, one participant experienced a brief cough episode, and another reported a headache. All events resolved without the need for medical treatment. Overall, the safety profile of CL22205 was satisfactory, with no major adverse events reported during the intervention period.

Table 9: Safety assessments- hematology and serum biochemistry parameters.

Parameters	Evaluation	Treatments	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
Hematology					
Hemoglobin (g/dL)	Baseline	Placebo	11.83 ± 0.80	-	-
		CL22205	11.76 ± 0.82	-	0.7517
	Day 84	Placebo	11.92 ± 0.64	0.4308	-
		CL22205	12.22 ± 0.48	< 0.0001	0.0456
Platelet count (lakhs/cu.mm)	Baseline	Placebo	2.89 ± 0.43	-	-
		CL22205	2.68 ± 0.47	-	0.0705
	Day 84	Placebo	2.86 ± 0.44	0.3410	-
		CL22205	2.71 ± 0.43	0.6550	0.2014
Erythrocyte sedimentation rate (mm/hr)	Baseline	Placebo	12.60 ± 1.81	-	-
		CL22205	11.74 ± 2.36	-	0.1202
	Day 84	Placebo	12.47 ± 1.41	0.4235	-
		CL22205	12.24 ± 1.27	0.1467	0.522
Red blood cells count (million cells/cu.mm)	Baseline	Placebo	4.20 ± 0.48	-	-
		CL22205	4.13 ± 0.23	-	0.4721
	Day 84	Placebo	4.26 ± 0.43	0.2836	-
		CL22205	4.17 ± 0.20	0.1008	0.3167
White blood cells (cells/cu.mm)	Baseline	Placebo	7733 ± 791	-	-
		CL22205	8023 ± 908	-	0.1924

Parameters	Evaluation	Treatments	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
	Day 84	Placebo	7777 ± 845	0.1868	-
		CL22205	8072 ± 898	0.4123	0.1978
Neutrophil (%)	Baseline	Placebo	56.17 ± 7.36	-	-
		CL22205	56.13 ± 6.82	-	0.9855
	Day 84	Placebo	56.07 ± 5.99	0.8969	-
		CL22205	56.31 ± 5.39	0.8922	0.8703
Lymphocytes (%)	Baseline	Placebo	36.27 ± 7.61	-	-
		CL22205	37.03 ± 6.28	-	0.6718
	Day 84	Placebo	36.23 ± 6.42	0.9646	-
		CL22205	36.72 ± 4.82	0.9719	0.7417
Eosinophil (%)	Baseline	Placebo	6.17 ± 1.56	-	-
		CL22205	5.40 ± 1.73	-	0.0766
	Day 84	Placebo	6.13 ± 1.55	0.8230	-
		CL22205	5.52 ± 1.60	0.2552	0.1376
Monocytes (%)	Baseline	Placebo	1.40 ± 0.81	-	-
		CL22205	1.43 ± 0.68	-	0.8638
	Day 84	Placebo	1.57 ± 0.68	0.2018	-
		CL22205	1.45 ± 0.57	0.7869	0.4727
Basophils (%)	Baseline	Placebo	0.00 ± 0.00	-	-
		CL22205	0.00 ± 0.00	-	-
	Day 84	Placebo	0.00 ± 0.00	-	-
		CL22205	0.00 ± 0.00	-	-
Serum biochemistry					
Fasting Blood Glucose (mg/dL)	Baseline	Placebo	90.57 ± 6.38	-	-
		CL22205	87.80 ± 6.13	-	0.0921
	Day 84	Placebo	85.23 ± 5.78	0.0001	-
		CL22205	84.31 ± 5.50	0.0001	0.5323
Serum Creatinine (mg/dL)	Baseline	Placebo	0.91 ± 0.13	-	-
		CL22205	0.96 ± 0.10	-	0.0708
	Day 84	Placebo	0.91 ± 0.09	1.000	-
		CL22205	0.93 ± 0.12	0.1474	0.3337

