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# Efficacy and Safety of a Multi-Ingredient Nutraceutical Supplement for Women's Health: A Randomized, Double-Blind, Placebo-Controlled Trial

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**ABSTRACT:** Women's health is known to show a wide range of variations with age, including hormonal fluctuations during the perimenopausal period and an eventual decrease in ovarian hormone production after menopause. This clinical trial evaluated the efficacy and safety of a multi-ingredient nutraceutical supplement (FemHealQA™) in perimenopausal and postmenopausal women. In this randomized, double-blind, placebo-controlled trial, a total of 78 women were enrolled and randomized in a 1:1:1 ratio to one of the three treatment arms. Assessments were conducted at five visits over six months. Primary outcomes, secondary outcomes, and inflammatory and metabolic biomarkers were measured. Analyses were conducted separately for postmenopausal (n = 39) and perimenopausal (n = 39) women. In postmenopausal women, both of the active treatments showed significantly lower MRS, GCS, WOMAC, and PSQI scores and higher BMD than placebo at Visit 5, whereas BMIS was non-significant. Among the laboratory parameters, HbA1c and RBG were significantly lower with both active regimens compared to the placebo at Visit 5. In perimenopausal women, both active treatments showed significantly lower MRS, GCS, and PSQI scores and higher BMD than placebo at Visit 5. Only the 2-

capsule regimen showed a significantly lower WOMAC score and a significantly higher Z-score than placebo. The laboratory parameters did not show any significant difference compared to placebo after the analyses. No adverse events were reported. At Visit 5, the active regimens showed significantly better menopausal symptoms, bone mineral density, and sleep quality outcomes than placebo, with joint function differences in selected groups only, suggesting their potential as a non-hormonal option for supporting women's health and menopausal well-being.

## 1. INTRODUCTION

Women's health involves dynamic physiological and functional changes across the life course, influenced by biological aging, lifestyle, genetic predisposition, environmental factors, and reproductive transitions. Menopause is a major stage in this context, and since people are now living longer all over the world, women spend a large part of their lives after menopause. The changes in ovarian hormone production that take place at this time are linked to a variety of physiological changes and menopausal symptoms (Harlow et al., 2012). Vasomotor symptoms, principally hot flashes and night sweats, affect up to 80% of women during the perimenopausal and postmenopausal stages, with considerable impact on quality of life, occupational functioning, and sleep quality (Armeni et al., 2023; Gibson et al., 2024). Estrogen plays a crucial role in maintaining bone health, regulating metabolism, and modulating immune and inflammatory responses. The decline in estrogen increases bone turnover, with bone resorption exceeding bone formation, increasing the risk of osteopenia and osteoporosis. Systemic low-grade inflammation, insulin resistance, and altered body composition further characterize these menopausal stages (Santen et al., 2010). Thus, treatments that can reduce inflammation, support skeletal health, and improve metabolic health may significantly benefit women during menopause.

Hormone replacement therapy remains the most effective treatment for menopausal vasomotor symptoms. However, its use is not appropriate for all women and depends on individual characteristics and contraindications, including a history of hormone-sensitive malignancies, thromboembolic disease, and certain cardiovascular risk factors (Santen et al., 2010). As a result, a substantial proportion of women seek non-hormonal, plant-based, or nutraceutical alternatives. Despite widespread use, the clinical evidence base for most such interventions remains limited, heterogeneous in design, and often focused on single-ingredient preparations (Castelo-Branco and Soveral, 2013; Kim and Yu, 2025). Therefore, there is a need for evidence-based, safe multi-ingredient formulations that address the various physiological mechanisms underlying menopausal symptoms.

The product under study is a multi-ingredient formulation (FemHealQA™) containing ingredients previously investigated for their potential effects on inflammation, blood glucose, bone health, and musculoskeletal symptoms. The blend contains Boswellia serrata extract standardized to acetyl-11-keto-β-boswellic acid (AKBA), which has been reported to inhibit 5-lipoxygenase (5-LOX), a key enzyme involved in the biosynthesis of leukotrienes from arachidonic acid during the inflammatory cascade, with reported anti-inflammatory and joint-protective properties (Safayhi et al., 1992; Sengupta et al., 2008). Fenugreek (Trigonella foenum-graecum) fiber contributes to glycemic control by delaying carbohydrate digestion and glucose absorption (Neelakantan et al., 2014; Shabil et al., 2023). Bromelain, a pineapple-derived cysteine protease, has been investigated for potential anti-inflammatory and analgesic effects through modulation of prostaglandin levels, reduction of bradykinin-mediated vascular permeability, and increased serum fibrinolytic activity (Rathnavelu et al., 2016). Vitamin K2-7 serves as a cofactor for the gamma-carboxylation of osteocalcin and matrix Gla protein (MGP), thereby contributing to normal bone mineralization and bone metabolism (Ma et al., 2022; Sato et al., 2020). Magnesium plays a role in osteoblast differentiation, parathyroid hormone regulation, and bone homeostasis (Liu et al., 2024). Altogether, these ingredients may target various biological processes associated with menopausal health.

The present randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy and safety of FemHealQA™ across two dosing regimens (2 capsules per day and 1 capsule per day) and two menopausal subpopulations (postmenopausal and perimenopausal women) over a six-month observation period.

## 2. MATERIALS AND METHODS

### 2.1 Baseline Characteristics and Demographics

Baseline demographics and characteristics such as age, body weight, menopausal status, and use of other concomitant medications were assessed before randomization to characterize treatment groups at the start of the study.

### 2.2 Informed Consent and Ethical Approval

This study was conducted in full accordance with the ethical principles established in the Declaration of Helsinki (2013 revision) and in compliance with International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice guidelines. This trial was conducted at a single clinical center in India, namely Shree Vinayak Hospital, Nashik, Maharashtra, India. The trial registration number is CTRI/2025/06/088943. The protocol, participant information sheet, and informed consent form were reviewed and approved before the initiation of any study-related procedures.

