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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

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ABSTRACT

Background: Vasomotor symptoms (VMS) and menstrual discomfort are prevalent and distressing manifestations during the menopausal transition in women, significantly impairing the quality of life (QoL). *Asparagus racemosus* Willd. (family: Asparagaceae) (Shatavari), a revered Rasayana herb in Ayurvedic medicine, has long been used to support female reproductive health.

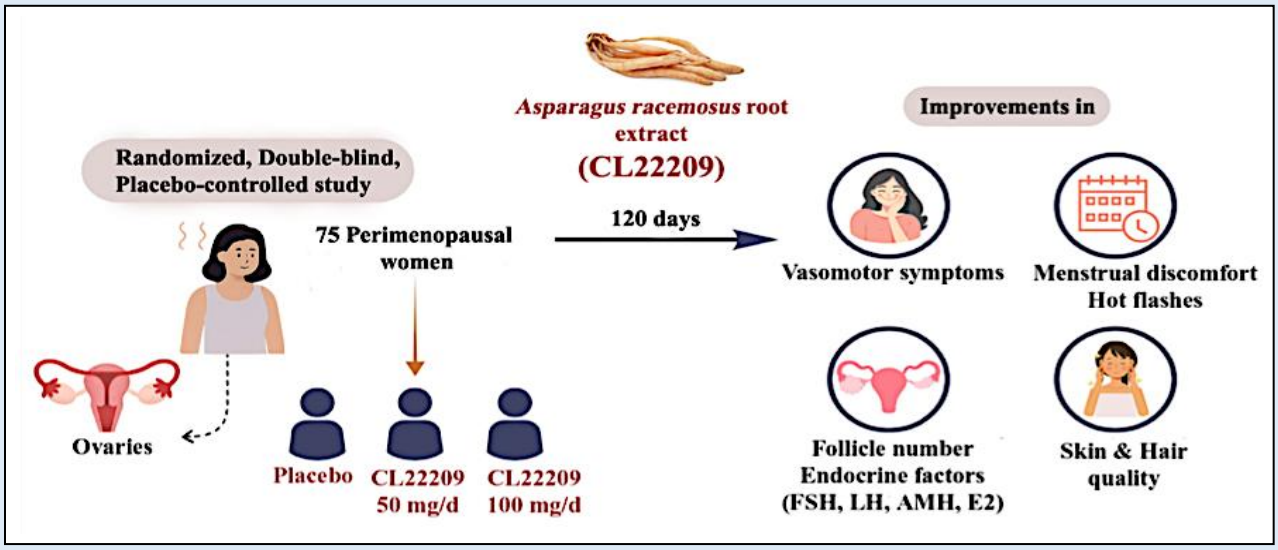
Objective: We investigated the therapeutic potential of CL22209, a standardized *A racemosus* root extract, in early perimenopausal women. Precisely, it assessed the extract's ability to alleviate vasomotor symptoms, menstrual discomfort, and hormonal dysregulation through a comprehensive evaluation of symptom scores, reproductive hormone levels, ovarian follicle counts, and patient-reported outcomes, and ensuring its safety and tolerability over a 120-day supplementation.

Methods: In this randomized, double-blind, placebo-controlled investigation, 75 early perimenopausal women (aged 40–50 years) with mild-to-moderate VMS were assigned to receive either CL22209 (50- or 100 mg/day) or placebo over a period of 120 consecutive days. The primary endpoint was the change in total Menopausal Rating Scale (MRS) scores. Secondary outcomes included Hot Flash Weekly Weighted Score (HFWWS), Menstrual Symptom Questionnaire (MSQ) score, follicle count via ultrasonography, and serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), and 17β-estradiol (E2) in the participants. Skin and hair quality, as well as patient-reported outcomes, were also assessed. Safety and tolerability were evaluated through monitoring of hematology, clinical biochemistry, urinalysis, and adverse events.

Results: Supplementation with CL22209 at both 50 mg and 100 mg/day significantly reduced MRS scores and HFWWS as compared to baseline and placebo ($p < 0.001$). Menstrual symptoms, particularly spasmodic and congestive dysmenorrhea, showed marked improvement. Notably, a dose-dependent modulation of FSH, LH, AMH, and E2 levels was observed. No serious adverse events were reported.

Conclusion: CL22209 demonstrates the efficacy and safety profile as a natural, non-hormonal intervention for alleviating perimenopausal symptoms, providing clinical benefits in symptom reduction, hormonal regulation, and dermatological well-being. The study provides the first clinical evidence of CL22209's dual central and peripheral endocrine modulation, positioning it as a novel functional food for integrative women's health support during the menopausal transition.

Keywords: *Asparagus racemosus* (Shatavari), Functional Food, Hormonal balance, Menopausal Rating Scale (MRS), Perimenopause. Phytoestrogens, Safety, Vasomotor symptoms.



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INTRODUCTION

Perimenopause refers to the transitional period preceding menopause, marked by progressive hormonal fluctuations and the gradual depletion of ovarian follicles. A wide array of physical, emotional, and neuroendocrine changes characterizes this phase. It typically spans 5 to 10 years, although its onset, duration, and severity can vary significantly among individuals [1].

A hallmark feature of perimenopause is the emergence of vasomotor symptoms (VMS)—including hot flashes and night sweats—which are precipitated by fluctuating levels of endogenous estradiol levels. These symptoms have a severe impact on daily functioning and overall well-being [2]. Vasomotor symptoms (VMS), including hot flashes and night sweats, affect approximately 80% of women during the menopausal transition, with regional variations reflecting lifestyle and dietary differences: 74–80% in the United States, 65–75% in Europe, and as low as 15–30% in Asia [2]. These symptoms often persist for 7–10 years. They may last over a decade in specific ethnic subgroups, as evidenced by the Study of Women's Health Across the Nation (SWAN) study, which reported prolonged symptom duration in Black and Hispanic women. Up to 25% of women experience severe, daily disruptions, with greater than fifty percent reporting adverse effects on sleep, emotional well-being, and occupational functioning, underscoring the significant quality-of-life burden of VMS globally [2-3].

Hormone Therapy (HT) remains the cornerstone intervention for alleviating VMS and improving quality of life during perimenopause. However, the use of hormone therapy remains limited due to associated health risks, notably elevated incidences of breast cancer, venous thromboembolism, and ischemic stroke [4]. In such cases, non-hormonal pharmacotherapies, including selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) such as Gabapentin, Pregabalin, and Clonidine, offer partial relief. Nonetheless, these therapies have adverse effects such as dry mouth, nausea, dizziness, reduced libido, and sleep disturbances [5]. Given these limitations, interest in Complementary and Alternative Medicine (CAM) is on the rise. Evidence supports the use of cognitive behavioral therapy, lifestyle modification, and plant-based interventions, particularly those involving phytoestrogens, as viable strategies to manage menopausal symptoms [5-7].

Asparagus racemosus, commonly known as Shatavari, is a revered medicinal herb in Ayurvedic medicine, long been used for promoting female reproductive health and vitality. The name "Shatavari" originates from Sanskrit as “a woman who possesses a hundred husbands,” reflecting its traditional use as a tonic for female reproductive health, fertility, vitality, vigor, and hormonal balance [8]. Recognized by both the Indian and British Pharmacopoeias, Shatavari is rich in phytoestrogens, notably steroidal saponins such as Shatavarins I–IV, which are reported to exert estrogen-like activity via interaction with estrogen receptors [9]. Additionally, bioactive compounds, including flavonoids, polyphenols, and alkaloids such as racemosol, racemofuran, asparagamine A, racemosides contribute to its antioxidant, neuroprotective, anti-inflammatory, and adaptogenic properties [9]. Studies suggest that Shatavari modulates the hypothalamic–pituitary–ovarian axis, enhances ovarian folliculogenesis, and supports hormonal homeostasis, making it a suitable candidate for managing stress-related reproductive disorders [10].

CL22209 is a proprietary extract of *A. racemosus* root, standardized to contain not less than 15% of total Shatavarins, developed to enhance the product’s estrogenic and rejuvenating abilities. Given the established role of steroidal saponins in modulating estrogen receptor activity, CL22209 is hypothesized to support hormonal regulation, symptom relief, and

overall quality of life in women experiencing perimenopause. A 120-day, randomized, double-blind, placebo-controlled trial was conducted to evaluate the tolerability, safety, efficacy, and mechanistic role of CL22209 supplementation in women undergoing the perimenopausal transition. This study assessed vasomotor disturbances (hot flashes), menstrual discomfort, mood fluctuations, and skin and hair quality and also measured serum levels of endocrine factors, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17β-estradiol (E2), and anti-Müllerian hormone (AMH). Moreover, the present investigation also evaluated the long-term tolerability and safety of CL22209 supplementation by measuring the participants' complete blood biochemistry, hematology, and urinalysis.

MATERIALS AND METHODS

Investigational Product: CL22209: CL22209 is a patent-pending formulation derived from the tuberous roots of *Asparagus racemosus*. The raw plant material used in this study was wild-harvested in the Morena district of Madhya Pradesh, India, and subjected to rigorous quality control procedures following taxonomic authentication of the plant material by a certified botanist and verified against an authenticated reference specimen in the herbarium. A voucher specimen (Accession No. 6243) has been preserved and registered at the Chemiloids Life Sciences R&D Center, located in Aswaraopet, Andhra Pradesh, India. This novel botanical formulation comprises three extraction components: (i) a water extract of the tuberous root, (ii) a hydro-alcohol extract of the spent raw material, and (iii) an adsorbent resin-treated aqueous extract. These components were combined in precise proportions to yield a homogeneous powder, in which eight parts of the combined extract were blended uniformly with two parts of pharmaceutical-grade excipients to produce the final formulation, designated as CL22209. The final extract was standardized to contain not less than 15% of total shatavarins, as quantified using high-performance liquid chromatography (HPLC) (Figure 1). CL22209 is produced in a Current Good Manufacturing Practices (cGMP) facility of Laila Nutraceuticals, Vijayawada, India.

