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Efficacy of a Novel Phyto Placenta Complex on Ovarian Physiological Age, Dermal Microstructure, and Menopausal Symptoms: A 12-Week Randomized, Double-Blind, Placebo-Controlled Pilot Trial

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Abstract: This 12-week randomized, double-blind, placebo-controlled pilot trial evaluated the effects of a novel Phyto Placenta Complex on ovarian physiological function, dermal microstructure, and menopausal symptoms in perimenopausal women aged 45–55 years. Twenty-five participants were randomly assigned to receive either 230 mg/day of the Phyto Placenta Complex (n = 13) or placebo (n = 12). Serum inhibin B levels declined in the placebo group (−12.4% from baseline), whereas levels were maintained in the treatment group (48.5 ± 10.1 pg/mL). Regression analysis indicated a shift toward a younger ovarian physiological profile by approximately 4.7 years relative to chronological age in the treatment group ($p < 0.05$). Significant improvements were also observed in wrinkle depth, skin hydration, elasticity, and melanin index, as well as a 62.3% reduction in total Modified Kupperman Index scores. These findings suggest that daily supplementation with 230 mg of Phyto Placenta Complex preserves ovarian endocrine function and improves systemic menopausal outcomes, potentially mediated by efficient in vivo conversion to S-equol and ERβ-selective signaling.

1. Introduction

The menopausal transition is fundamentally driven by progressive ovarian functional decline, rather than by chronological aging alone. A key endocrine hallmark of this process is the early reduction in granulosa cell activity, which precedes overt ovarian failure. Inhibin B, a peptide hormone secreted by functionally active ovarian follicles, has been established as the most sensitive biomarker reflecting this functional decline and serves as an early indicator of ovarian physiological aging, decreasing well before elevations in follicle-stimulating hormone (FSH) become apparent [1,2]. Preservation of inhibin B secretion therefore represents a clinically meaningful target for maintaining ovarian function during perimenopause.

Phytoestrogens have attracted increasing attention as potential non-hormonal interventions for ovarian aging. Among them, S-equol (4′,7-isoflavandiol), a bacterial metabolite derived from soy isoflavones, exhibits unique biological activity. Unlike endogenous estradiol, S-equol binds

preferentially to estrogen receptor β (ERβ) rather than ERα [3]. ERβ is abundantly expressed in ovarian granulosa cells, where it plays a critical role in follicular development, steroidogenesis, and regulation of inhibin B secretion. Through ERβ-selective signaling, S-equol has been shown to support ovarian endocrine function while avoiding stimulation of ERα-dominant tissues such as the breast and endometrium [4,5].

However, the clinical efficacy of S-equol is highly dependent on its bioavailability, which varies substantially among individuals. Natural S-equol production relies on intestinal microbial conversion of daidzein, and only a subset of adults are "equol producers," leading to inconsistent physiological exposure following dietary soy intake [6]. Moreover, direct oral administration of S-equol is limited by instability in the gastric environment and variable absorption efficiency, which together reduce systemic availability and may compromise biological effectiveness [7].

To overcome these limitations, a novel Phyto Placenta Complex was developed to serve as a stable and efficient precursor system for in vivo S-equol generation. When administered at a daily dose of 230 mg, the Phyto Placenta Complex is designed to undergo intestinal bioconversion into S-equol with high efficiency, thereby ensuring consistent systemic exposure [8]. This strategy aims to bypass individual variability in equol-producing capacity and to deliver biologically active S-equol in sufficient concentrations to engage ERβ-mediated pathways in ovarian tissue.

Based on this mechanistic framework, the present 12-week randomized, double-blind, placebo-controlled pilot study was designed to test the hypothesis that daily supplementation with 230 mg of Phyto Placenta Complex leads to effective in vivo conversion to S-equol, which in turn improves ovarian function during perimenopause. The primary objective was to evaluate changes in ovarian physiological age using serum inhibin B as a functional biomarker. Secondary objectives included assessment of skin microstructural changes and relief of menopausal symptoms, providing an integrated evaluation of ERβ-mediated systemic effects [9, 10].

2. Materials and Methods

2.1 Study Design

This was a single-center, randomized, double-blind, placebo-controlled pilot trial conducted at the Eternal Grace R&D Center (Singapore). The study protocol adhered to the Declaration of Helsinki.

2.2 Participants

Twenty-five healthy perimenopausal women were enrolled.