### 2.3 Investigational Product

FemHealQA™ is a multi-ingredient nutraceutical supplement supplied as a capsule (450 mg). The formulation contains Boswellia serrata extract standardized to 60% AKBA and subjected to proprietary processing (60% AKBA-QA) (3.45% w/w), fenugreek (Trigonella foenum-graecum) fiber (17.93% w/w), bromelain (27.58% w/w), vitamin K2-7 (0.01% w/w), and magnesium oxide (51.03% w/w). The matching placebo capsule was identical in appearance, size, weight, and color to the active capsule and contained an inert filler. For the preparation of 60% AKBA-QA, the standardized 60% AKBA extract was exposed to a proprietary processing method before being incorporated into FemHealQA™, and the full operating protocol is commercially confidential.

### 2.4 Study Design

A randomized, double-blind, placebo-controlled, three-arm parallel-group clinical trial was conducted over a total observation period of six months per participant. Participants attended five visits: Visit 1 (Day 1, screening and enrollment), Visit 2 (Month 1), Visit 3 (Month 3), Visit 4 (Month 5), and Visit 5 (Month 6). Visit 4 was scheduled one month before the final assessment visit to allow for dispensing of the final study product and assessment of interim compliance before study completion.

### 2.5 Study Population

#### 2.5.1 Inclusion Criteria

Eligible participants were women who experienced at least one predefined moderate-to-severe menopausal symptom (hot flashes, night sweats, mood disturbance, or sleep disruption) in conjunction with joint discomfort and were otherwise in good general health without significant comorbid conditions. Menopausal status was classified at screening by the investigator based on menstrual history and clinical assessment in accordance with the Stages of Reproductive Aging Workshop +10 (STRAW+10) criteria.

#### 2.5.2 Exclusion Criteria

Key exclusion criteria included current or recent use of hormone replacement therapy or hormonal treatments (within three months before enrollment), a history of hormone-dependent malignancy (breast, ovarian, or endometrial cancer), significant cardiovascular, hepatic, or renal disease, body mass index (BMI) >35 kg/m², and known hypersensitivity to any formulation ingredient. Women who had participated in another interventional clinical trial within three months before enrollment were also excluded from the study.

#### 2.5.3 Subpopulation Stratification

The participants were classified at screening according to menopausal status as postmenopausal or perimenopausal (Figure 1). Separate analyses of the two subpopulations were performed post hoc and were therefore considered exploratory. Postmenopausal women were defined as having ≥12 consecutive months of amenorrhea without an alternative pathological cause (n = 39 total, 13 per arm), while perimenopausal women were characterized by menstrual irregularity consistent with the early or late menopausal transition (n = 39 total, 13 per arm).

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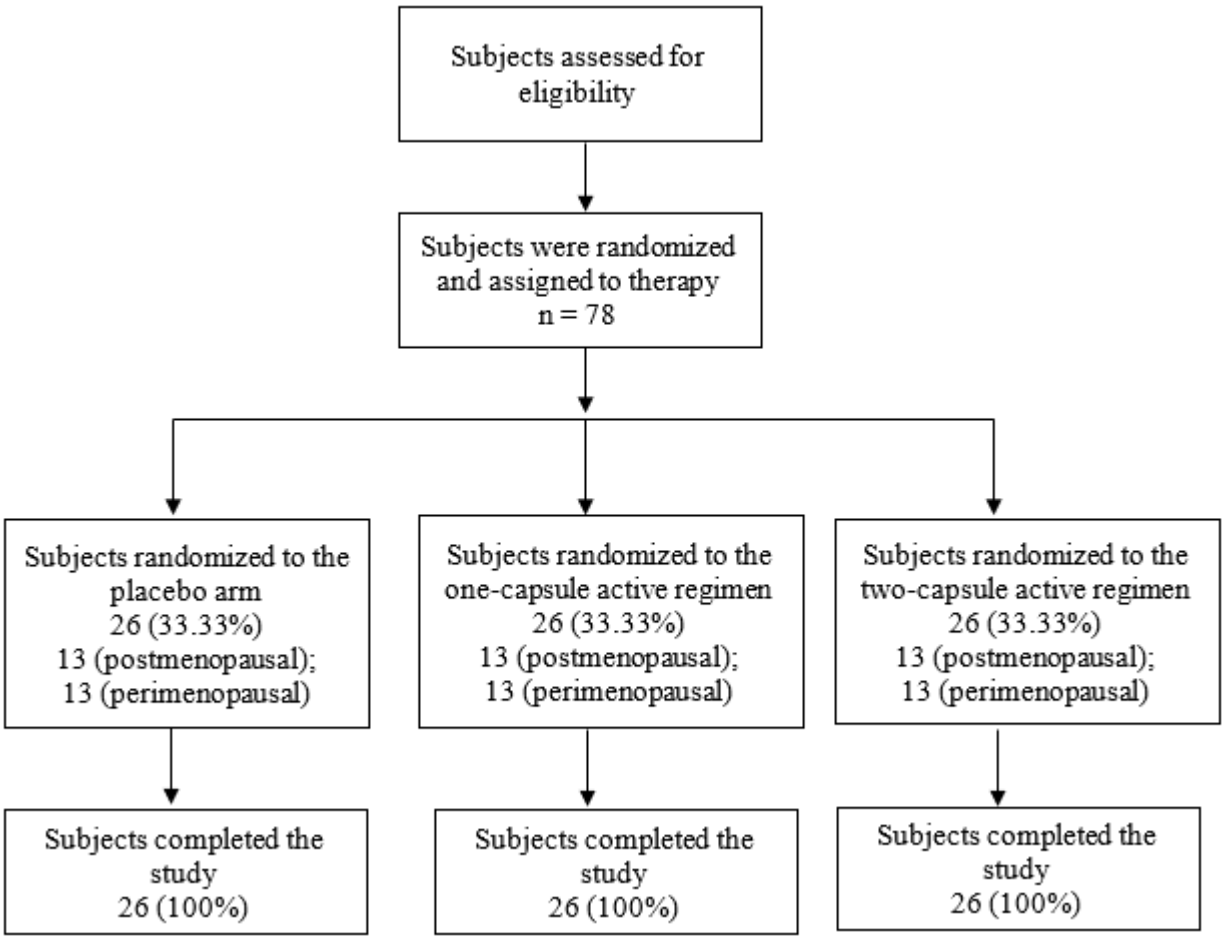



**Figure 1:** CONSORT flow diagram

### 2.6 Randomization and Blinding

Randomization was performed in a 1:1:1 ratio across the three treatment arms using a computer-generated allocation sequence. Allocation concealment was maintained through the use of sequentially numbered, opaque, sealed envelopes, which were opened at the point of enrollment. Double-blinding was maintained by using capsules that were identical in appearance, size, and color for both the active and placebo preparations.