Parameters	Evaluation	Treatments	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
Blood Urea Nitrogen (mg/dL)	Baseline	Placebo	11.57 ± 2.33	-	-
		CL22205	11.70 ± 2.04	-	0.8143
	Day 84	Placebo	12.53 ± 3.37	0.0939	-
		CL22205	11.55 ± 1.88	0.7381	0.1746
Blood Uric Acid (mg/dL)	Baseline	Placebo	4.38 ± 0.63	-	-
		CL22205	4.45 ± 0.54	-	0.6777
	Day 84	Placebo	4.44 ± 0.60	0.2931	-
		CL22205	4.32 ± 0.49	0.0617	0.3918
Serum Sodium (mEq/L)	Baseline	Placebo	140.43 ± 2.71	-	-
		CL22205	139.77 ± 2.71	-	0.3451
	Day 84	Placebo	140.37 ± 2.37	0.8012	-
		CL22205	140.03 ± 2.49	0.4149	0.6013
Serum Potassium (mEq/L)	Baseline	Placebo	4.11 ± 0.19	-	-
		CL22205	4.12 ± 0.18	-	0.7798
	Day 84	Placebo	4.09 ± 0.14	0.2817	-
		CL22205	4.11 ± 0.17	0.1695	0.5557
Alanine aminotransferase (IU/L)	Baseline	Placebo	28.50 ± 5.71	-	-
		CL22205	29.27 ± 6.29	-	0.623
	Day 84	Placebo	29.43 ± 5.42	0.0578	-
		CL22205	29.03 ± 5.67	0.8132	0.7835
Aspartate aminotransferase (IU/L)	Baseline	Placebo	27.47 ± 4.27	-	-
		CL22205	25.73 ± 5.21	-	0.1643
	Day 84	Placebo	27.53 ± 3.66	0.9286	-
		CL22205	26.00 ± 5.30	0.4574	0.2000
Serum Alkaline Phosphatase (IU/L)	Baseline	Placebo	105.70 ± 13.74	-	-
		CL22205	107.80 ± 10.52	-	0.5088
	Day 84	Placebo	106.60 ± 12.91	0.1503	-
		CL22205	109.07 ± 10.09	0.2714	0.4175
Serum Bilirubin (mg/dL)	Baseline	Placebo	0.70 ± 0.14	-	-
		CL22205	0.64 ± 0.13	-	0.0707
	Day 84	Placebo	0.69 ± 0.13	0.3256	-

Parameters	Evaluation	Treatments	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
		CL22205	0.64 ± 0.11	0.7869	0.0960
Serum Albumin (g/dL)	Baseline	Placebo	4.02 ± 0.34	-	-
		CL22205	3.99 ± 0.64	-	0.8205
	Day 84	Placebo	4.06 ± 0.32	0.0898	-
		CL22205	4.07 ± 0.27	0.4234	0.8731
Creatinine kinase(U/L)	Baseline	Placebo	72.23 ± 18.93	-	-
		CL22205	71.07 ± 19.05	-	0.8128
	Day 84	Placebo	69.47 ± 15.35	0.1080	-
		CL22205	71.31 ± 19.61	0.5864	0.6885
Low-density lipoprotein (mg/dL)	Baseline	Placebo	114.47 ± 11.75	-	-
		CL22205	115.30 ± 7.83	-	0.7478
	Day 84	Placebo	115.20 ± 10.51	0.3336	-
		CL22205	116.17 ± 6.99	0.1293	0.6764
High-density lipoprotein (mg/dL))	Baseline	Placebo	43.63 ± 2.19	-	-
		CL22205	44.30 ± 3.65	-	0.3952
	Day 84	Placebo	44.07 ± 2.50	0.1868	
		CL22205	44.52 ± 2.47	0.6748	0.4897
Very high-density lipoprotein (mg/dL))	Baseline	Placebo	27.60 ± 2.75	-	-
		CL22205	28.57 ± 4.24	-	0.2998
	Day 84	Placebo	27.90 ± 2.62	0.1303	-
		CL22205	28.79 ± 3.23	0.5203	0.2496
Triglycerides (mg/dL)	Baseline	Placebo	139.20 ± 13.35	-	-
		CL22205	143.27 ± 20.72	-	0.3705
	Day 84	Placebo	140.73 ± 10.32	0.1900	-
		CL22205	145.59 ± 16.45	0.1602	0.1828
Total cholesterol (mg/dL)	Baseline	Placebo	186.23 ± 13.88	-	-
		CL22205	189.90 ± 11.39	-	0.2683
	Day 84	Placebo	187.33 ± 13.32	0.3472	-
		CL22205	191.97 ± 9.42	0.3240	0.1281