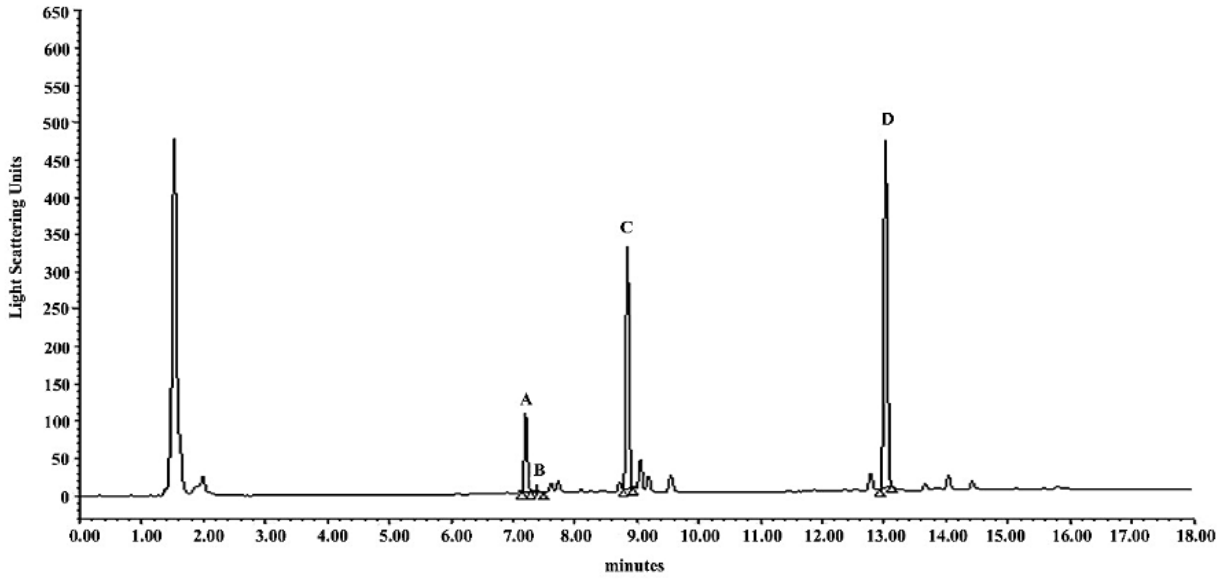

Figure 1: A representative HPLC chromatogram depicts active shatavarins peaks A, B, C, and D as Shatavarin I, Shatavarin IX, Dehydroshatavarin I, and Shatavarin IV eluted at 7.205, 7.385, 8.848, and 13.018 minutes, respectively.

Study protocol registration and ethics approval: This study was prospectively registered with the Clinical Trials Registry of India (CTRI) under the registration number CTRI/2023/10/058694. Ethical approval (no. ECR/1261/Inst/UP/2019) was obtained from the Institutional Ethics Committee of Lifeline Hospital and Research Centre, Azamgarh, Uttar Pradesh, India. Prior to enrolment, all participants received detailed verbal and written information regarding the nature, objectives, procedures, and potential risks and benefits of the study. Each participant provided written informed consent, following the principles outlined in the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines [11-12].

Participant selection criteria and sample size estimation: Recruited participants were sexually active women [age: 40-50 y; body mass index (BMI): 22-29 kg/m²] and classified as early perimenopausal based on the STRAW+10 criteria (stage -2). This classification requires the presence of irregular menstrual cycles, without skipped periods, and a cycle length variability exceeding seven days compared to the participant's typical cycle. The complete inclusion and exclusion criteria are summarized in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion Criteria
• Females aged 40–50 years, BMI 22–29 kg/m², sexually active
• Early perimenopause (STRAW −2): irregular cycles >7 days, FSH >20 IU/L (Day 3–5)
• MRS total score ≥18
• Normal thyroid profile and fasting glucose <125 mg/dL
• Clinically healthy (based on history, vitals, hematology, biochemistry, urine tests)
• Use of non-hormonal contraception
• Willingness and ability to provide informed consent
Exclusion Criteria
• Hormonal, herbal, steroid, or recreational drug use in past 6 months
• History of CVD, thromboembolism, or cancer (gynecologic/other within 5 years), recent surgery
• Ovarian cysts ≥4 cm on pelvic USG
• Systolic blood pressure ≥ 160 or diastolic blood pressure ≥100 mmHg
• Pregnant, nursing, or active infectious/contagious disease

A total sample size of 75 participants (25 per group) was calculated to provide 80% statistical power at a 95% confidence level (two-tailed $\alpha = 0.05$) to detect a mean difference of 14.4 points in the total Menopause Rating Scale (MRS) scores between the treatment and placebo groups. The calculation assumed a pooled standard deviation (SD) of 7 and an anticipated dropout rate of 10%, based on effect size estimates derived from previously published clinical research and statistical analysis [13].

Study Design: This randomized, double-blind, placebo-controlled, three-arm clinical trial was conducted at Lifeline Hospital and Research Centre, Azamgarh, Uttar Pradesh, India, between November 2023 and June 2024. Participant recruitment was carried out through the hospital's outpatient departments (OPDs), targeting women presenting with menopausal complications consistent with early perimenopause. After screening for eligibility, participants were randomized into one of three groups: (i) Placebo, (ii) CL22209 50 mg/day, and (iii) CL22209 100 mg/day (Figure 1).

Randomization and Blinding: Randomization was performed using block randomization generated through the SAS PROC PLAN procedure to ensure equal distribution across study arms [14]. Upon enrolment, each participant was assigned a unique sequential identification number. The randomization sequence was prepared by an independent statistician not involved in participant recruitment or clinical assessments to maintain allocation concealment. The participants and investigators were blinded to the intervention groups. Blinding was maintained throughout the study: the randomization codes were securely preserved by the statistician and remained undisclosed until the final database lock and completion of statistical analyses.

Intervention and Follow-up: Each participant received the investigational product (IP), either (i) Placebo, (ii) CL22209 50 mg/day, or (iii) CL22209 100 mg/day, stored in high-density polyethylene (HDPE) bottles containing size '1' hard gelatin capsules, sufficient until the next scheduled visit. Participants were instructed to ingest one capsule daily, with or after a meal. Study visits were scheduled at screening, baseline (day 1), and follow-up assessments on days 30, 60, and 120 of the intervention (Figure 2).

At each visit, adherence to the intervention was assessed via capsule count. Participants were considered non-adherent if more than 10% of the capsules dispensed remained unused. General health, well-being, and the presence of any adverse events (AEs) were evaluated and recorded by the study investigators at every visit. Additionally, the principal investigator (PI) conducted detailed physical examinations and safety monitoring to assess the clinical status and document any emergent or ongoing AEs.

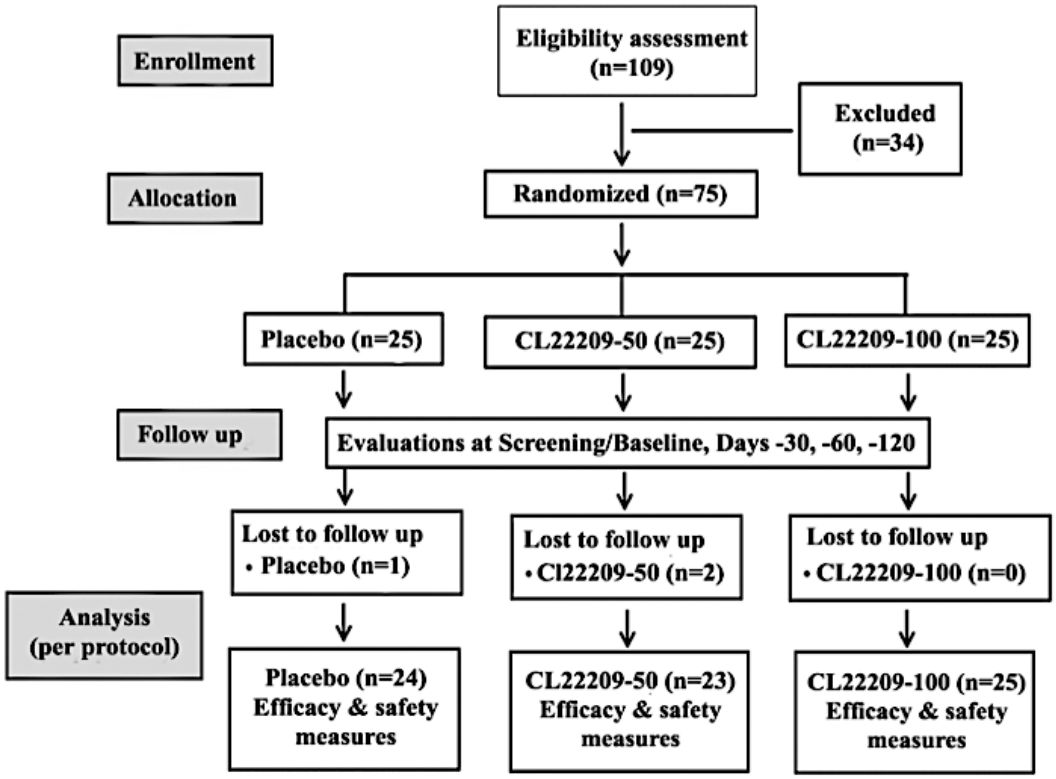

Figure 2: A CONSORT-compliant flow diagram outlines the sequential progression of participants from initial recruitment through randomization, intervention allocation, follow-up, and study completion.

Outcome measures

Menopause Rating Scale (MRS): The MRS is a validated and internationally recognized instrument developed to assess the severity of menopausal symptoms across three primary domains: somatic, psychological, and urogenital [15]. The MRS enables both clinical and research-based quantification of symptom burden among peri- and postmenopausal women. The scale comprises 11 self-reported items, each rated on a 6-point Likert-type scale, where 0 indicates an absence of symptoms, and 5 represents symptoms of very severe intensity. The cumulative MRS score ranges from 0 to 55, with higher scores reflecting greater overall symptom severity. The MRS scores were evaluated in all participants at baseline and follow-up assessments on days 30, 60, and 120 of supplementation. Participants completed the questionnaire independently, following standard instructions provided by the study coordinators to ensure consistency. The MRS served as a primary outcome measure for evaluating treatment-related changes in overall menopausal symptomatology and domain-specific effects of the intervention.

Hot Flash Weekly Weighted Score (HFWWS): To quantitatively assess the burden of vasomotor symptoms, particularly hot flashes, the Hot Flash Weekly Weighted Score (HFWWS) was employed as a validated metric that integrates both the frequency and severity of hot flashes over seven days. This composite score provides a more nuanced and standardized evaluation of symptom intensity as compared to frequency-based measures alone [16].

The HFWWS was calculated using the following weighted formula: HFWWS = (Number of slight hot flashes × 1) + (Number of moderate hot flashes × 2) + (Number of severe hot flashes × 3)

Participants were instructed to maintain daily symptom diaries, in which they recorded the number of hot flashes experienced per day, categorized by severity level (i) slight, (ii) moderate, or (iii) severe, based on predefined descriptors. Study coordinators provided clear guidance and diary templates to ensure consistency and reliability of self-reported data.