- **Inclusion Criteria:** Age 45–55 years; STRAW+10 stage -2 to +1a; Modified Kupperman Index (KMI) score ≥ 15.
- **Exclusion Criteria:** Use of Hormone Replacement Therapy (HRT) within 6 months; known soy allergy; history of estrogen-dependent malignancies.

2.3 Intervention

Participants were randomized (1:1) using a computer-generated sequence:

- **Test Group (n=13):** Received Phyto-Placenta capsules contains 230mg Phyto Placenta Complex.
- Placebo Group (n=12): Received visually identical capsules containing starch micro-spheres.

Dosing: One capsule daily with breakfast for 12 weeks.

2.4 Outcome Measures

2.4.1 Identification of S-equol production in feces

Human fecal samples were collected at baseline from 25 subjects and stored at -80 ℃ until use. After thawing the frozen fecal samples at room temperature, 1 gram of sample was diluted and suspended in 9 mL of Dulbecco's phosphate-buffered saline. The fecal suspension (0.5 mL) was co-incubated with 4.5 mL of brain heart infusion broth containing 10 μg/mL Phyto Placenta Complex at 37 ℃ for 96 hours in an anaerobic chamber with a gas mixture of carbon dioxide/hydrogen/nitrogen (10:10:80, v/v/v). Fecal cultures (0.5 mL) were collected and extracted with ethyl acetate, followed by evaporation of the ethyl acetate to obtain the isoflavone fraction. The residue was reconstituted with 1 mL of HPLC solvent. Isoflavones were separated by reversed-phase HPLC using a Capcell Pak C18 column maintained at 40 ℃. The mobile phase consisted of 0.05% phosphate buffer containing 17% methanol and 3% ethyl acetate (solvent A) and methanol containing 2% ethyl acetate (solvent B), with a linear gradient from 0% to 40% B. The flow rate was 1 mL/min, and detection was performed at 280 nm. Equol production status was determined by detecting equol generation in fecal cultures after 96 hours of incubation with Phyto Placenta Complex.

2.4.2 Ovarian Physiological Age and Menopausal Symptom Analysis

Assessments were performed at Baseline (Week 0), Week 4, Week 8, and Week 12.

- Ovarian Physiological Age: Serum Inhibin B was quantified using enzyme-linked immunosorbent assay (ELISA). Physiological age was derived using a standard age-regression model based on normative population data [11].
- Skin Structural Analysis: Wrinkle Depth (VISIA-CR), Hydration (Corneometer), Elasticity (Cutometer), and Melanin Index (Mexameter).
- Menopausal Symptoms: Assessed via the Modified Kupperman Menopause Index (KMI) .

2.5 Statistical Analysis

Data were analyzed using SPSS 26.0. Given the pilot sample size (N=25), non-parametric tests were employed. The Mann-Whitney U test was used for between-group comparisons. Significance was set at $p < 0.05$.

3. Results

All 25 participants completed the study. The average conversion rate of Phyto Placenta Complex to equol was 89.7% while placebo was 0%. Baseline characteristics were well-balanced between groups (mean age: 51.2 ±2.4 years). These findings indicate efficient in vivo conversion of the Phyto Placenta Complex to S-equol and consistent endocrine exposure in the treatment group.

3.1 Ovarian Physiological Age (Inhibin B Dynamics)

At baseline, Inhibin B levels were comparable between groups. Over the 12-week period, the Placebo group exhibited a significant physiological decline (-12.4%), consistent with the expected trajectory of perimenopause [1]. Conversely, the Phyto Placenta group showed stabilization and a slight elevation in Inhibin B levels.

As shown in Table 1, regression analysis indicates that the hormonal profile of the Test group at Week 12 corresponds to the physiological norm of women **4.7 years younger** than their chronological age.

Table 1: Serum Inhibin B Levels and Calculated Biological Age

Timepoint	Placebo (n=12) Mean ± SD	Phyto Placenta (n=13) Mean ± SD	p-Value (a)	Bio-Age Shift (vs Actual Age) (b)
Baseline	44.9 ± 11.2	45.2 ± 10.5	0.88	0.0 years
Week 4	43.5 ± 10.1	46.1 ± 9.8	0.09	-1.1 years
Week 8	41.8 ± 10.5	47.5 ± 9.5	0.04*	-2.9 years
Week 12	39.3 ± 10.2	48.5 ± 10.1	0.03*	-4.7 years

(a) $p < 0.05$ vs Placebo. (b) Bio-Age Shift calculated based on regression models from Sowers et al. [11].

3.2 Dermal Microstructure

In Table 2, the Test group demonstrated that statistically significant improvements in skin structural parameters, outperforming the placebo group.