### 2.7 Treatment Arms and Dosing Regimen

Three treatment arms were evaluated. For uniformity, all groups received two capsules daily. Participants assigned to the 2-capsule active regimen (Arm 1) received two active capsules of the study product daily. Participants assigned to the 1-capsule active regimen (Arm 2) received one active capsule of the study product and one identically appearing placebo capsule daily. The placebo group (Arm 3) received two identically appearing placebo capsules. All participants were instructed to take their assigned capsules at the same time each day, accompanied by water. Treatment was dispensed at Visits 1 through 4. Participants were advised to continue their usual dietary habits, physical activity, and medications throughout the study unless otherwise indicated for medical reasons.

### 2.8 Outcome Measures

#### 2.8.1 Primary outcomes

The Menopause Rating Scale (MRS) is a validated 11-item self-report instrument that assesses somatic, psychological, and urogenital symptom domains of menopause, with each item scored on a 0 – 4 ordinal scale, with higher scores indicating greater symptom severity (Heinemann et al., 2004). The Greene Climacteric Scale (GCS) is a validated 21-item self-report instrument

that assesses vasomotor, psychological, and somatic climacteric symptoms, with each item scored on a 4-point response scale, with higher scores indicating a greater symptom burden (Greene, 1998). Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine at Visits 1 and 5 and expressed as g/cm$^2$, with T-scores and Z-scores recorded as standardized derivatives of the same measurement.

### 2.8.2 Secondary outcomes

Joint pain, stiffness, and physical function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a validated 24-item Likert-format instrument with a total score range of 0–96, where higher scores indicate greater disease burden (Bellamy et al., 1988). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a validated 19-item self-report questionnaire yielding a global score of 0–21, with scores above 5 indicating poor sleep quality (Buysse et al., 1989). Mood was assessed using the Brief Mood Introspection Scale (BMIS), a 16-item adjective-based instrument assessing pleasant-unpleasant and arousal-calm mood dimensions (Mayer and Gaschke, 1988). Laboratory assessments included serum calcium, serum iron, hemoglobin, glycated hemoglobin (HbA1c), random blood glucose (RBG), erythrocyte sedimentation rate (ESR), vitamin D, and estrogen levels.

### 2.8.3 Safety outcomes

Treatment-emergent adverse events (TEAEs) were recorded at each visit through clinical examination and spontaneous reporting. Serious adverse events (SAEs) were defined per ICH E6 criteria.

### 2.9 Statistical Analysis

The results are presented as mean ± standard deviation (SD). At Visit 5, each of the active treatment regimens (the 2-capsule regimen and the 1-capsule regimen) was compared with the placebo group within each menopausal subpopulation. Normality was evaluated by means of the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was carried out, followed by Bonferroni's multiple comparison test, and Bonferroni-adjusted p-values were provided. For outcomes analyzed using non-parametric methods, the Kruskal-Wallis test was performed, followed by pairwise comparisons adjusted using the two-stage linear step-up procedure of Benjamini, Krieger, and Yekutieli (BKY) to control the false discovery rate at Q = 0.05. Interpretation of the BKY analyses was based on q-values and discovery status. A two-sided significance level of 0.05 was applied to the Bonferroni-adjusted comparisons. All the statistical analyses were performed using GraphPad Prism Version 8.0 (GraphPad Software, San Diego, CA, USA).

## 3. RESULTS AND DISCUSSION

### 3.1 Baseline Characteristics

Baseline demographic and clinical characteristics are presented in Table 1. In the postmenopausal subpopulation, mean age ranged from 59.92 to 63.77 years across treatment arms, and mean body weight ranged from 56.31 to 61.31 kg. In the perimenopausal subpopulation, mean age ranged from 36.46 to 39.15 years. Concomitant medication use was summarized descriptively.

**Table 1.** Baseline characteristics of the participants.

| Parameter | Two-capsule active regimen | One-capsule active regimen | Placebo |
|---|---|---|---|
| **Postmenopausal Women (n = 39)** | | | |
| Age (years) | 63.77 ± 8.55 | 59.92 ± 9.03 | 60.00 ± 6.47 |
| Weight (kg) | 61.31 ± 6.84 | 56.31 ± 7.46 | 59.69 ± 5.86 |
| Concomitant medications, n (%) | 6 (46.15%) | 5 (38.46%) | 9 (69.23%) |
| **Perimenopausal Women (n = 39)** | | | |
| Age (years) | 37.23 ± 4.00 | 39.15 ± 4.20 | 36.46 ± 2.76 |

| | | | |
|---|---|---|---|
| Weight (kg) | 55.92 ± 4.52 | 58.61 ± 5.73 | 60.63 ± 7.64 |
| Concomitant medications, n (%) | 1 (7.69%) | 1 (7.69%) | 0 (0%) |
| Values are expressed as mean ± SD. Concomitant medication use is expressed as n (%) | | | |

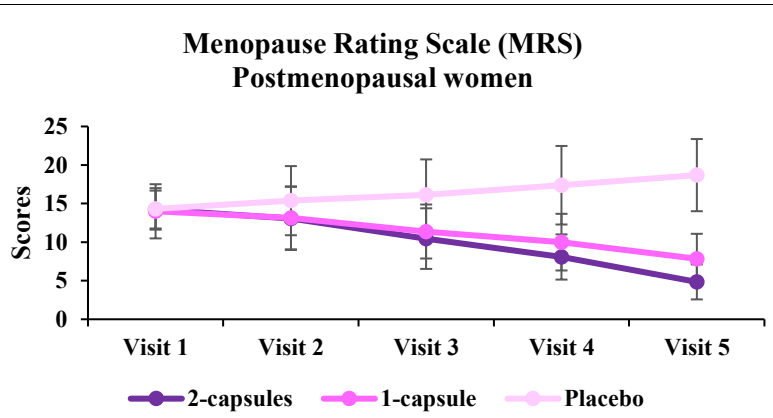
### 3.2 Primary Outcomes

#### 3.2.1 Menopause Rating Scale (MRS)

In postmenopausal women, the average MRS scores decreased from Visit 1 to Visit 5 in the 2-capsule group (14.23 ± 2.45 to 4.85 ± 2.27) and the 1-capsule group (14.00 ± 3.51 to 7.85 ± 3.24), while they increased in the placebo group (14.31 ± 2.69 to 18.69 ± 4.68). By Visit 5, both of the active treatment groups showed significantly lower MRS scores compared to the placebo group (Bonferroni-adjusted p-value < 0.0001).