Menstrual Symptoms Questionnaire (MSQ): The MSQ is a validated, multi-dimensional tool designed to assess the severity and frequency of menstruation-related symptoms, with specific sensitivity to both spasmodic and congestive dysmenorrhea [17]. It evaluates symptom burden across five domains: (i) Pain-related symptoms (e.g., abdominal cramps, back pain, headaches), (ii) Gastrointestinal disturbances (e.g., nausea, bloating, constipation, diarrhea), (iii) Affective symptoms (e.g., irritability, mood swings, anxiety, depression), (iv) Cognitive and behavioral changes (e.g., fatigue, sleep disruption, impaired focus), and (v) Systemic manifestations (e.g., breast tenderness, swelling, dizziness). Participants rated each symptom by severity and frequency, generating domain-specific and composite scores. The MSQ scores were recorded at baseline and on days 30, 60, and 120 of treatment to assess changes related to therapy over time.

Ultrasonography Assessments: Transabdominal ultrasonography was performed using the TUS-X100 System (Canon Medical Systems, Otawara, Japan) with a PUV-375BT convex array transducer (2–6 MHz) optimized for high-resolution pelvic imaging. All evaluations were conducted under standardized conditions by trained sonographers using inbuilt imaging software (version 4.0). To enhance visualization, participants consumed 1 liter of water one hour before scanning to ensure bladder distension and improved acoustic coupling. Scans were conducted in the supine position to assess antral follicle count (AFC), ovarian size, and stromal morphology.

Biomarker Analysis: Fasting venous blood samples were collected during the early follicular phase (Days 3–5 of the menstrual cycle) at both baseline (Day 1) and post-intervention (Day 120) to assess endocrine markers related to ovarian function and hormonal regulation. Blood was drawn under standardized conditions, allowed to clot at room temperature, and centrifuged at 3000 rpm for 15 minutes to isolate serum, which was subsequently aliquoted and stored at –80°C until analysis.

Quantitative determination of the serum biomarkers [Follicle-Stimulating Hormone (FSH): Cat# E-EL-H1143; Luteinizing Hormone (LH): Cat# E-EL-H6019; Anti-Müllerian Hormone (AMH): Cat# E-OSEL-H0004; 17β-Estradiol (E2): Cat# EH2RB] was performed using enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's validated protocols (Elabscience Biotechnology Inc., Houston, TX, USA). The detection limits of FSH, LH, AMH, and E2 assay kits are 0.94 mIU/mL, 0.10 mIU/mL, 46.88 pg/mL, and 0.9 ng/mL, respectively.

Hair and Skin quality Subjective Self-Assessment of Hair Quality (SSAHQ): The SSAHQ is a patient-reported outcome measure specifically designed to evaluate perceived hair and scalp health [18]. This four-item questionnaire captures key parameters reflecting cosmetic and dermatological well-being. Participants rated the following domains using a graded scale: (i) Hair fall rate – categorized from excessive shedding (>100 strands/day) to minimal loss (<10 strands/day); (ii) Hair texture – rated from coarse/frizzy to smooth/soft; (iii) Hair volume – from thin/sparse to thick/full and (iv) Scalp condition – specifically, scalp itching, ranging from none to severe pruritus.

Acne Severity Grading: Acne severity was evaluated using a standardized clinical grading system, widely recognized for its clarity and ease of implementation in dermatological assessments [19]. The scale categorizes acne as follows: Grade 1, non-inflammatory lesions (comedones); Grade 2, papular acne (mild inflammation); Grade 3, pustular acne (moderate inflammation); and Grade 4, nodulocystic acne (severe inflammation and deeper involvement).

Self-Assessment of Skin Quality: The skin condition was evaluated using the Subject's Self-Assessment of Skin Questionnaire, a validated instrument designed to capture participant-perceived improvements in facial skin quality [20]. Seven parameters were assessed: Radiance, Freshness, Luminosity, Smoothness, Texture, Firmness, and Hydration. Each parameter was rated on a 0-10 visual analog scale (VAS), where 0 represented the poorest skin quality and 10 represented the optimal skin quality.

Other Assessments: Patient satisfaction and treatment outcomes or effectiveness were assessed using the Integrative Medicine Patient Satisfaction Scale (IMPSS) [21] and the Integrative Medicine Outcome Scale (IMOS) [21]. Participants self-reported their experiences and the perceived efficacy on a five-point scale from highly effective to not effective in IMOS and from very satisfied to not very satisfied in IMPSS.

Safety Parameters: Comprehensive safety assessments were conducted during screening and at the end of the intervention period (day 120) to monitor participant well-being and detect any treatment-emergent adverse effects. These evaluations included vital sign measurements, fasting blood biochemistry, urinalysis, and systematic adverse event (AE) reporting, all conducted by the principles of Good Clinical Practice (GCP). A detailed serum biochemistry panel was performed to evaluate metabolic, hepatic, renal, electrolyte, and cardiovascular-muscular function. The

measured parameters included fasting blood glucose (FBG), total cholesterol, HDL-C, LDL-C, and triglycerides; Alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and albumin; creatinine, blood urea nitrogen (BUN), and uric acid; sodium, potassium, and creatine kinase (CK). The hematological evaluation included red blood cell (RBC) count, hemoglobin (Hb), platelet count, total and differential leukocyte counts, and erythrocyte sedimentation rate (ESR). Urinalysis assessed pH, color, specific gravity, and the presence of protein, glucose, and RBC.

Statistical Analysis: Efficacy analyses were performed on the per-protocol (PP) population, which included 49 participants who received at least one dose of the investigational product and completed a minimum of one post-baseline efficacy assessment. Safety analyses were conducted using the intent-to-treat (ITT) population, defined as all participants who received at least one dose of the study supplement, regardless of adherence or protocol deviations. Baseline demographic and clinical characteristics between treatment arms (CL22209 and placebo) were compared using Chi-square tests for categorical variables and unpaired t-tests for continuous variables to ensure randomization balance.

For outcomes assessed across multiple time points, repeated measures analysis of variance (ANOVA) was used to evaluate within-group changes over time. To control multiple comparisons, Bonferroni post hoc corrections were applied. Between-group comparisons at specific time points were analyzed using one-way ANOVA, also followed by Bonferroni-adjusted post hoc testing to identify pairwise significance. For parameters measured at two time-points within the same group (e.g., baseline vs. day 120), paired t-tests were employed. Statistical significance was defined as $p < 0.05$ under a two-tailed hypothesis with a 95% confidence interval (CI). All statistical analyses were performed using validated software (SPSS v26.0), and data are reported as mean ± standard deviation (SD).

RESULTS

Baseline Characteristics: A total of seventy-five perimenopausal women (age: 40-50 years; BMI: 22-29 kg/m²) were recruited in this study; the subjects were randomized in a 1:1:1 ratio to receive either placebo, CL22209 (50 mg/day), or CL22209 (100 mg/day) over a period of 120 consecutive days of supplementation. At baseline, the demographic profiles were comparable across the groups. However, the total MRS scores between the CL22209 groups and placebo were significantly different. Adherence to the investigational product (IP) was high in the study groups. Mean compliances were 98.10%, 93.97%, and 99.93% in the placebo, CL22209 50 mg/day, and CL22209 100 mg/day groups, respectively.

Table 2: Participants' demographic and baseline characteristics.

Parameters	Mean ± SD	p-value (vs. placebo)	95% CI (vs. placebo)
Age (years)			
Placebo (n=25)	43.36 ± 2.75	-	-
CL22209-50mg (n=25)	42.80 ± 2.20	0.4306	-0.86, 1.98

Parameters	Mean ± SD	p-value (vs. placebo)	95% CI (vs. placebo)
CL22209-100mg (n=25)	43.44 ± 2.50	0.9148	-1.41, 1.57
BMI (kg/m^2)			
Placebo (n=25)	23.75 ± 1.26	-	-
CL22209-50mg (n=25)	23.90 ± 1.14	0.6772	-0.53, 0.83
CL22209-100mg (n=25)	24.14 ± 0.61	0.1713	-0.17, 0.95
Height (cm)			
Placebo (n=25)	160.08 ± 3.34	-	-
CL22209-50mg (n=25)	158.40 ± 5.14	0.177	-0.79, 4.15
CL22209-100mg (n=25)	158.00 ± 4.20	0.0586	-0.08, 4.24
Body weight (kg)			
Placebo (n=25)	60.87 ± 3.67	-	-
CL22209-50mg (n=25)	59.93 ± 3.45	0.3534	-1.09, 2.97
CL22209-100mg (n=25)	60.31 ± 3.41	0.5763	-1.45, 2.57
MRS score			
Placebo (n=25)	38.63 ± 1.74	-	-
CL22209-50mg (n=25)	36.17 ± 1.47	<0.001	1.54, 3.38
CL22209-100mg (n=25)	36.52 ± 1.87	<0.001	1.08, 3.14

Values are presented as mean ± SD. Data are analyzed using unpaired t-test for intergroup comparisons.

BMI: Body mass index, MRS: Menopausal rating scale, CI: Confidence interval

Only three participants discontinued the study due to voluntary withdrawal of consent: one subject from the placebo group and two from the CL22209-50 mg/day group. Therefore, efficacy analyses were performed in per-protocol populations: placebo (n = 24), CL22209 at 50 mg/day (n = 23), and CL22209 at 100 mg/day (n = 25).

Menopausal Rating Scale (MRS) score: CL22209 significantly reduced the severity of menopausal symptoms. On day 120, the total MRS score decreased by 51.42% ($p < 0.001$) and 72.95% ($p < 0.001$) in the 50- and 100 mg/day groups, respectively, while the placebo group showed a 22.86% ($p < 0.001$) reduction compared to baseline. Both treatment groups demonstrated statistically significant improvements over the placebo ($p < 0.001$) at the study's completion (Table 3). The subscale analysis also revealed that at the end of the trial, the Somatic, Psychological, and Urogenital symptoms were also significantly ($p < 0.001$) improved in the low (43.04%, 52.26%, 23.26%) and high dose (70.46%, 73.04%, 53.73%) groups, respectively, as compared to the placebo (Table 3).