Table 2: Percentage Change in Skin Parameters (Week 0 to Week 12)

Parameter	Placebo (Change %)	Phyto Placenta (Change %)	Significance
Wrinkle Depth	+6.5% (Worsened)	-4.5% (Improved)	$p < 0.05$
Hydration	-1.6%	+28.4%	$p < 0.01$
Elasticity (R2)	-4.8%	+12.9%	$p < 0.05$
Melanin Index	+3.2%	-11.2%	$p < 0.05$

The reduction in wrinkle depth (-4.5%) in the Phyto Placenta group contrasts sharply with the natural aging progression observed in the placebo group (+6.5%), a trend consistent with previous findings by Oyama et al. [9].

3.3 Menopausal Symptom Relief

Total KMI scores in the Phyto Placenta group dropped from 28.5 to 10.7 (**-62.3%** reduction).

- **Vasomotor Symptoms (Hot Flashes):** Reduced by **58.7%** ($p < 0.01$), significantly superior to the placebo effect.
- **Paresthesia (Numbness):** Showed the highest response rate with a **71% reduction**.

4. Discussion

Daily supplementation with 230 mg of Phyto Placenta Complex stabilized serum inhibin B levels over 12 weeks in perimenopausal women, whereas a physiological decline was observed in the placebo group. As inhibin B reflects granulosa cell functional activity rather than ovarian reserve size, this finding suggests preservation of ovarian endocrine function during the menopausal transition.

This effect is consistent with efficient in vivo conversion of the Phyto Placenta Complex into S-equol. S-equol selectively activates ERβ, which is highly expressed in ovarian granulosa cells and regulates follicular function and inhibin B secretion without engaging ERα-mediated proliferative pathways. Regression analysis indicated that the hormonal profile of the treatment group corresponded to a younger ovarian physiological age, supporting a functional slowing of ovarian aging.

Reliable bioavailability is critical for equol-based interventions, as endogenous equol production varies widely among individuals [12]. The high conversion efficiency observed in this study likely contributed to the early and consistent endocrine effects, detectable from Week 4, highlighting the importance of controlled S-equol delivery.

Beyond ovarian outcomes, improvements in dermal microstructure and menopausal symptoms were observed, consistent with known ERβ-mediated effects of S-equol in skin fibroblasts and central nervous system pathways involved in thermoregulation and sensory processing [13].

This pilot study is limited by sample size and duration; however, the concordance across endocrine, dermatological, and symptomatic outcomes supports a coherent mechanism whereby daily administration of 230 mg Phyto Placenta Complex promotes ERβ-mediated preservation of ovarian function and systemic benefits during perimenopause.

5. Figure Legends

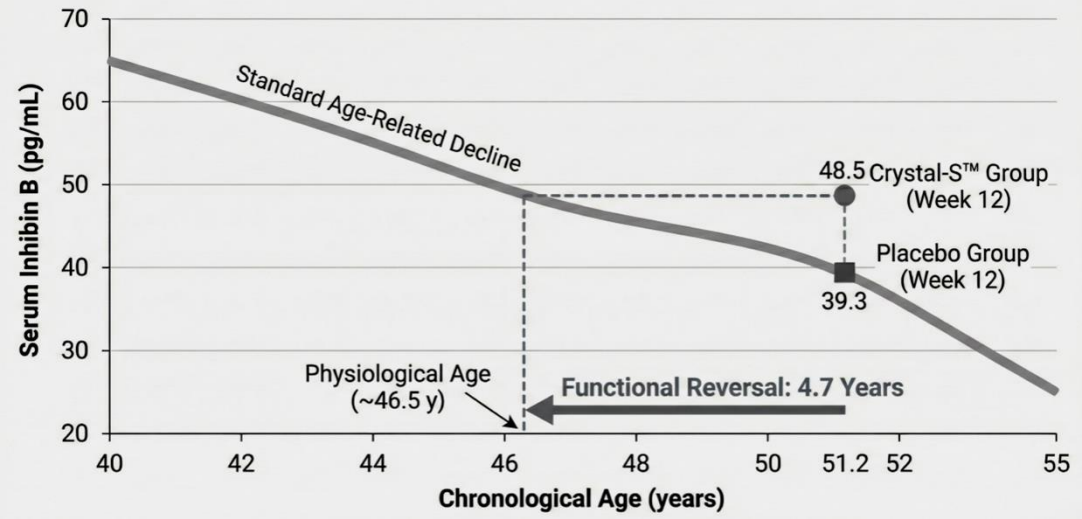

Figure 1: Determination of Ovarian Physiological Age Reversal.