The data from the screening visit is considered the baseline data. A p-value < 0.05 is considered statistically significant. Intragroup comparisons (vs. baseline) were analyzed using a paired t-test, and the difference between the groups (CL22205 *vs*. placebo) at screening and the end of the study (day 84) was analyzed using one-way ANOVA. At baseline: placebo (n = 30), CL22205 (n = 30), day 84: placebo (n = 30), CL22205 (n = 29).

DISCUSSION

In the present study, daily supplementation with CL22205, a standardized *A. racemosus* root extract, over 84 consecutive days resulted in significant improvements across multiple reproductive and metabolic domains in women diagnosed with PCOS. Notably, CL22205 exhibited marked reductions in ovarian volume, cyst size, and follicle number, which are consistent with amelioration of polycystic morphology. These outcomes align with prior reports demonstrating that *A. racemosus* may regulate menstrual cycle and improve ovarian health in reproductive disorders [23]. Improvements in menstrual cycle regularity among CL22205-supplemented participants further suggest restoration of normal ovulatory rhythm.

A key mechanistic finding of this study was a significant reduction in the LH: FSH ratio, reflecting improved regulation of the HPO axis. Irregular Gonadotropin-releasing hormone (GnRH) pulsatility in PCOS increases LH secretion relative to FSH, stimulating theca cell androgen synthesis, while impairing granulosa cell aromatase activity [24-25]. In the present study, the reduction in the LH: FSH ratio observed with CL22205 suggests partial normalization of GnRH-dependent endocrine signaling. This particular shift favors estrogen biosynthesis, promotes dominant follicle selection, and may contribute to the observed reductions in follicle count and progressive normalization of menstrual cyclicity in the participants.

Hyperandrogenism is a central clinical and physiological hallmark of PCOS, manifesting as hirsutism, acne, and elevated circulating androgens [26]. CL22205 supplementation reduced total testosterone, increased SHBG, and significantly improved androgen-dependent clinical symptoms. Decreased hirsutism scores and reduced acne severity at the end of the study indicate substantial clinical improvement, suggesting attenuation of androgen imbalance. Similar improvements in acne and hirsutism have been reported with pharmacologic insulin sensitizers such as metformin, supporting the concept that lowering androgen excess ameliorates dermatologic manifestations [27-28]. Thus, CL22205 appears to exert coordinated endocrine and symptomatic benefits relevant to androgen excess.

Mechanistically, the phytochemical profile of CL22205 provides strong support for the observed clinical findings. Shatavari root is particularly rich in steroidal saponins, predominantly shatavarins, which have been demonstrated to exhibit estrogenic and selective estrogen receptor modulator (SERM)-like activity [14, 29-30]. Through interaction with estrogen receptors (ERα and ERβ), these phytoestrogenic compounds may influence central and peripheral endocrine signaling [23], thereby improving ovarian stromal homeostasis and limiting excessive recruitment of small antral follicles, a hallmark of polycystic ovarian morphology. In addition, modulation of estrogenic feedback at the hypothalamic–pituitary axis may help normalize gonadotropin secretion patterns, supporting coordinated follicular development and ovulatory function.

Moreover, improvements in insulin resistance, evidenced by significant reductions in HOMA-IR, represent another important metabolic benefit of CL22205 supplementation. Insulin resistance and compensatory hyperinsulinemia not only exacerbate metabolic dysfunction but also potentiate ovarian androgen production, reduce SHBG synthesis, and contribute to anovulation [31-32]. The observed improvements in insulin sensitivity following CL22205 supplementation may play a vital role in moderating this amplification loop, with downstream effects including reduced testosterone levels, enhanced SHBG production, and improved menstrual cyclicity. This integrative metabolic–endocrine response is consistent with observations reported for other botanicals, such as *Trigonella foenum-graecum*, which has been suggested to influence insulin sensitivity and androgen balance in women with PCOS [33].