In perimenopausal women, the average MRS scores decreased from Visit 1 to Visit 5 for both the 2-capsule (6.31 ± 0.75 to 1.00 ± 0.41) and 1-capsule active regimens (9.46 ± 6.42 to 5.85 ± 5.87). For the placebo group, the average MRS scores increased from Visit 1 to Visit 5 (6.46 ± 1.51 to 8.92 ± 2.53). The Kruskal-Wallis test at Visit 5 was significant (p < 0.0001), and both of the comparisons between the active treatments and placebo were considered discoveries after BKY analysis (q < 0.0001 and q = 0.0416, respectively). The results are shown in Figures 2A and B.

**A)**




**B)**

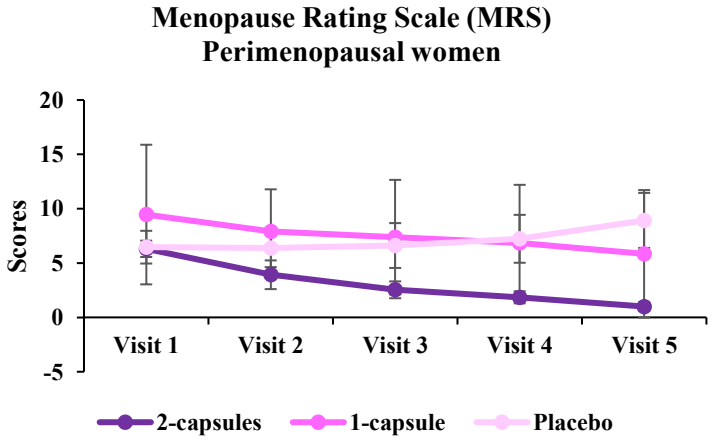


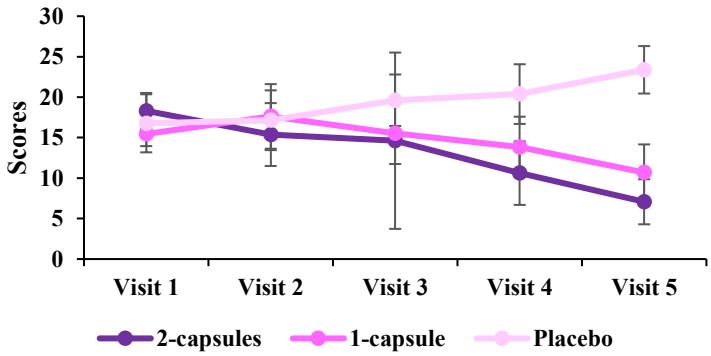

**Figure 2:** MRS scores over the six-month study period. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.2.2 Greene Climacteric Scale (GCS)

In postmenopausal women, the average GCS scores decreased from Visit 1 to Visit 5 in both the 2-capsule group (18.31 ± 2.21 to 7.08 ± 2.78) and the 1-capsule group (15.46 ± 1.51 to 10.69 ± 3.47), while they increased in the placebo group (16.77 ± 3.59 to 23.38 ± 2.93). By Visit 5, both active treatments were found to be significantly different compared to placebo (Bonferroni-adjusted p-value < 0.0001).

In perimenopausal women, the average GCS scores reduced from Visit 1 to Visit 5 in both the 2-capsule group (16.54 ± 5.33 to 4.38 ± 1.26) and the 1-capsule group (14.69 ± 5.20 to 10.69 ± 4.52), while they increased in the placebo group (16.31 ± 5.27 to 18.54 ± 1.51). By Visit 5, both active treatments were found to be significantly different compared to placebo (Bonferroni-adjusted p-value < 0.0001). The results are shown in Figures 3A and B.

A)




B)

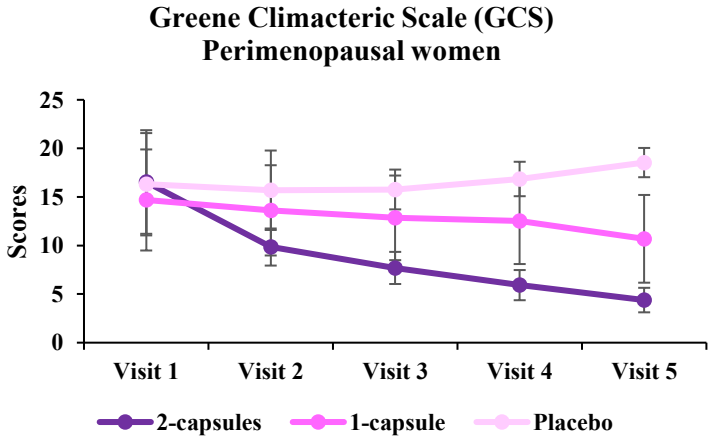



**Figure 3:** GCS scores over the six-month study period. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.2.3 Bone Mineral Density (BMD)

In postmenopausal women, the mean BMD increased from Visit 1 to Visit 5 in both the 2-capsule group (0.77 ± 0.13 to 0.96 ± 0.10) and the 1-capsule group (0.77 ± 0.16 to 0.88 ± 0.17), while it decreased in the placebo group (0.73 ± 0.18 to 0.69 ± 0.18). At Visit 5, both of the active treatments had a significantly higher BMD compared to the placebo (Bonferroni-adjusted p-values were 0.0002 and 0.0085 for the 2-capsule and 1-capsule groups, respectively).