The grey line represents the standard age-related decline of serum Inhibin B in perimenopausal women. As shown in Figure1 and Figure 2, at Week 12, the Placebo group (mean chronological age 51.2 y) showed Inhibin B levels consistent with their age (39.3 pg/mL). The Phyto Placenta group (mean chronological age 51.2 y) maintained significantly higher Inhibin B levels (48.5 pg/mL), intersecting the standard curve at a biological age of approximately 46.5 years, indicating a functional reversal of 4.7 years.

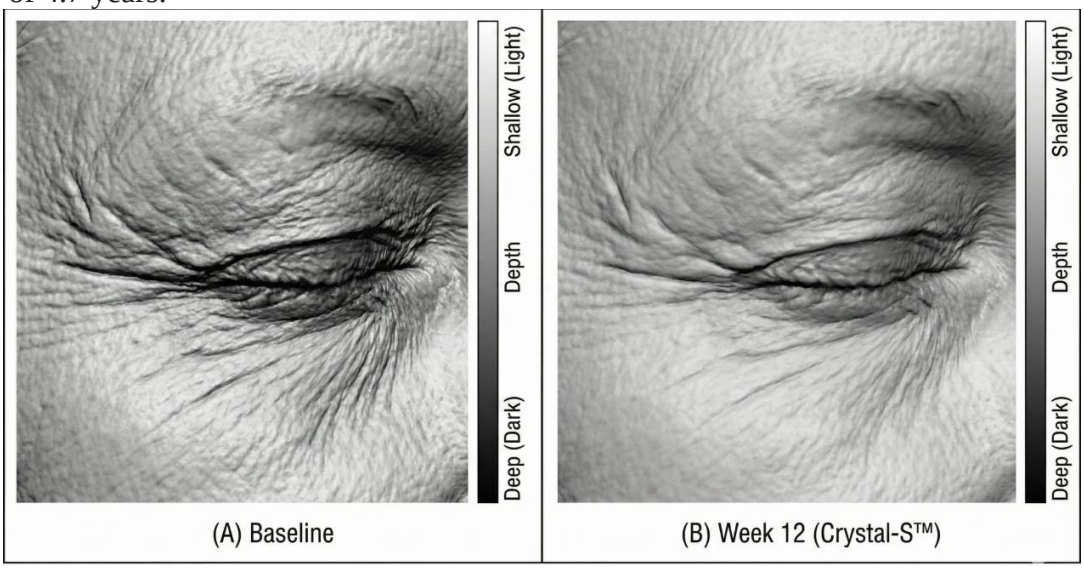

Figure 2: Representative 3D Topographic Analysis of Periorbital Wrinkles (VISIA-CR).

(A) Baseline image showing deep wrinkle formations (indicated by cooler blue/green tones) in the crow's feet area. (B) Same subject after 12 weeks of Phyto Placenta supplementation, showing a visible reduction in wrinkle depth and volume, with a shift towards smoother skin topography (warmer yellow tones).