Table 3: Assessment of Menopausal Rating Scale (MRS) scores

Groups	Evaluation days	Score (Mean ± SD)	Change from baseline (Mean ± SD)	p-value (vs. baseline)	p-value (vs. placebo)	95% CI vs. placebo
Somatic symptoms						
Placebo	Baseline	13.92 ± 1.44	-	-	-	-
	Day 30	12.67 ± 1.27	-1.3 ± 1.59	0.005	-	-
	Day 60	11.83 ± 1.69	-2.1 ± 2.26	<0.001	-	-
	Day 120	10.92 ± 1.38	-3.0 ± 2.1	<0.001	-	-
CL22209-50 mg	Baseline	14 ± 1.21	-	-	1.000	-0.68, 0.84
	Day 30	12.22 ± 1.44	-1.8 ± 1.68	<0.001	1.000	-0.35, 1.25
	Day 60	9.48 ± 1.59	-4.5 ± 1.93	<0.001	<0.001	1.39, 3.31
	Day 120	6.22 ± 1.41	-7.78 ± 1.62	<0.001	<0.001	3.88, 5.52
CL22209-100 mg	Baseline	14.28 ± 0.89	-	-	1.000	-0.59, 1.32
	Day 30	11.24 ± 1.36	-3.0 ± 1.31	<0.001	0.001	0.67, 2.19
	Day 60	7.08 ± 1.00	-7.2 ± 1.19	<0.001	<0.001	3.96, 5.54
	Day 120	3.24 ± 1.23	-11.04 ± 1.31	<0.001	<0.001	6.93, 8.43
Psychological						
Placebo	Baseline	13.88 ± 0.54	-	-	-	-
	Day 30	12.67 ± 1.55	-1.2 ± 1.74	0.015	-	-
	Day 60	11.75 ± 1.48	-2.1 ± 1.36	<0.001	-	-
	Day 120	10.83 ± 1.46	-3.04 ± 1.46	<0.001	-	-
CL22209-50 mg	Baseline	11.22 ± 1.17	-	-	<0.001	2.14, 3.18
	Day 30	9.57 ± 1.04	-1.7 ± 1.53	0.001	<0.001	2.32, 3.88
	Day 60	7.96 ± 1.58	-3.3 ± 1.81	<0.001	<0.001	2.89, 4.69
	Day 120	5.17 ± 1.30	-6.04 ± 1.69	<0.001	<0.001	4.85, 6.47
CL22209-100 mg	Baseline	11.44 ± 1.04	-	-	<0.001	1.97, 2.91
	Day 30	9.36 ±1.38	-2.1 ± 1.55	<0.001	<0.001	2.47, 4.15
	Day 60	6.44 ± 1.04	-5.0 ± 1.44	<0.001	<0.001	4.57, 6.03
	Day 120	2.92 ± 1.12	-8.52 ± 1.66	<0.001	<0.001	7.17, 8.65

Groups	Evaluation days	Score (Mean ± SD)	Change from baseline (Mean ± SD)	p-value (vs. baseline)	p-value (vs. placebo)	95% CI vs. placebo
Urogenital						
Placebo	Baseline	10.83 ± 0.82	-	-	-	-
	Day 30	10.46 ± 0.88	-0.4 ± 1.24	0.921	-	-
	Day 60	8.96 ± 1.12	-1.9 ± 1.23	<0.001	-	-
	Day 120	8.04 ± 1.08	-2.79 ± 1.32	<0.001	-	-
CL22209-50 mg	Baseline	10.96 ± 0.82	-	-	1.000	-0.34, 0.60
	Day 30	10.09 ± 0.90	-0.9 ± 1.06	0.004	0.660	-0.15, 0.89
	Day 60	8.57 ± 1.34	-2.4 ± 1.56	<0.001	1.000	-0.33, 1.11
	Day 120	6.17 ± 1.56	-4.79 ± 1.83	<0.001	<0.001	1.08, 2.66
CL22209-100 mg	Baseline	10.80 ± 0.82	-	-	1.000	-0.44, 0.50
	Day 30	9.52 ± 0.65	-1.3 ± 1.31	<0.001	<0.001	0.49, 1.38
	Day 60	6.84 ± 0.99	-4.0 ± 1.21	<0.001	<0.001	1.51, 2.73
	Day 120	3.72 ± 1.28	-7.08 ± 1.61	<0.001	<0.001	3.64, 5.00
Total scores						
Placebo	Baseline	38.63 ± 1.74	-	-	-	-
	Day 30	35.79 ± 1.74	-2.83 ± 2.65	<0.001	-	-
	Day 60	32.54 ± 2.80	-6.1 ± 3.17	<0.001	-	-
	Day 120	29.79 ± 2.98	-8.83 ± 3.74	<0.001	-	-
CL22209-50 mg	Baseline	36.17 ± 1.47	-	-	<0.001	1.54, 3.38
	Day 30	31.87 ± 2.16	-4.3 ± 2.8	<0.001	<0.001	2.77, 5.07
	Day 60	26.00 ± 3.32	-10.2 ± 3.24	<0.001	<0.001	4.74, 8.34
	Day 120	17.57 ± 3.09	-18.6 ± 3.07	<0.001	<0.001	10.44, 14.00
CL22209-100 mg	Baseline	36.52 ± 1.87	-	-	<0.001	1.08, 3.14
	Day 30	30.12 ± 2.03	-6.4 ± 2.61	<0.001	<0.001	4.58, 6.76
	Day 60	20.36 ± 1.35	-16.2 ± 1.97	<0.001	<0.0001	10.92, 13.44
	Day 120	9.88 ± 2.64	-26.64 ± 3.50	<0.001	<0.0001	18.29, 21.53

Values present as mean ± SD; placebo (n = 24), CL22209-50 (n = 23), and CL22209-100 (n = 25) A p-value < 0.05 indicates significance within each group for comparison (vs. baseline) using repeated measures ANOVA with Bonferroni correction and an intergroup significance (vs. placebo) using ANOVA with Post Hoc Bonferroni.

Menstrual Symptoms and Vasomotor Outcomes: Post-intervention analysis revealed significant, gradual, and dose-dependent improvements in both menstrual symptoms and vasomotor disturbances following supplementation of CL22209, as assessed by the Menstrual Symptoms Questionnaire (MSQ) and Hot Flash Weekly Weighted Scores (HFWWS) (Table 4).

In the congestive dysmenorrhea subdomain of the MSQ, participants receiving CL22209 demonstrated significant symptom relief. At the end of the study, the 50 mg/day and 100 mg/day groups showed mean improvements of 166.75% ($p < 0.001$) and 178.87% ($p < 0.001$), respectively, from baseline, whereas the placebo group showed a 35.99% ($p < 0.001$) improvement. Similar improvements were observed in the spasmodic dysmenorrhea domain scores, with 57.69% and 62.31% reductions ($p < 0.001$ vs. baseline) in the 50 mg/day and 100 mg/day CL22209 groups, respectively; the placebo group recorded 20.27% ($p<0.001$) reduction at the end of the study. Post-trial, the changes in dysmenorrhea subdomain scores in both CL22209 groups were significant ($p < 0.001$) compared to the placebo group (Table 4).

Table 4: Assessment of Menstrual symptoms Questionnaire (MSQ) scores and Hot flashes Weekly Weighted Scores (HFWWS)

Groups	Evaluation days	Mean ± SD	Change from baseline (Mean ± SD)	p-value (vs. baseline)	p-value (vs. placebo)	95% CI vs. placebo
Menstrual symptoms questionnaire (MSQ) scores						
Congestive dysmenorrhea						
Placebo	Baseline	19.17 ± 1.88	-	-	-	-
	Day 30	23.21 ± 2.57	4.0 ± 3.24	<0.001	-	-
	Day 60	25.42 ± 2.98	6.3 ± 4.07	<0.001	-	-
	Day 120	26.04 ± 1.85	6.9 ± 3.07	<0.001	-	-
CL22209-50 mg	Baseline	19.13 ± 2.56	-	-	1.000	-1.24, 1.32
	Day 30	29.52 ± 2.06	10.4 ± 2.81	<0.001	<0.001	4.94, 7.68
	Day 60	40.35 ± 1.85	21.2 ± 3.23	<0.001	<0.001	13.47, 16.39
	Day 120	51.04 ± 2.65	31.9 ± 3.60	<0.001	<0.001	23.66, 26.34
CL22209-100 mg	Baseline	19.12 ± 2.19	-	-	1.000	-1.11, 1.21
	Day 30	30.36 ± 2.29	11.2 ± 3.07	<0.001	<0.001	5.75, 8.55
	Day 60	42.16 ± 2.29	23.0 ± 3.09	<0.001	<0.001	15.22, 18.26
	Day 120	53.28 ± 1.65	34.2 ± 2.66	<0.001	<0.001	26.23, 28.25
Spasmodic dysmenorrhea						
Placebo	Baseline	48.83 ± 2.65	-	-	-	-
	Day 30	45.79 ± 2.77	-3.0 ± 3.68	0.003	-	-
	Day 60	41.38 ± 3.67	-7.5 ± 4.67	<0.001	-	-
	Day 120	38.96 ± 3.43	-9.9 ± 4.19	<0.001	-	-

Groups	Evaluation days	Mean ± SD	Change from baseline (Mean ± SD)	p-value (vs. baseline)	p-value (vs. placebo)	95% CI vs. placebo
CL22209-50 mg	Baseline	50.78 ± 3.37	-	-	0.069	0.23, 3.67
	Day 30	42.17 ± 2.42	-8.6 ± 3.49	<0.001	<0.001	2.09, 5.15
	Day 60	32.04 ± 2.12	-18.7 ± 3.48	<0.001	<0.001	7.57, 11.11
	Day 120	21.52 ± 2.04	-29.3 ± 3.86	<0.001	<0.001	15.77, 19.11
CL22209-100 mg	Baseline	53.12 ± 1.88	-	-	<0.001	2.98, 5.60
	Day 30	43.84 ± 2.46	-9.3 ± 2.54	<0.001	0.043	0.45, 3.45
	Day 60	32.88 ± 2.42	-20.3 ± 2.18	<0.001	<0.001	6.72, 10.28
	Day 120	20.00 ± 2.18	-33.1 ± 2.49	<0.001	<0.001	17.32, 20.60
Hot Flashes Weekly Weighted Scores (HFWWS)						
Placebo	Baseline	32.33 ± 2.92	-	-	-	-
	Day 28	35.88 ± 1.14	3.54 ± 2.80	0.003	-	-
	Day 56	35.08 ± 1.09	2.75 ± 2.84	<0.001	-	-
	Day 119	34.84 ± 1.10	2.51 ± 2.58	<0.001	-	-
CL22209-50 mg	Baseline	33.35 ± 2.84	-	-	1.000	-0.62, 2.66
	Day 28	33.04 ± 5.61	-0.30 ± 7.60	1.000	0.005	0.49, 5.19
	Day 56	27.66 ± 1.59	-5.68 ± 3.59	<0.001	<0.001	6.62, 8.22
	Day 119	24.14 ± 0.85	-9.21 ± 3.00	<0.001	<0.001	10.12, 11.28
CL22209-100 mg	Baseline	31.40 ± 2.08	-	-	1.000	-0.51, 2.37
	Day 28	28.42 ± 2.53	-2.98 ± 3.76	<0.001	<0.001	6.32, 8.59
	Day 56	22.58 ± 1.64	-8.82 ± 2.78	<0.001	<0.001	11.69, 13.30
	Day 119	18.90 ± 0.68	-12.50 ± 2.12	<0.001	<0.001	15.42, 16.46

Values present as mean ± SD; placebo (n = 24), CL22209-50 (n = 23), and CL22209-100 (n = 25) A p value < 0.05 indicates significance within each group for comparison (vs. baseline) using repeated measures ANOVA with Bonferroni correction and an intergroup significance (vs. placebo) using ANOVA with Post Hoc Bonferroni.