In women going through perimenopause, the average BMD increased from Visit 1 to Visit 5 in the 2-capsule active regimen (0.93 ± 0.17 to 1.09 ± 0.16) and in the 1-capsule active regimen (0.89 ± 0.19 to 1.05 ± 0.17), while it decreased in the placebo group (0.93 ± 0.13 to 0.77 ± 0.09). At Visit 5, both of the treatments had a significantly higher BMD compared to the placebo (Bonferroni-adjusted p-value < 0.0001). The results are shown in Figures 4A and B.

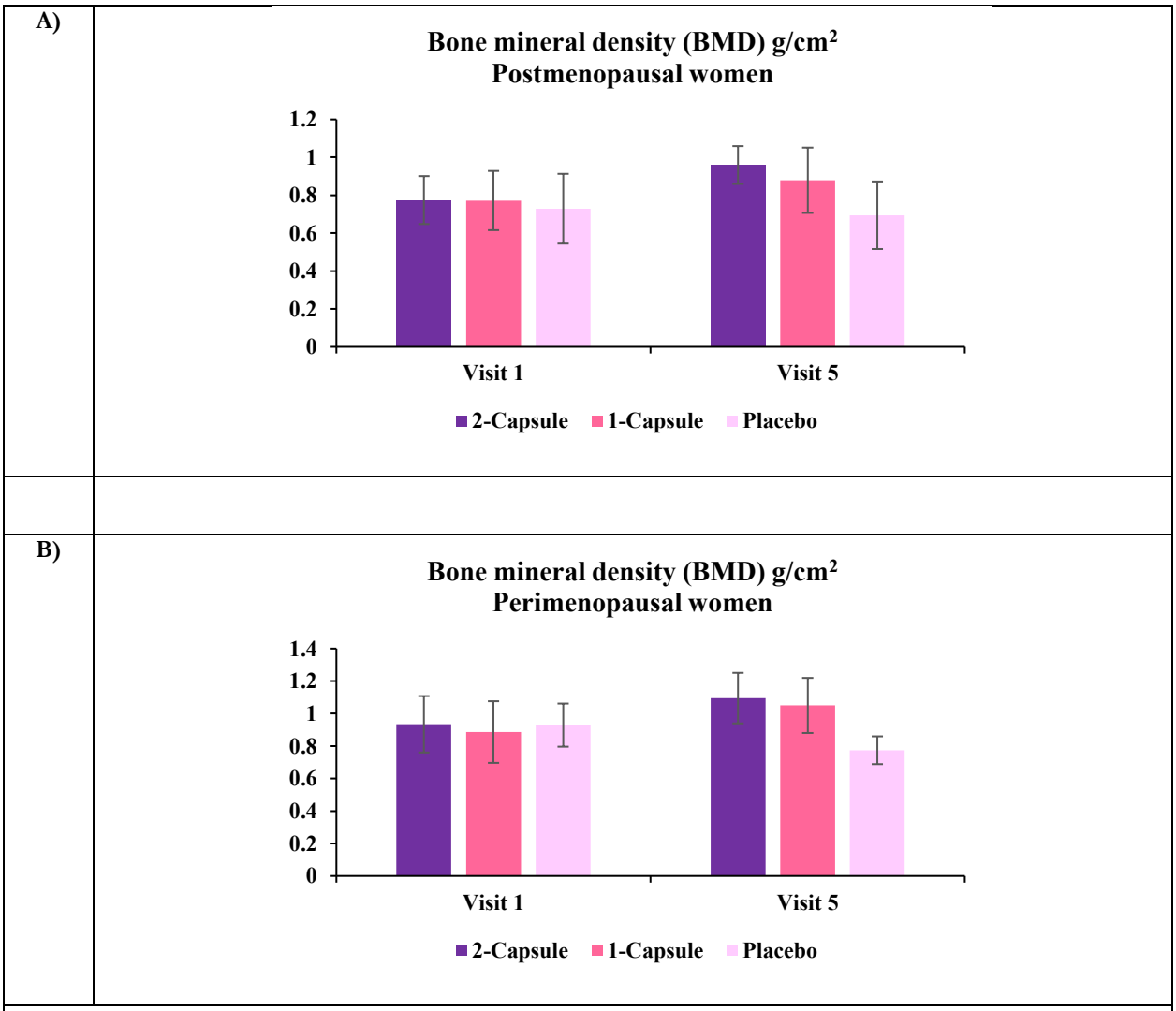



**Figure 4:** BMD at baseline (Visit 1) and Visit 5. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.2.4 T-score and Z-score

In postmenopausal women, the mean T-score changed between Visit 1 and Visit 5 from -3.12 ± 0.72 to -0.74 ± 0.81 when 2 capsules were administered, from -2.85 ± 1.10 to -2.10 ± 1.08 when 1 capsule was administered, and from -3.00 ± 1.23 to -3.23 ± 1.26 in the placebo group. At Visit 5, the Kruskal-Wallis test was significant ($p < 0.0001$), and both of the comparisons between the active treatments and the placebo were identified as discoveries after applying the BKY procedure ($q < 0.0001$ and $q = 0.0378$ for the 2-capsule and 1-capsule groups, respectively).

The mean Z-scores in postmenopausal women changed between Visit 1 and Visit 5 from -2.10 ± 0.80 to -0.11 ± 0.83 when given 2 capsules, from -1.78 ± 1.24 to -0.91 ± 1.19 when given 1 capsule, and from -2.01 ± 1.29 to -2.42 ± 1.20 with the placebo. In each case, the comparisons between the active treatments and placebo at Visit 5 were identified as discoveries after the BKY procedure ($q < 0.0001$ and $q = 0.0056$ for the 2-capsule and 1-capsule groups, respectively).

In perimenopausal women, the T-score at Visit 5 was found to be significantly different for both active treatments as compared to placebo (Bonferroni-adjusted p-value < 0.0001 and p = 0.0099 for the 2-capsule and 1-capsule groups, respectively), while for the Z-scores it was only the 2-capsule active regimen that differed significantly compared to placebo (Bonferroni-adjusted p-value < 0.0001 and p = 0.0593 for the 2-capsule and 1-capsule groups, respectively). The results for T-scores and Z-scores of both postmenopausal and perimenopausal women are shown in Table 2.