The observed anthropometric improvements, including reductions in body weight and central adiposity, provide additional metabolic support to the endocrine benefits of CL22205 supplementation. Central (abdominal) obesity is closely associated with insulin resistance, dyslipidemia, and heightened cardiometabolic risk, often independently of overall adiposity as reflected by BMI [34-37]. Given the bidirectional relationship between adiposity, insulin resistance, and ovarian dysfunction in PCOS, even modest reductions in waist and hip circumferences may have meaningful metabolic and reproductive implications [38]. Mechanistically, botanicals rich in phytoestrogens and polyphenols have been shown to influence energy homeostasis, adipocyte differentiation, inflammatory signaling, and lipid oxidation pathways, thereby supporting improvements in body composition [39-40]. Emerging evidence further suggests that plant-derived estrogenic compounds may modulate adipose tissue metabolism through estrogen receptor–mediated pathways, contributing to reduced visceral fat accumulation and improved metabolic flexibility [41-42]. Collectively, these mechanisms provide a plausible biological basis for the observed anthropometric benefits following CL22205 supplementation.

Importantly, CL22205 was well tolerated during the 84-day intervention, with no clinically significant alterations observed in hematological parameters, serum biochemistry, or organ-specific safety biomarkers. Reported adverse events were transient and mild. In contrast, these safety concerns are particularly notable in the context of PCOS, where long-term pharmacotherapies such as insulin sensitizers and hormonal agents are often limited by gastrointestinal intolerance or diverse metabolic side effects [10, 28]. The tolerability profile observed in the present trial is consistent with safety outcomes reported in a separate study conducted on perimenopausal women, in which an extended duration (120-day) of CL22205 supplementation did not report clinically meaningful adverse effects or biochemical safety parameters (e.g., hepatic, renal, or hematological markers) [15]. Taken together, these observations support the overall safety and tolerability of CL22205 across diverse female populations.

CONCLUSION

In conclusion, CL22205 demonstrated clinically relevant improvements in reproductive, endocrine, and metabolic parameters in women diagnosed with PCOS, together with a favorable safety and tolerability profile. The multi-targeted nature of these effects aligns with the functional food paradigm, in which bioactive compounds influence physiological processes beyond basic nutritional roles. The steroidal saponins (shatavarins) present in *Asparagus racemosus* exhibit phytoestrogenic and metabolic-modulatory properties that may contribute to endocrine balance, insulin responsiveness, and ovarian function, key areas of interest within functional food and nutrition research. Collectively, the present findings support the relevance of CL22205 as a food-derived, bioactive-rich intervention and warrant larger, longer-term trials to confirm efficacy, assess long-term safety, and further elucidate its underlying mechanisms of action.

List of Abbreviations: AE: Adverse event; AMH: Anti-Müllerian hormone; ANCOVA: Analysis of covariance; BMI: Body mass index; CONSORT: Consolidated standards of reporting trials; E2 – 17β-estradiol; ER: Estrogen receptor, FSH: Follicle-stimulating hormone; GAGS: Global acne grading system; HOMA-IR: Homeostatic model assessment for insulin resistance; HPLC: High-performance liquid chromatography; HPO axis: Hypothalamic–pituitary–ovarian axis; ITT: Intention-to-treat; LH: Luteinizing hormone; mFG: Modified Ferriman–Gallwey score; PCOS: Polycystic Ovary Syndrome; PP: Per-protocol; SD: Standard deviation; SHBG: Sex hormone-binding globulin; TT: Total Testosterone

Authors' Contributions: SK and AMY designed the trial; SS and AIY conducted the study; SS and SD captured the data; SK, SD, and AIY analyzed the data; SS and AIY drafted the manuscript; SD and AMY reviewed and finalized the manuscript.