Furthermore, 120 days of supplementation with CL22209 gradually and significantly reduced the hot flash burden (HFWWS), with decreases of 27.62% and 39.81% ($p < 0.001$ vs. baseline) in the low and high dose groups, respectively. These changes are also significant ($p < 0.001$) compared to the placebo. In contrast, the hot flash burden was worsened in the placebo group, showing a 7.76% ($p<0.001$) increase in HFWWS at the end of the study (Table 4).

Ovarian Follicle Count: Figure 2 illustrates the changes in ovarian follicle counts, as assessed by transabdominal ultrasonography at baseline and days 30, 60 and 120 of treatment. CL22209 supplementation resulted in a statistically significant and progressive increase in follicle numbers in both treatment groups, beginning as early as day 30 and maintained through the end of the study. Post-trial, in the CL22209-50 mg/day group, the mean follicle count rose from 11.00 ± 1.98 at baseline to

14.78 ± 1.20, showing a 34.4% increase, and the CL22209-100 mg/day group demonstrated a greater improvement, with mean counts increasing from 10.64 ± 1.73 to 16.16 ± 1.03, which corresponds to a 51.9% increase. These increases are significant ($p < 0.001$ vs. baseline and placebo). The placebo group exhibited statistically significant changes in the follicle counts at the end of the study (**Figure 3**).

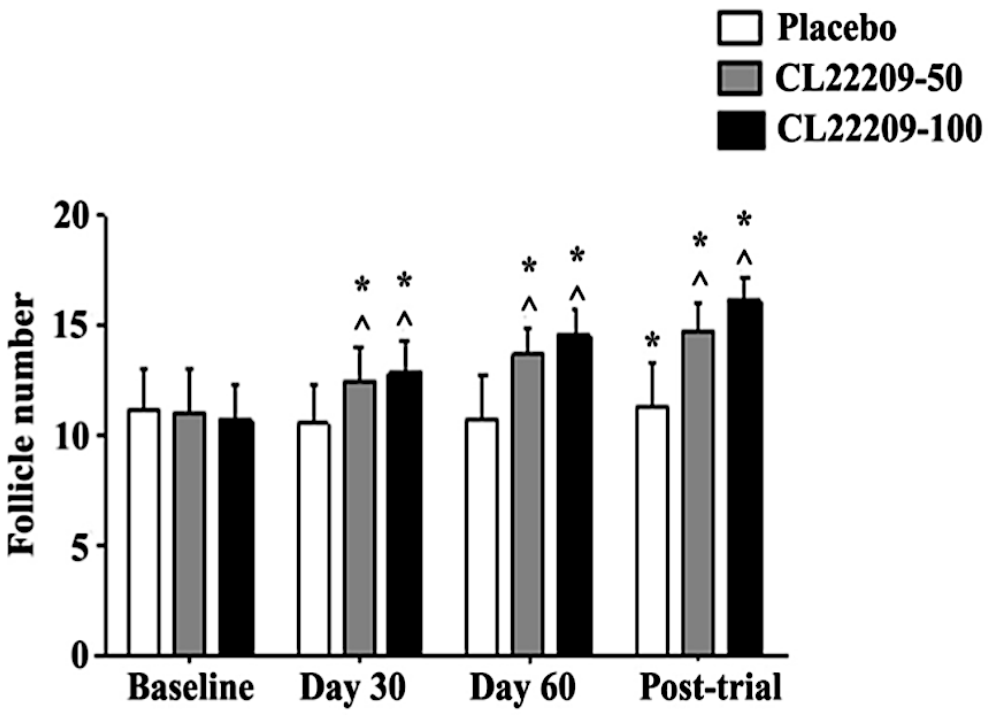

Figure 3: Bar chart illustrates the progressive increase in ovarian follicle count among participants receiving CL22209 supplementation compared to placebo. Data are presented as mean ± SD for each group: placebo (n = 24), CL22209-50 mg (n = 23) and CL22209-100 mg (n=25). * Denotes statistical significance compared to baseline within the same group ($p < 0.05$, repeated measures ANOVA with Bonferroni correction); ^ indicates significant difference versus placebo at corresponding time points ($p < 0.05$, one-way ANOVA with post hoc Bonferroni test).

Serum endocrine biomarkers: **Figure 4** presents modulations on key endocrine biomarker levels in the serum samples of CL22209-supplemented participants. Participants' blood samples were collected on 3-5 days of their menstrual cycle at the screening visit and after 120 days of supplementation these samples are referred to aspre- and post-trial, respectively.

Follicle-stimulating hormone (FSH*)*: Following 120 days of CL22209 supplementation, the FSH levels markedly declined, with reductions of 52.1% in the 50 mg/day group and 61.04% in the 100 mg/day group ($p < 0.001$), respectively, as compared to baseline; in contrast, the placebo group showed a 3.74% increase ($p<0.001$) (Figure 4A).

Luteinizing Hormone *(LH)*: Post-trial, serum LH concentrations were significantly reduced ($p < 0.001$) by 29.8% in the 50 mg/day group and 42.7% in the 100 mg/day group. In comparison, the placebo group showed a 10.3% increase ($p < 0.001$) compared to baseline. These changes in the low- and high-dose groups of CL22209 were statistically significant ($p < 0.001$, compared to placebo) (Figure 4B).

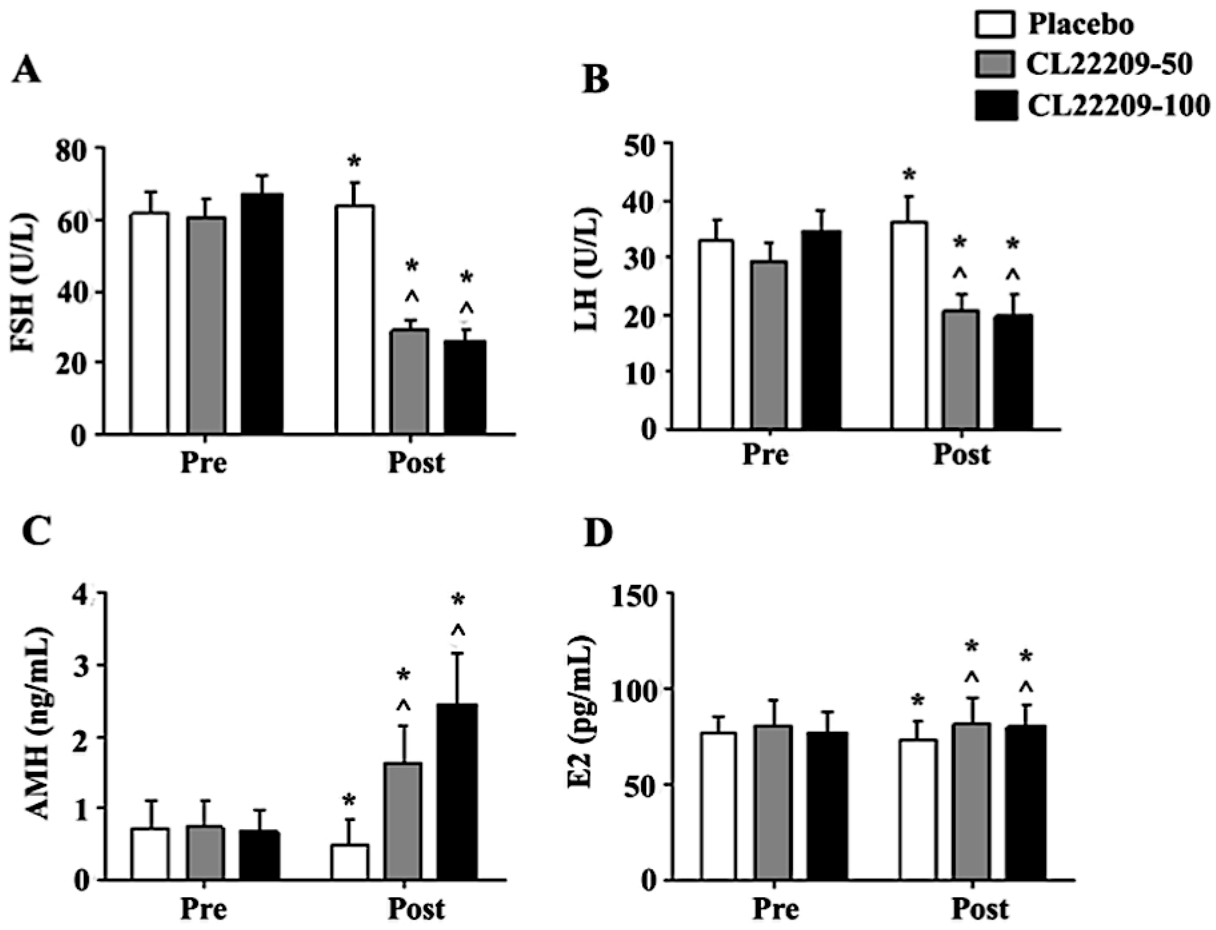

Figure 4: Bar graphs depict serum hormonal modulations in participants supplemented with CL22209 compared to placebo. Panels represent changes in (A) Follicle-Stimulating Hormone (FSH), (B) Luteinizing Hormone (LH), (C) Anti-Müllerian Hormone (AMH), and (D) 17β-Estradiol. Data are shown as mean ± SD for each group: placebo (n = 24), CL22209-50 mg (n = 23), and CL22209-100 mg (n=25), measured at screening (pre) and after 120 days of intervention (post), as described in the Materials and Methods. * Denotes statistical significance compared to baseline within the same group ($p < 0.05$, repeated measures ANOVA with Bonferroni correction); ^ indicates significant difference versus placebo at corresponding time points ($p < 0.05$, one-way ANOVA with post hoc Bonferroni test).