**Table 2.** T-scores and Z-scores at baseline (Visit 1) and Visit 5.

| Daily Regimen | Visit 1 | Visit 5 |
|---|---|---|
| **T-score in postmenopausal women** | | |
| 2-Capsule | -3.12 ± 0.72 | -0.74 ± 0.81 |
| 1-Capsule | -2.85 ± 1.10 | -2.10 ± 1.08 |
| Placebo | -3.00 ± 1.23 | -3.23 ± 1.26 |
| **T-score in perimenopausal women** | | |
| 2-Capsule | -0.77 ± 1.04 | -0.01 ± 0.93 |
| 1-Capsule | -1.22 ± 1.01 | -0.57 ± 0.82 |
| Placebo | -0.71 ± 0.82 | -1.47 ± 0.49 |
| **Z-score in postmenopausal women** | | |
| 2-Capsule | -2.10 ± 0.80 | -0.11 ± 0.83 |
| 1-Capsule | -1.78 ± 1.24 | -0.91 ± 1.19 |
| Placebo | -2.01 ± 1.29 | -2.42 ± 1.20 |
| **Z-score in perimenopausal women** | | |
| 2-Capsule | 0.07 ± 0.81 | 0.66 ± 0.70 |
| 1-Capsule | -0.79 ± 1.11 | -0.41 ± 0.81 |
| Placebo | -0.42 ± 0.81 | -1.05 ± 0.63 |
| Values are expressed as mean ± SD. | | |

### 3.3 Secondary Outcomes

#### 3.3.1 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

In postmenopausal women, the mean WOMAC scores decreased from Visit 1 to Visit 5 in both the 2-capsule group (67.43 ± 6.65 to 13.94 ± 6.56) and the 1-capsule group (64.06 ± 7.78 to 47.99 ± 18.62), while they increased in the placebo group (65.41 ± 12.53 to 71.62 ± 15.67). At Visit 5, both the active treatments were found to be significantly different compared to placebo (Bonferroni-adjusted p-value < 0.0001 and p = 0.0004, respectively).

In perimenopausal women, the mean WOMAC scores reduced from Visit 1 to Visit 5 in both the 2-capsule group (22.40 ± 10.18 to 5.52 ± 3.02) and the 1-capsule group (32.06 ± 12.13 to 19.20 ± 12.41), whereas they were almost the same in the placebo group (27.22 ± 15.17 to 27.16 ± 9.81). At Visit 5, the regimen involving 2 capsules was found to be significantly different compared to placebo (Bonferroni-adjusted p-value < 0.0001), while the 1-capsule regimen did not differ significantly from placebo (Bonferroni-adjusted p = 0.0712). The results are shown in Figures 5A and B.

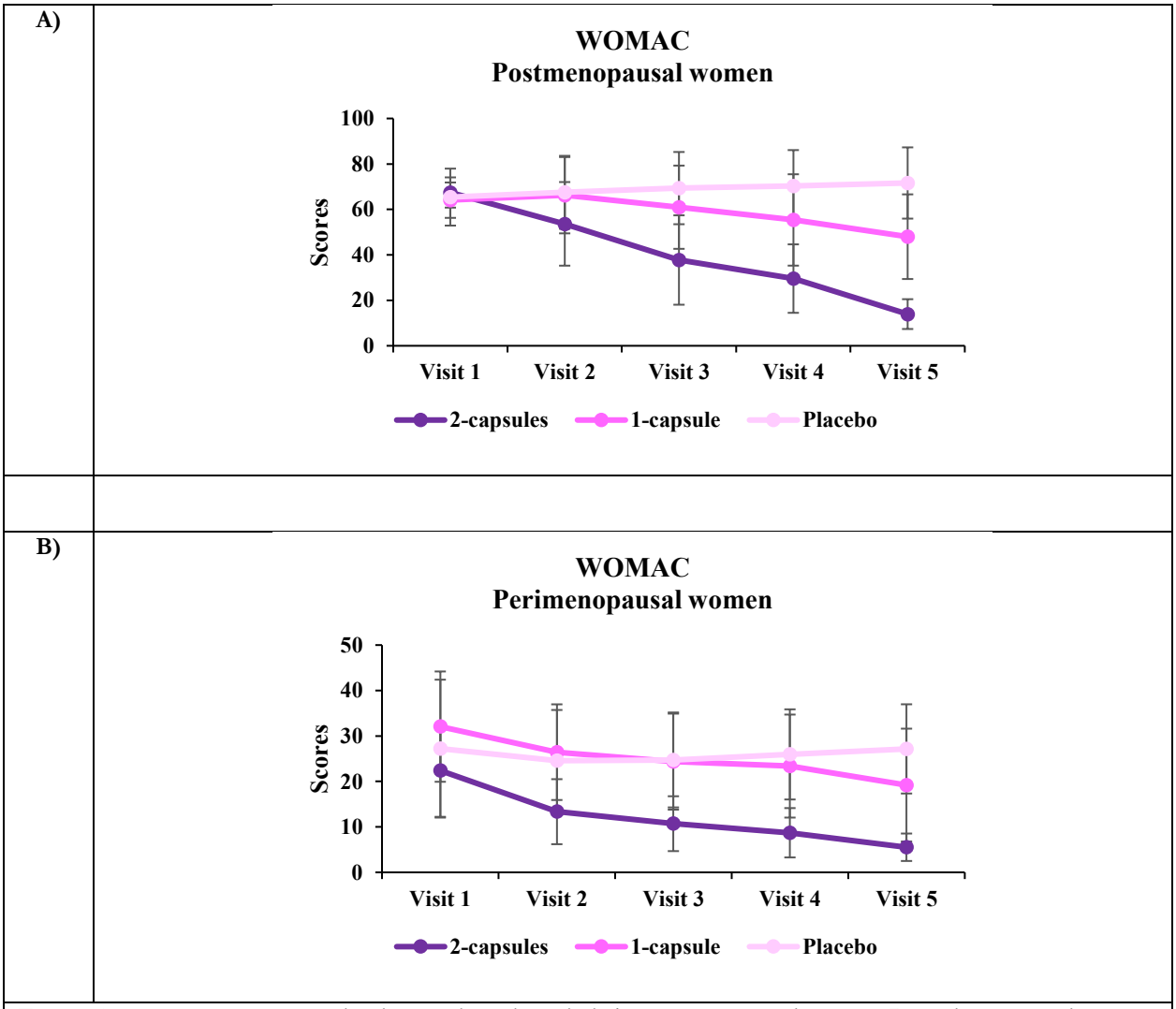



**Figure 5:** WOMAC scores over the six-month study period. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.3.2 Pittsburgh Sleep Quality Index (PSQI)