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REFERENCES

1. Awonuga AO, Camp OG, Abu-Soud HM. A review of nitric oxide and oxidative stress in typical ovulatory women and in the pathogenesis of ovulatory dysfunction in polycystic ovary syndrome. *Reprod Biol Endocrinol*. 2023;21:111. DOI: https://doi.org/10.1186/s12958-023-01159-6
2. Dong J, Rees DA. Polycystic ovary syndrome: pathophysiology and therapeutic opportunities. *BMJ Med.* 2023;2:e000548. DOI: https://doi.org/10.1136/bmjmed-2023-000548
3. Zheng L, Xu X, Zhou JZ, Hong L, He YF, Fang YX, et al. The burden of polycystic ovary syndrome-related infertility in 204 countries and territories, 1990–2021: an analysis of the Global Burden of Disease Study 2021. *Front Endocrinol (Lausanne)*. 2025;16:1559246. DOI: https://doi.org/10.3389/fendo.2025.1559246
4. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. *J Clin Med.* 2023;12:1454. DOI: https://doi.org/10.3390/jcm12041454
5. Daniele S, Chelucci E, Scarfò G, Artini PG. Molecular research on polycystic ovary syndrome (PCOS). *Biomedicines.* 2023;11:1358. DOI: https://doi.org/10.3390/biomedicines11051358
6. Chang KJ, Chen JH, Chen KH. The pathophysiological mechanism and clinical treatment of polycystic ovary syndrome: a molecular and cellular review of the literature. *Int J Mol Sci.* 2024;25(16):9037. DOI: https://doi.org/10.3390/ijms25169037
7. Lonardo MS, Cacciapuoti N, Guida B, Di Lorenzo M, Chiurazzi M, Damiano S, et al. Hypothalamic–ovarian axis and adiposity relationship in polycystic ovary syndrome: physiopathology and therapeutic options for the management of metabolic and inflammatory aspects. *Curr Obes Rep.* 2024;13(1):51–70. DOI: https://doi.org/10.1007/s13679-023-00531-2
8. Longo M, Liuzzi F, De Carlini S, La Marca A. The role of luteinizing hormone in follicle development: from physiology to new clinical implications. *Reprod Biol Endocrinol.* 2025;23(Suppl 1):22. DOI: https://doi.org/10.1186/s12958-025-01353-8
9. Rashid R, Mir SA, Kareem O, Ali T, Ara R, Malik A, et al. Polycystic ovarian syndrome: current pharmacotherapy and clinical implications. *Taiwan J Obstet Gynecol*. 2022;61:40–50. DOI: https://doi.org/10.1016/j.tjog.2021.11.009
10. Ee C, Tay CT. Pharmacological management of polycystic ovary syndrome. *Aust Prescr*. 2024;47(4):109–112. DOI: https://doi.org/10.18773/austprescr.2024.030
11. Shimoda H, Takeda S, Takarada T, Kato Y, Shimizu N, Toda K, et al. Hydroxypterocarpans with estrogenic activity in Aguaje, the fruit of Mauritia flexuosa (Peruvian moriche palm). *Bioact Compd Health Dis*. 2019;2(4):64-77. DOI: https://doi.org/10.31989/bchd.v2i4.585
12. Takara T, Yamamoto K, Suzuki N, Yamashita S, Iio S, Noguchi H, et al. Moriche Palm (Aguaje) Extract improves indefinite complaints in Japanese females: arandomized, placebo-controlled, double-blind trial. *Funct Foods Health Dis*. 2020;10(9):379-396. DOI: https://www.doi.org/10.31989/ffhd.v10i9.742
13. Martirosyan DM, Ekblad M. Functional foods classification system: exemplifying through analysis of bioactive compounds. *Funct Food Sci*. 2022; 2(4): 94-123. DOI: https://www.doi.org/ffs.v2i4.919
14. Akhtar S, Gupta AK, Naik B, Kumar V, Ranjan R, Jha AK, et al. Exploring pharmacological properties and food applications of *Asparagus racemosus* (Shatavari). *Food Chem Adv.* 2024;4:100689. DOI: https://doi.org/10.1016/j.focha.2024.100689
15. Yadav P, Yadav S, Vedururu SS, Kumari G. A standardized *Asparagus racemosus* root extract improves hormonal balance and menstrual health and reduces vasomotor symptoms in perimenopausal women: a randomized, double-blind, placebo-controlled study. *J Am Nutr Assoc.* 2025;1–11. DOI: https://doi.org/10.1080/27697061.2025.2510474
16. Yadav P, Yadav S, Vedururu SS, Kumari G. Clinical assessment of CL22209, a standardized proprietary extract of *Asparagus*

racemosus, for mitigating vasomotor and menstrual symptoms in perimenopausal women: A randomized, double-blind, placebo-controlled study. *Funct Foods in Health Dis*. 2025;15(7):415-443.
DOI: https://doi.org/10.31989/ffhd.v15i7.1684