Anti-Müllerian Hormone (AMH): Following 120 days of CL22209 supplementation, AMH, a clinical marker of ovarian reserve, showed significant increases ($p < 0.001$ vs. baseline) of 124.66% and 269.69% in the 50 mg/da and 100 mg/day groups, respectively. In contrast, the placebo group experienced a 30.5% decline ($p < 0.001$ vs. baseline) (Figure 4C).

17β-Estradiol (E2): Post trial, the serum E2 levels were mild but significantly ($p < 0.001$ vs. baseline) increased by 1.33% and 5.28% in the 50 mg/day and 100 mg/day groups, respectively, while the placebo group showed a 4.18% decline ($p < 0.001$ vs. baseline). At the end of the study, the changes in the active groups were statistically significant ($p < 0.001$) compared to the placebo group (Figure 4D).

Acne Severity and Skin Quality*:* Following 120 days of CL22209 supplementation, acne grade scores declined ($p < 0.001$) by 46% and 56.6% in the 50 mg/day and 100 mg/day groups, respectively, vs. baseline.

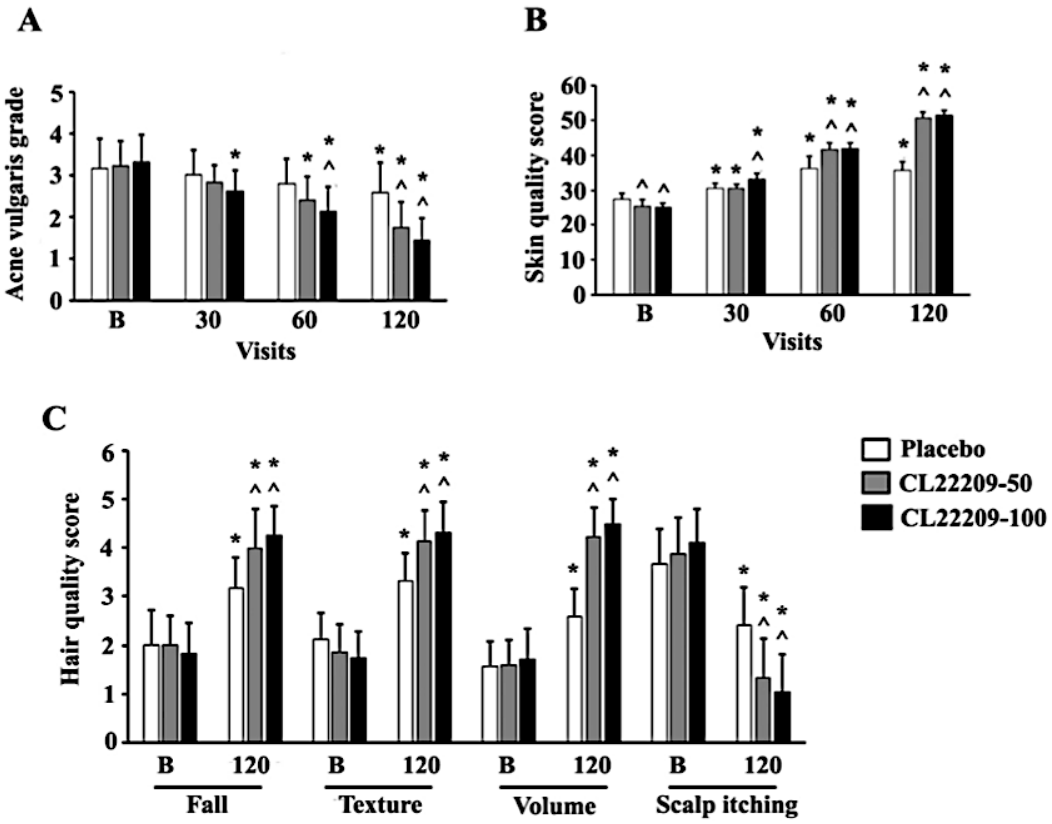

Figure 5: Modulation of dermatological and hair quality outcomes in perimenopausal women following CL22209 supplementation. Data are expressed as mean ± SD; placebo (n = 24), CL22209-50 mg (n = 23) and CL22209-100 mg (n = 25). (A) Acne severity, assessed via a standardized acne grading scale, shows a significant reduction over time in both the CL22209-50 mg and CL22209-100 mg groups compared to the placebo. (B) Self-assessed skin quality scores increased progressively in the treatment groups. (C) Hair quality parameters—fall, texture, volume, and scalp itching—showed marked improvement from baseline (B) to 120 days (120) in both CL22209 groups, as indicated. * Indicates significance vs. baseline ($p < 0.05$, repeated measures ANOVA with Bonferroni correction); ^ indicates significance vs. placebo at corresponding time points ($p < 0.05$, one-way ANOVA with post hoc Bonferroni test).

The placebo group also showed an 18.6% reduction ($p < 0.001$) in the acne severity score as compared to baseline (Figure 5A). Similarly, the perceived skin quality, assessed using the Self-Assessment of Skin Quality Questionnaire, significantly improved in the CL22209-supplemented groups. At the end of the study, the skin quality assessment scores increased by 99.1% and 104.5% in the 50 mg/day and 100 mg/day groups, respectively, as compared to baseline ($p < 0.001$), and by 29.2% ($p < 0.001$) in the placebo group (Figure 5B).

Hair quality assessment: Figure 5C depicts improvements in the hair quality parameters in the CL22209 cohorts. At the end of the study, the low and high doses of CL22209 supplemented groups reported 100% and 130.4% decline in hair fall, 120.9% and 145.5% improvements in hair texture, 162.1% and 160.5% increases in hair volume, and 65.1% and 74.8% reductions in scalp itching, respectively, as compared to baseline. These parameters were also improved ($p < 0.001$ vs. baseline) in the placebo group. However, the comparison analyses between the groups (placebo vs. low and high dose CL22209) revealed that these changes were significant (Figure 5C).

Integrative Medicine Patient Satisfaction and Outcome Scales (IMPSS & IMOS): CL22209 supplementation resulted in significantly higher patient satisfaction and

perceived treatment effectiveness compared to placebo. By day 120, IMPSS and IMOS scores reduced ($p<0.001$) by 30.32% and 29.89% in the 50 mg/day group and 48.78% and 44.57% in the 100 mg/day group, whereas 18.44% and 10.17% in the placebo group, respectively, as compared to day 30 of the study (Table 5).

Table 5: Assessment of Integrative Medicine Patient Satisfaction Scale (IMPSS), Integrative Medicine Outcome Scale (IMOS) scores

Groups	Evaluation	Mean ± SD	Change from baseline (Mean ± SD)	p-value (vs. baseline)	p-value (vs. placebo)	95% CI (vs. placebo)
Integrative Medicine Patient Satisfaction Scale (IMPSS) scores						
Placebo	Day 30	3.58 ± 0.58	-	-	-	-
	Day 60	3.08 ± 0.28	-0.5 ± 0.51	<0.001	-	-
	Day120	2.92 ± 0.28	-0.7 ± 0.56	<0.001	-	-
CL22209-50mg	Day 30	3.43 ± 0.51	-	-	1.000	-0.17, 0.47
	Day 60	2.74 ± 0.45	-0.7 ± 0.47	<0.001	0.188	0.12, 0.56
	Day120	2.39 ± 0.50	-1.0 ± 0.47	<0.001	0.002	0.29, 0.77
CL22209-100 mg	Day 30	3.28 ± 0.61	-	-	0.524	0.22, 0.91
	Day 60	2.52 ± 0.65	-0.8 ± 0.44	<0.001	0.003	0.27, 0.85
	Day120	1.68 ± 0.56	-1.6 ± 0.50	<0.001	<0.001	0.98, 1.50
Integrative Medicine Outcome Scale (IMOS) scores						
Placebo	Day 30	4.13 ± 0.54	-	-	-	-
	Day 60	3.83 ± 0.48	-0.3 ± 0.55	0.048	-	-
	Day120	3.71 ± 0.46	-0.4 ± 0.65	<0.001	-	-
CL22209-50 mg	Day 30	3.78 ± 0.52	-	-	0.173	0.04, 0.66
	Day 60	3.43 ± 0.51	-0.4 ± 0.57	0.024	0.045	0.11, 0.69
	Day120	2.65 ± 0.49	-1.1 ± 0.55	<0.001	<0.001	0.78, 1.34
CL22209-100 mg	Day 30	3.68 ± 0.56	-	-	0.024	0.13, 0.77
	Day 60	3.00 ± 0.50	-0.7 ± 0.56	<0.001	<0.001	0.55, 1.11
	Day120	2.04 ± 0.61	-1.6 ± 0.57	<0.001	<0.001	1.36, 1.98

Values present as mean ± SD; placebo (n = 24), CL22209-50 (n = 23), and CL22209-100 (n = 25). A p-value < 0.05 indicates significance within each group for comparison (vs. baseline) using repeated measures ANOVA with Bonferroni correction and an intergroup significance (vs. placebo) using ANOVA with Post Hoc Bonferroni.

Safety assessments and adverse events: CL22209 was well-tolerated with no clinically significant alterations in hematological or biochemical parameters, including liver enzymes, renal function markers, lipid profile, and complete blood counts (Table 6). All values remained within reference ranges. During the intervention, three participants reported mild and transient adverse events: one each reported nausea and bloating in the placebo and one in CL22209-50 mg/day groups, respectively.

Table 6: Safety assessments- Hematology and complete clinical biochemistry.