In postmenopausal women, the average PSQI scores decreased from Visit 1 to Visit 5 in both the 2-capsule group (6.31 ± 2.90 to 1.69 ± 1.03) and the 1-capsule group (5.85 ± 2.44 to 2.31 ± 1.03), whereas they remained almost unchanged in the placebo group (5.77 ± 2.20 to 6.15 ± 2.64). The Kruskal-Wallis test at Visit 5 was significant ($p = 0.0002$), and both of the active versus placebo comparisons were considered discoveries after applying the BKY procedure ($q = 0.0001$ and $q = 0.0038$ for the 2-capsule group and 1-capsule group, respectively).

In women going through the perimenopausal stage, the average PSQI scores decreased from Visit 1 to Visit 5 in both the 2-capsule group (3.23 ± 1.96 to 1.31 ± 1.11) and the 1-capsule group (4.15 ± 2.23 to 1.54 ± 0.78), whereas they increased in the placebo group (3.85 ± 1.86 to 4.46 ± 2.03). The Kruskal-Wallis test at Visit 5 was significant ($p < 0.0001$), and both of the comparisons between the active treatments and the placebo were identified as discoveries after applying the BKY procedure ($q < 0.0001$ and $q = 0.0007$ for the 2-capsule group and 1-capsule group, respectively). The results are shown in Figures 6A and B.

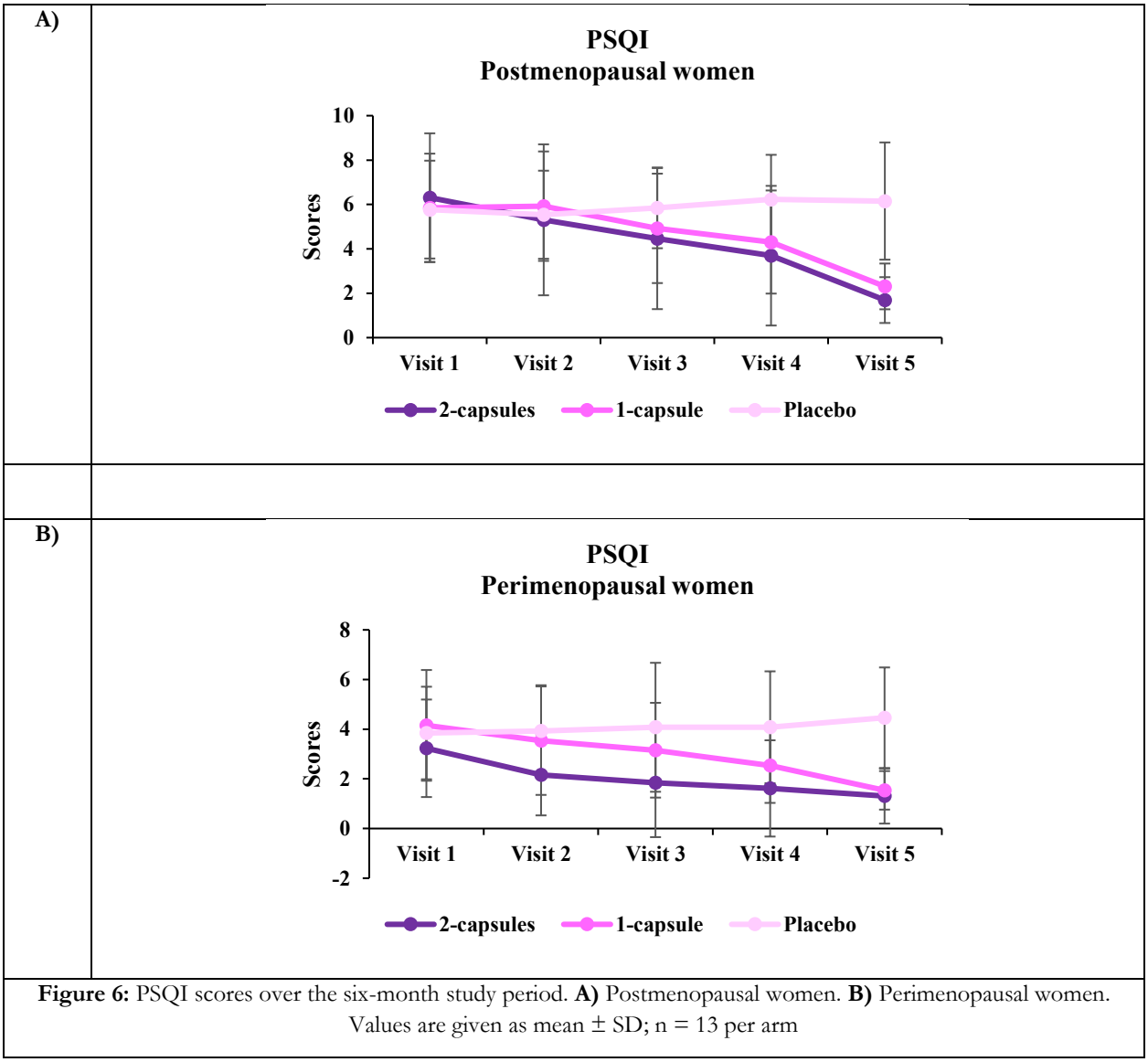



**Figure 6:** PSQI scores over the six-month study period. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.3.3 Brief Mood Introspection Scale (BMIS)

The BMIS scores showed some variation between the various assessments and did not exhibit a consistent directional pattern similar to that of the MRS, GCS, WOMAC, or PSQI. In postmenopausal women, the mean BMIS scores for the 2-capsule, 1-capsule, and placebo groups were 48.62 ± 6.02, 43.31 ± 6.93, and 45.92 ± 3.86 at baseline (Visit 1) and 44.54 ± 2.70, 44.69 ± 4.01, and 44.85 ± 6.90 at Visit 5, respectively. Neither of the active treatments differed significantly compared to placebo at Visit 5 (Bonferroni-adjusted p-value > 0.9999). For perimenopausal women, the corresponding baseline values were 43.54 ± 4.05, 43.54 ± 3.78, and 46.62 ± 4.27, as compared with 41.08 ± 2.29, 43.08 ± 6.74, and 45.00 ± 4.65 at Visit 5. Neither active treatment differed significantly from placebo (Bonferroni-adjusted p-values of 0.0981 and 0.6493, respectively). Because there was variation at the intermediate time points and no significant between-group difference at Visit 5, the Visit 5 comparisons did not detect a difference in BMIS scores. The results are shown in Figures 7A and B.