17. Christ JP, Cedars MI. Current guidelines for diagnosing polycystic ovary syndrome. *Diagnostics.* 2023;13:1113.
DOI: https://doi.org/10.3390/diagnostics13061113
18. Yang J, Wang M, Zhou D, Ye H, Huang G, Lian X, et al. Follicular sphericity based on three-dimensional transvaginal ultrasound algorithms predicts ovarian responsiveness to in vitro fertilization. *J Ovarian Res.* 2025;18(1):197.
DOI: https://doi.org/10.1186/s13048-025-01771-7
19. Elliott J, Liu K, Motan T. Guideline No. 444: hirsutism—evaluation and treatment. *J Obstet Gynaecol Can.* 2023;45(12):102272.
DOI: https://doi.org/10.1016/j.jogc.2023.102272
20. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. *Int J Dermatol.* 1997;36:416–418.
DOI: https://doi.org/10.1046/j.1365-4362.1997.00099.x
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412–419.
DOI: https://doi.org/10.1007/BF00280883
22. Kuek S, Wang W, Gui S. Efficacy of Chinese patent medicine Tian Gui capsule in patients with polycystic ovary syndrome: a randomized controlled trial. *Zhong Xi Yi Jie He Xue Bao*. 2011;9:965–972.
DOI: https://doi.org/10.3736/jcim20110907
23. Oyovwi MO, Chijiokwu EA, Ben-Azu B, Ugwuishi EW, Jeroh E. Shatavari (*Asparagus racemosus*): a promising ally for fertility. *Curr Nutr Rep.* 2025;14:108.
DOI: https://doi.org/10.1007/s13668-025-00694-5
24. Lonardo MS, Cacciapuoti N, Guida B, Di Lorenzo M, Chiurazzi M, Damiano S, et al. Hypothalamic–ovarian axis and adiposity relationship in polycystic ovary syndrome: physiopathology and therapeutic options for the management of metabolic and inflammatory aspects. *Curr Obes Rep.* 2024;13(1):51–70.
DOI: https://doi.org/10.1007/s13679-023-00531-2
25. Longo M, Liuzzi F, De Carlini S, La Marca A. The role of luteinizing hormone in follicle development: from physiology to new clinical implications. *Reprod Biol Endocrinol*. 2025;23(Suppl 1):22.
DOI: https://doi.org/10.1186/s12958-025-01353-8
26. Wang K, Li Y, Chen Y. Androgen excess: a hallmark of polycystic ovary syndrome. *Front Endocrinol (Lausanne).* 2023;14:1273542.
DOI: https://doi.org/10.3389/fendo.2023.1273542
27. Fontes AFS, Reis FM, Cândido AL, Gomes KB, Tosatti JAG. Influence of metformin on hyperandrogenism in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized clinical trials. *Eur J Clin Pharmacol.* 2023;79(4):445–460.
DOI: https://doi.org/10.1007/s00228-023-03461-z
28. Melin J, Forslund M, Alesi S, Piltonen T, Romualdi D, Spritzer PM, et al. Metformin and combined oral contraceptive pills in the management of polycystic ovary syndrome: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2024;109(2):e817–e836.
DOI: https://doi.org/10.1210/clinem/dgad465
29. Sharma R, Jaitak V. *Asparagus racemosus* (Shatavari) targeting estrogen receptor α: an in vitro and in silico mechanistic study. *Nat Prod Res.* 2020;34(11):1571–1574.
DOI: https://doi.org/10.1080/14786419.2018.1517123
30. Ademola J, Ajgaonkar A, Debnath T, Debnath K, Langade J. Efficacy and safety of Shatavari root extract (*Asparagus racemosus*) for menopausal symptoms: a randomized, double-blind, three-arm, placebo-controlled study. *Front Reprod Health.* 2025;7:1654503.
DOI: https://doi.org/10.3389/frph.2025.1654503
31. Wang K, Li Y. Signaling pathways and targeted therapeutic strategies for polycystic ovary syndrome. *Front Endocrinol (Lausanne).* 2023;14:1191759.
DOI: https://doi.org/10.3389/fendo.2023.1191759
32. Zhao H, Zhang J, Cheng X, Nie X, He B. Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation, and treatment. *J Ovarian Res.* 2023;16(1):9.
DOI: https://doi.org/10.1186/s13048-022-01091-0
33. Sankhwar P, Jaiswar SP, Yadav S, Awasthi V, Goel A, Kumar P, et al. Beneficial effects of a novel fenugreek seed extract (*Trigonella foenum-graecum*, Furocyst®) in women with polycystic ovary syndrome: a follow-up compliance clinical investigation. *J Am Nutr Assoc.* 2023;42(7):691–699.
DOI: https://doi.org/10.1080/27697061.2022.2145526
34. Chew HSJ, Dalakoti M, Leow MKS, Sun L, Ang JHC, Foo R. Waist circumference remains the better predictor of insulin resistance compared to the 2025 Lancet Commission