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
Hematology					
Hemoglobin (g/dL)	Baseline	Placebo	12.60 ± 0.41	-	-
		CL22209-50 mg	12.69 ± 0.56	-	0.5126
		CL22209-100 mg	12.52 ± 0.43	-	0.5165
	Day 120	Placebo	12.80 ± 0.29	0.0975	-
		CL22209-50 mg	12.79 ± 0.38	0.506	0.8878
		CL22209-100 mg	12.84 ± 0.38	0.0023	0.7167
Platelet count (10^3/cu.mm)	Baseline	Placebo	244.80 ± 20.68	-	-
		CL22209-50 mg	237.56 ± 33.57	-	0.3631
		CL22209-100 mg	246.24 ± 22.08	-	0.8129
	Day 120	Placebo	251.42 ± 20.77	<0.001	-
		CL22209-50 mg	242.61 ± 32.77	<0.001	0.2748
		CL22209-100 mg	252.36 ± 21.53	<0.001	0.8767
ESR (mm/hr)	Baseline	Placebo	7.20 ± 2.22	-	
		CL22209-50 mg	7.28 ± 2.28	-	0.9005
		CL22209-100 mg	6.64 ± 2.36	-	0.3916
	Day 120	Placebo	6.67 ± 1.52	0.4541	-
		CL22209-50 mg	6.78 ± 1.78	0.3919	0.8113
		CL22209-100 mg	6.32 ± 1.65	0.5504	0.4492
RBC count (10^6/mm^3)	Baseline	Placebo	4.22 ± 0.29	-	-
		CL22209-50 mg	4.14 ± 0.30	-	0.3455
		CL22209-100 mg	4.26 ± 0.29	-	0.6342

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
	Day 120	Placebo	4.19 ± 0.26	0.6756	-
		CL22209-50 mg	4.16 ± 0.24	0.6343	0.7581
		CL22209-100 mg	4.24 ± 0.22	0.7928	0.489
Total WBC count ($10^3/mm^3$)	Baseline	Placebo	8.52 ± 1.03	-	-
		CL22209-50 mg	8.15 ± 1.39	-	0.2825
		CL22209-100 mg	8.40 ± 1.18	-	0.7043
	Day 120	Placebo	8.09 ± 1.07	0.1378	-
		CL22209-50 mg	8.12 ± 1.06	0.9326	0.9342
		CL22209-100 mg	7.80 ± 1.25	0.0178	0.391
Neutrophil (%)	Baseline	Placebo	63.76 ± 5.71	-	-
		CL22209-50 mg	63.92 ± 7.07	-	0.9302
		CL22209-100 mg	63.96 ± 6.17	-	0.9058
	Day 120	Placebo	63.21 ± 5.05	0.6885	-
		CL22209-50 mg	62.61 ± 6.34	0.6128	0.721
		CL22209-100 mg	63.12 ± 5.00	0.4744	0.9512
Lymphocytes (%)	Baseline	Placebo	26.28 ± 5.83	-	-
		CL22209-50 mg	26.44 ± 6.61	-	0.9281
		CL22209-100 mg	26.48 ± 5.90	-	0.9046
	Day 120	Placebo	27.88 ± 4.39	0.0756	-
		CL22209-50 mg	28.91 ± 5.12	0.1395	0.4589
		CL22209-100 mg	27.84 ± 4.61	0.2313	0.9784
Eosinophil (%)	Baseline	Placebo	4.48 ± 0.87	-	-
		CL22209-50 mg	4.44 ± 1.19	-	0.8929
		CL22209-100 mg	4.28 ± 0.98	-	0.4495
	Day 120	Placebo	3.92 ± 0.78	0.0012	-
		CL22209-50 mg	3.57 ± 0.95	0.0337	0.1695
		CL22209-100 mg	3.92 ± 1.00	0.2047	0.9897

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
Monocytes (%)	Baseline	Placebo	5.48 ± 0.87		
		CL22209-50 mg	5.20 ± 1.19		0.3474
		CL22209-100 mg	5.28 ± 0.94		0.4383
	Day 120	Placebo	5.00 ± 1.47	0.1979	
		CL22209-50 mg	4.91± 1.38	0.4373	0.8357
		CL22209-100 mg	5.12 ± 1.13	0.5743	0.75
Basophils (%)	Baseline	Placebo	0.00 ± 0.00	-	--
		CL22209-50 mg	0.00 ± 0.00	-	0
		CL22209-100 mg	0.00 ± 0.00	-	0
	Day 120	Placebo	0.00 ± 0.00	0	-
		CL22209-50 mg	0.00 ± 0.00	0	0
		CL22209-100 mg	0.00 ± 0.00	0	0
Biochemistry					
Fasting Blood Glucose (mg/dL)	Baseline	Placebo	88.30 ± 6.34	-	-
		CL22209-50 mg	87.72 ± 5.56	-	0.7351
		CL22209-100 mg	87.68 ± 4.56	-	0.694
	Day 120	Placebo	85.10 ± 4.04	0.0207	
		CL22209-50 mg	84.12 ± 4.03	0.0003	0.7351
		CL22209-100 mg	85.65 ± 4.36	0.0595	0.6496
Creatinine (mg/dL)	Baseline	Placebo	0.78 ± 0.11	-	-
		CL22209-50 mg	0.74 ± 0.13	-	0.2719
		CL22209-100 mg	0.80 ± 0.09	-	0.4657
	Day 120	Placebo	0.74 ± 0.09	0.27	-
		CL22209-50 mg	0.79 ± 0.09	0.0882	0.0583
		CL22209-100 mg	0.82 ± 0.11	0.5567	0.0174
Blood urea nitrogen (mg/dL)	Baseline	Placebo	13.16 ± 1.64	-	-
		CL22209-50 mg	12.85 ± 1.94	-	0.5416

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
		CL22209-100 mg	12.96 ± 1.63	-	0.6644
	Day 120	Placebo	13.32 ± 1.83	0.8341	-
		CL22209-50 mg	12.82 ± 1.84	0.8182	0.3588
		CL22209-100 mg	12.87 ± 1.74	0.8364	0.3839
Blood Uric Acid (mg/dL)	Baseline	Placebo	5.34 ± 0.75	-	-
		CL22209-50 mg	5.34 ± 0.87	-	0.9862
		CL22209-100 mg	5.30 ± 0.62	-	0.8052
	Day 120	Placebo	4.45 ± 0.66	0.0001	-
		CL22209-50 mg	4.52 ± 0.69	0.0009	0.702
		CL22209-100 mg	4.57 ± 0.69	0.0018	0.5315
Sodium (mmol/L)	Baseline	Placebo	139.17 ± 1.95	-	-
		CL22209-50 mg	138.33 ± 1.46	-	0.0911
		CL22209-100 mg	138.74 ± 2.40	-	0.4882
	Day 120	Placebo	140.06 ± 1.49	0.0985	-
		CL22209-50 mg	139.76 ± 1.36	0.0007	0.4661
		CL22209-100 mg	139.75 ± 1.50	0.0255	0.4651
Potassium (mmol/L)	Baseline	Placebo	4.10 ± 0.42	-	-
		CL22209-50 mg	4.13 ± 0.39	-	0.7613
		CL22209-100 mg	4.04 ± 0.28	-	0.5908
	Day 120	Placebo	3.98 ± 0.34	0.2259	-
		CL22209-50 mg	4.00 ± 0.22	0.0931	0.779
		CL22209-100 mg	4.12 ± 0.34	0.3349	0.1433
Alkaline Phosphate (IU/L)	Baseline	Placebo	121.84 ± 21.34	-	-
		CL22209-50 mg	123.64 ± 19.75	-	0.7582
		CL22209-100 mg	124.40 ± 16.66	-	0.6385
	Day 120	Placebo	121.50 ± 12.73	0.8251	-
		CL22209-50 mg	124.17 ± 12.54	0.6157	0.472

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
		CL22209-100 mg	122.56 ± 11.35	0.4387	0.7595
Aspartate Aminotransferase (U/L)	Baseline	Placebo	27.00 ± 2.10	-	-
		CL22209-50 mg	26.87 ± 2.94	-	0.8511
		CL22209-100 mg	25.95 ± 3.06	-	0.1625
	Day 120	Placebo	26.31 ± 2.87	0.3215	-
		CL22209-50 mg	25.97 ± 2.48	0.3489	0.6719
		CL22209-100 mg	26.56 ± 3.27	0.4537	0.7726
Alanine Aminotransferase (U/L)	Baseline	Placebo	31.42 ± 4.23	-	-
		CL22209-50 mg	31.48 ± 6.45	-	0.965
		CL22209-100 mg	30.17 ± 4.73	-	0.3303
	Day 120	Placebo	30.83 ± 3.91	0.4379	-
		CL22209-50 mg	29.98 ± 4.76	0.1083	0.5036
		CL22209-100 mg	30.03 ± 4.34	0.8513	0.5007
Bilirubin (mg/dL)	Baseline	Placebo	0.70 ± 0.20	-	-
		CL22209-50 mg	0.68± 0.23	-	0.6981
		CL22209-100 mg	0.74 ± 0.15	-	0.4263
	Day 120	Placebo	0.58 ± 0.20	0.0465	-
		CL22209-50 mg	0.58 ± 0.14	0.1323	0.8814
		CL22209-100 mg	0.73 ± 0.27	0.8069	0.0273
Albumin (gm/dL)	Baseline	Placebo	4.27 ± 0.37	-	-
		CL22209-50 mg	4.21 ± 0.34	-	0.5787
		CL22209-100 mg	4.22 ± 0.35	-	0.6248
	Day 120	Placebo	4.36 ± 0.30	0.2535	-
		CL22209-50 mg	4.24 ± 0.26	0.7286	0.134
		CL22209-100 mg	4.29 ± 0.31	0.4059	0.4168
Creatine Kinase (U/L)	Baseline	Placebo	96.73 ± 21.17	-	-
		CL22209-50 mg	90.45 ± 19.54	-	0.2808

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
		CL22209-100 mg	89.68 ± 18.76	-	0.2183
	Day 120	Placebo	90.17 ± 16.07	0.0464	-
		CL22209-50 mg	88.70 ± 15.99	0.6677	0.756
		CL22209-100 mg	89.70 ± 12.34	0.992	0.9103
Lipid profile					
Low-density lipoprotein (mg/dL)	Baseline	Placebo	85.56 ± 5.28	-	-
		CL22209-50 mg	83.71 ± 6.93	-	0.2241
		CL22209-100 mg	84.07 ± 5.81	-	0.2592
	Day 120	Placebo	80.43 ± 5.76	0.0012	-
		CL22209-50 mg	82.98 ± 6.20	0.1249	0.1503
		CL22209-100 mg	82.78 ± 4.46	0.1729	0.1153
High-density lipoprotein (mg/dL)	Baseline	Placebo	61.53 ± 5.61	-	-
		CL22209-50 mg	58.98 ± 5.76	-	0.1196
		CL22209-100 mg	61.57 ± 8.05	-	0.9859
	Day 120	Placebo	63.48 ± 5.11	0.125	-
		CL22209-50 mg	60.82 ± 3.99	0.0169	0.0532
		CL22209-100 mg	62.28 ± 7.64	0.3305	0.5218
Very low-density lipoprotein (mg/dL)	Baseline	Placebo	23.84 ± 2.60	-	-
		CL22209-50 mg	23.48 ± 3.48	-	0.6841
		CL22209-100 mg	23.73 ± 2.51	-	0.8839
	Day 120	Placebo	22.38 ± 2.96	0.0201	-
		CL22209-50 mg	22.91 ± 2.48	0.3461	0.5068
		CL22209-100 mg	22.33 ± 2.87	0.0408	0.9571
Triglycerides (mg/dL)	Baseline	Placebo	130.41 ± 9.20	-	-
		CL22209-50 mg	128.66 ± 10.38	-	0.5315
		CL22209-100 mg	130.12 ± 9.20	-	0.9123
	Day 120	Placebo	126.05 ± 7.37	0.0391	-