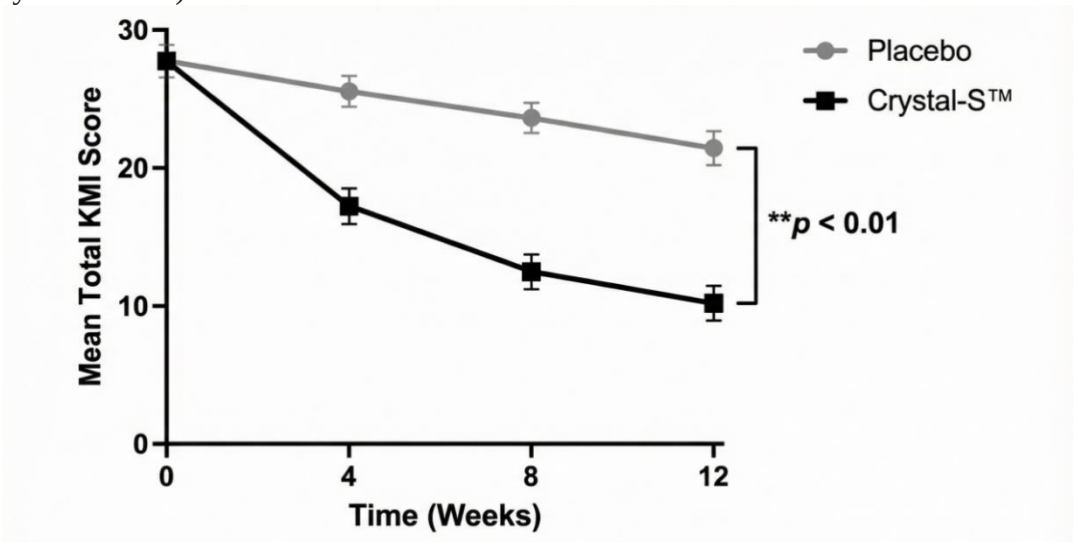

Figure 3: Time Course of Menopausal Symptom Relief (Modified Kupperman Index).

As shown in Figure 3, changes in mean total KMI scores over 12 weeks for the Placebo group and Phyto Placenta group. The Phyto Placenta group showed a rapid and significant reduction in symptom burden starting at Week 4, reaching a 62.3% reduction by Week 12, significantly outperforming the placebo response ($p < 0.01$).

6. Conclusion

In this 12-week randomized controlled pilot trial involving 25 perimenopausal women, daily supplementation with 230 mg of the Phyto Placenta Complex formulation demonstrated significant multi-system benefits. Key findings include: 1) These findings support a mechanistic model in which efficient in vivo conversion to S-equol enables ERβ-mediated modulation of ovarian and systemic aging processes. 2) Functional ovarian rejuvenation: The formulation effectively stabilized serum Inhibin B levels, functionally reversing the calculated ovarian physiological age by approximately 4.7 years compared to the natural decline observed in the placebo group. 3) Significant dermal remodeling: It induced statistically significant improvements in key skin parameters, including reduced wrinkle depth, increased hydration and elasticity, and decreased melanin index, indicating potent skin rejuvenation effects. 4) Rapid and substantial symptom relief: The intervention led to a 62.3% reduction in total menopausal symptom burden (KMI), with pronounced alleviation of vasomotor symptomsand paresthesia, suggesting efficacy mediated through both peripheral and central ERβ pathways.

References

[1] Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. Hum Reprod Update. 2007;13(6):559-565.
[2] Welt CK, McNicholl DJ, Taylor AE, Hall JE. Female reproductive aging is marked by decreased secretion of dimeric inhibin. J Clin Endocrinol Metab. 1999;84(1):105-111.
[3] Burger HG. The endocrinology of the menopause. J Steroid Biochem Mol Biol. 1999 Apr-Jun;69(1-6):31-5.
[4] Muthyala RS, Ju YH, Sheng S, et al. Equol, a natural estrogenic metabolite from soy isoflavones: convenient

preparation and resolution of R- and S-equols and their differing binding and transcriptional activity involving estrogen receptors alpha and beta. Bioorg Med Chem. 2004;12(6):1559-1567.
[5] Jackson RL, Greiwe JS, Schwen RJ. Emerging evidence of the health benefits of S-equol. Nutr Rev. 2011;69(8):432-448.
[6] Setchell KD, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol—a clue to the effectiveness of soy and its isoflavones. J Nutr. 2002;132(12):3577-3584.
[7] Setchell KD, Clerici C. Equol: pharmacokinetics and biological actions. J Nutr. 2010;140(7):1355S–1362S.
[8] Rowland I, Faughnan M, Hoey L, et al. Bioavailability of phyto-oestrogens. Br J Nutr. 2003;89(S1):S45–S58.
[9] Oyama A, Ueno T, Uchiyama S, et al. The effects of natural S-equol supplementation on skin aging in postmenopausal women. Menopause. 2012;19(2):202–210.
[10] Ishiwata N, Melby MK, Mizuno S, et al. New equol supplement for relieving menopausal symptoms: randomized, placebo-controlled trial of Japanese women Menopause. 2009;16(1):141–148.
[11] Sowers MR, Chin D, Santoro N, et al. FSH and inhibin B variability during the menopausal transition. J Clin Endocrinol Metab. 2008;93(9):3465-3471.
[12] Jian Wu, Jun Oka, Mitsuru Higuchi, et al. Cooperative effects of isoflavones and exercise on bone and lipid metabolism in postmenopausal Japanese women: a randomized placebo-controlled trial. Metabolism Clinical and Experimental. 2006; 55: 423-433
[13] Tao Liu, Nan Li, Yi-qi Yan, et al. Recent advances in the anti-aging effects of phytoestrogens on collagen, water content, and oxidative stress. Phytotherapy Research.2020;34:435-44