definition on clinical obesity. *Diabetes Obes Metab.* 2025;27(11):6775–6778.
DOI: https://doi.org/10.1111/dom.70052

35. Papagianni O, Bountziouka V, Maniati E, Pegkos A, Dimou C, Karantonis HC, et al. The frequency of consumption of selective functional foods with functionality is related to improved anthropometric obesity indices: A cross-sectional study in Greek and Cypriots adults. *Funct Food Sci*. 2024;4(4):134-152.
DOI: https://doi.org/10.31989/ffs.v4i4.1274
36. Cizmarova B, Birkova A, Hubkova B. Chemical composition of olive oil – an essential component of the Mediterranean diet and its impact on human health. *Funct Food Sci*. 2022;2(6):136-143. DOI: https://www.doi.org/ffs.v2i6.940
37. Hasnani D, Fortes SI, López ACL, Chavda V: Insulin resistance and its biochemical basis in metabolic syndrome. In Biochemical Mechanisms for Metabolic Syndrome (Advances in Biochemistry in Health and Disease). Volume 31. Edited by Gandhi T, Mehta A. Cham (CH): Springer; 2024.
DOI: https://doi.org/10.1007/978-3-031-75686-3_2
38. Keyif B, Yavuzcan A. Visceral and dysfunctional adiposity indices as predictors of insulin resistance and metabolic syndrome in women with polycystic ovary syndrome: a cross-sectional study. *Medicina (Kaunas).* 2025;61(3):424.
DOI: https://doi.org/10.3390/medicina61030424
39. He L, Su Z, Wang S. The anti-obesity effects of polyphenols: a comprehensive review of molecular mechanisms and signaling pathways in regulating adipocytes. *Front Nutr*. 2024;11:1393575.
DOI: https://doi.org/10.3389/fnut.2024.1393575
40. Rendine M, Marino M, Martini D, Riso P, Møller P, Del Bo' C. Effect of (poly)phenols on lipid and glucose metabolism in 3T3-L1 adipocytes: an integrated analysis of mechanistic approaches. *Curr Obes Rep.* 2025;14(1):64.
DOI: https://doi.org/10.1007/s13679-025-00656-6
41. Steiner BM, Berry DC. The regulation of adipose tissue health by estrogens. *Front Endocrinol (Lausanne).* 2022; 13:889923.
DOI: https://doi.org/10.3389/fendo.2022.889923
42. Bardhi O, Dubey P, Palmer BF, Clegg DJ. Oestrogens, adipose tissue, and environmental exposures influence obesity and diabetes across the lifecycle. *Proc Nutr Soc.* 2024;83(4):263–270. DOI: https://doi.org/10.1017/S0029665124000119