Parameters	Evaluation Days	Groups	Mean ± SD	p-value (vs. baseline)	p-value (vs. placebo)
		CL22209-50 mg	125.60 ± 7.25	0.1139	0.8339
		CL22209-100 mg	124.72 ± 6.62	0.0028	0.5092
Total cholesterol (mg/dL)	Baseline	Placebo	171.95 ± 8.99	-	-
		CL22209-50 mg	167.71 ± 9.77	-	0.1164
		CL22209-100 mg	169.37 ± 10.74	-	0.3602
	Day 120	Placebo	167.50 ± 8.50	0.0117	-
		CL22209-50 mg	165.60 ± 9.35	0.1876	0.4694
		CL22209-100 mg	167.81 ± 9.95	0.2863	0.9075

Values present as mean ± SD; At baseline, placebo (n = 25), CL22209-50 (n = 25), and CL22209-100 (n = 25); at day 120, placebo (n = 24), CL22209-50 (n = 23), and CL22209-100 (n = 25). A p value < 0.05 indicates significance. Intragroup comparison (vs. baseline) analyzed using paired t test; intergroup comparison (vs. placebo) analyzed using unpaired independent t test.

DISCUSSION

Perimenopause is characterized by a gradual and often erratic decline in ovarian follicular activity, typically manifested by elevated gonadotropins (FSH, LH), reduced ovarian hormones (AMH, E2), and increased variability in menstrual cycles. This transition reflects a decline in ovarian reserve and steroidogenic competence, governed by the hypothalamic-pituitary-ovarian (HPO) axis. Disruption in the HPO axis contributes to the increased inter-cycle and intra-cycle variability in menstrual cycles, a clinical hallmark of the perimenopausal stage [22]. These physiological changes result in the loss of regular cyclical hormonal rhythms, finally transitioning into the hypoestrogenic and anovulatory state of menopause [23].

The present study demonstrated that CL22209, a standardized *A. racemosus* extract containing 15% shatavarins, significantly reduced vasomotor symptoms (VMS) over a 120-day intervention. The improvement is reasonably linked to shatavarins' affinity for estrogen receptors α and β, as shown *in silico* and *in vitro* studies [24]. Furthermore, *A. racemosus* has been shown to modulate neurotransmitters such as serotonin and norepinephrine, key mediators in thermoregulation, supporting its mechanistic role in reducing VMS [25-26]. Earlier, preclinical investigations have shown that *A. racemosus* enhances aromatase-mediated estradiol biosynthesis and protects ovarian tissue against oxidative injury, supporting steroidogenic function [10]. In the present study, the mildly elevated estradiol levels following CL22209 supplementation may be attributed to the phytoestrogenic constituents present in *A racemosus*, particularly shatavarins and sarsasapogenin. Taken together, the present observations suggest that CL22209 mildly promotes endogenous estrogenic activity, which helps balance the declining estrogen levels in perimenopausal women.

The reductions in serum FSH and LH levels following CL22209 treatment suggest a potential normalization of hypothalamic-pituitary-gonadal (HPG) axis homeostasis, possibly via enhanced negative feedback mechanisms. In perimenopausal women, elevated gonadotropins (FSH, LH) are characteristic of reduced ovarian follicular reserve and diminished secretion of estradiol and inhibin,

which weakens the inhibitory tone of GnRH neurons [27]. The downregulation of gonadotropins with CL22209 administration may thus reflect a restoration of this feedback loop. This efficacy aligns with the bioactivity of the steroidal saponins (e.g., shatavarins) and phytoestrogens present in *A. racemosus*. These compounds have been reported to show affinity for estrogen receptors (ER-α and ER-β), acting as selective estrogen receptor modulators (SERMs) [24, 28]. Their central effects likely influence GnRH pulse frequency and amplitude at the hypothalamic level, thereby reducing the secretion of FSH and LH. Furthermore, recent animal studies and clinical trials suggest that the phytoestrogens in CL22209 may induce estrogenic effects selectively in the hypothalamus and pituitary without promoting peripheral proliferative activity, indicating a neuroendocrine-mediated action suitable for perimenopausal hormonal dysregulation [29].

The concurrent rise in AMH levels in the CL22209-supplemented participants is noteworthy. AMH, secreted by the granulosa cells of preantral and small antral follicles, serves as a reliable endocrine biomarker of ovarian reserve. During the perimenopausal transition, AMH levels naturally declined due to accelerated depletion of the primordial follicle pool and cumulative oxidative stress within the ovarian microenvironment, leading to granulosa cell apoptosis and impaired folliculogenesis [30]. The significant upregulation of AMH with CL22209 supplementation suggests that granulosa cell function is either preserved or restored. This effect may be attributed to the phytoestrogenic saponins in *A racemosus*, which have demonstrated potent antioxidant and anti-apoptotic activity in preclinical models [10, 31, 32]. By attenuating reactive oxygen species (ROS) generation and lipid peroxidation, these compounds may mitigate granulosa cell loss, preserve the follicular niche, and sustain AMH production. Moreover, reduction in FSH levels and potential upregulation of FSH receptor sensitivity, as observed in the CL22209-treated groups, may further support follicle recruitment and growth [28]. Collectively, these findings suggest that CL22209 exerts multifaceted ovarian support through endocrine modulation, cryoprotection, and enhanced responsiveness to gonadotropins, thereby supporting ovarian reserve during perimenopause.

Dermatological and cosmetic changes during perimenopause, such as acne, skin dryness, and hair thinning, are closely linked to declining estradiol (E2) levels, which impair dermal collagen synthesis, reduce hydration, and increase sebaceous gland activity [33-34]. The observed reduction in acne severity and improvement in skin texture in CL22209-supplemented volunteers may be attributed to the phytoestrogens (e.g., shatavarins) in *A. racemosus*, which modulate ER-α/β and suppress androgenic sebaceous activities. Reduced estrogen levels during perimenopause reduce antagonism to androgens (testosterone, dihydrotestosterone), leading to increased sebum secretion and acneiform eruptions [33]. Similarly, estrogen's role in promoting hair follicular growth and prolonging the anagen phase explains the significant improvements in hair quality observed in the CL22209-treated groups [35].

Collectively, our observations highlight CL22209 as a comprehensive endocrine modulator exerting both central and peripheral physiological activities. Its dual regulatory effect attenuates hypothalamic-pituitary gonadotropin output while supporting ovarian folliculogenesis and steroidogenesis; these align with the adaptogenic and gonadotropic harmonization properties traditionally attributed to *A. racemosus*. Furthermore, the dose-dependent hormonal normalization was accompanied by significant improvements in validated clinical indices (MRS, IMOS, IMPSS), indicating a meaningful translation of endocrine modulation into symptomatic relief. Importantly, CL22209 demonstrated

an excellent safety profile, with stable hematological, biochemical, and hormonal parameters and no serious adverse events. In contrast to menopausal hormone therapy (MHT) and selective estrogen receptor modulators (SERMs), which carry risks such as breast cancer, thromboembolism, and worsening vasomotor symptoms, CL22209 exhibited no such complications. Its tolerability and tissue-selective estrogenic effects highlight its promise as a safe, non-hormonal alternative for managing perimenopausal symptoms.

Overall, this randomized, double-blind, placebo-controlled trial is among the first to clinically evaluate an enriched and standardized *A racemosus* root extract specifically in perimenopausal women. The study establishes a direct association between symptom relief, such as reductions in hot flashes and menstrual discomfort, and objective endocrine markers including FSH, LH, estradiol, AMH, and ovarian follicle count. Notably, CL22209 demonstrated the potential to improve hormonal balance and enhance ovarian reserve. These findings extend beyond traditional anecdotal or preclinical evidence, offering robust clinical support for Shatavari as a natural, multi-targeted therapeutic option to promote women's health.

CONCLUSION

The demonstrated clinical efficacy and safety profile of CL22209, a standardized *Asparagus racemosus* root extract, highlights its promising potential as a phytoceutical for functional food applications aiming at improving women's health**.** CL22209 demonstrated significant efficacy in alleviating a broad spectrum of perimenopausal symptoms, including vasomotor disturbances, menstrual irregularities, hormonal imbalances, and dermatological concerns, without any adverse events. CL22209 modulated key reproductive hormones (FSH, LH, AMH, and E2) and significantly increased ovarian follicle counts, suggesting improved ovarian function and potential delay of reproductive aging. These findings align with the growing body of evidence supporting the adaptogenic and hormone-balancing effects of *A. racemosus* in women's health, reinforcing the feasibility of integrating CL22209 as a bioactive ingredient in functional foods or dietary supplements designed for perimenopausal and menopausal support**.**

ABBREVIATIONS: AMH: Anti-Müllerian Hormone; ANOVA: Analysis of Variance; CI: Confidence Interval; CTRI: Clinical Trial Registry of India; E2: 17β-Estradiol; ELISA: Enzyme-Linked Immunosorbent Assay; FSH: Follicle-Stimulating Hormone; HDPE: High-Density Polyethylene; HFWWS: Hot Flash Weekly Weighted Score; HPO Axis: Hypothalamic–Pituitary–Ovarian Axis; HRT: Hormone Replacement Therapy; IMPSS: Integrative Medicine Patient Satisfaction Scale; IMOS: Integrative Medicine Outcome Scale; ITT: Intent-to-Treat; LH: Luteinizing Hormone; MRS: Menopausal Rating Scale; MSQ: Menstrual Symptoms Questionnaire; PP: Per-Protocol; QoL: Quality of Life; ROS: Reactive Oxygen Species; SERM: Selective Estrogen Receptor Modulator; USG: Ultrasonography; VMS: Vasomotor Symptoms.

AUTHORS' CONTRIBUTIONS: SY, GK designed the trial; PY, GK conducted the study; PY, SSV captured the data; PY, SSV analyzed the data; PY, SY drafted the manuscript; SSV, GK reviewed and finalized the manuscript.

Conflict of interest: The authors declare that there is no conflict of interest in conducting the research and publishing the data.

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