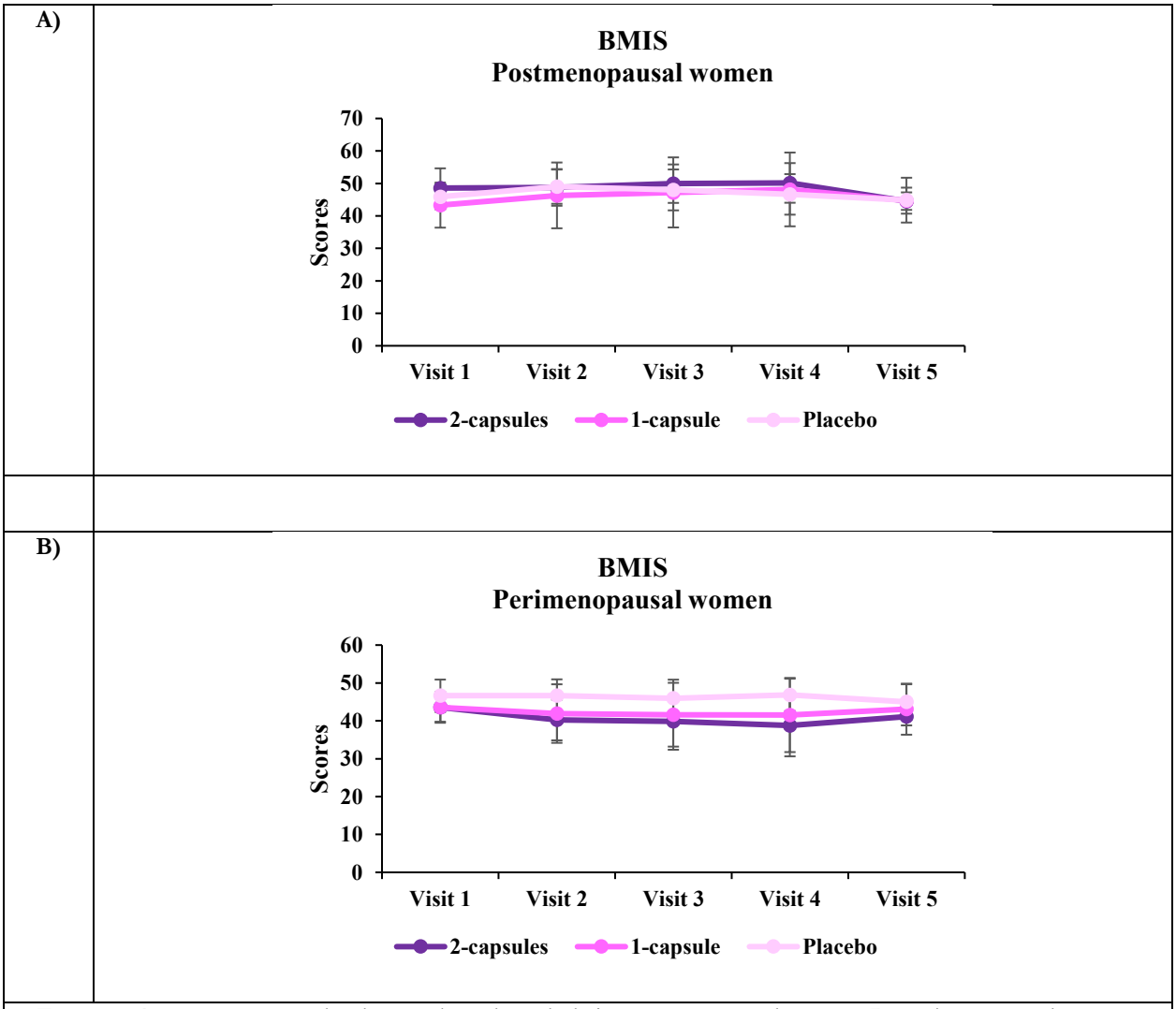



**Figure 7:** BMIS scores over the six-month study period. **A)** Postmenopausal women. **B)** Perimenopausal women. Values are given as mean ± SD; n = 13 per arm

### 3.3.4 Metabolic and Inflammatory Biomarkers

#### 3.3.4.1 Postmenopausal

In the postmenopausal women group, the HbA1c values at Visit 1 and Visit 5 for the two-capsule group were 6.69 ± 0.56% and 6.04 ± 0.47%, respectively. At Visit 5, HbA1c was significantly lower in both active treatment groups than in the placebo group (Bonferroni-adjusted p-values of 0.0038 and 0.0310 for the 2-capsule group and 1-capsule group, respectively). RBG also decreased in the 2-capsule group from 168.8 ± 24.12 to 107.9 ± 10.67 and in the one-capsule group from 169 ± 27 to 128.8 ± 17.22, whereas in the placebo group it showed a decrease from 174.4 ± 18.88 to 147.6 ± 20.13 mg/dL. Significant differences were observed between the active treatments and placebo at Visit 5 (Bonferroni-adjusted p-values < 0.0001 and 0.0122 for the 2-capsule group and 1-capsule group, respectively).

Other laboratory findings, such as ESR, were not found to be different from the placebo as a result of the BKY analysis, and estrogen, calcium, iron, vitamin D, and hemoglobin also showed no significant differences between the active and placebo groups at Visit 5 after conducting the outcome-specific multiple comparison tests. The results are shown in Table 3.

#### 3.3.4.2 Perimenopausal

In the perimenopausal participants, no significant differences from placebo were found at Visit 5 for all parameters such as HbA1c, RBG, ESR, estrogen, calcium, iron, vitamin D, and hemoglobin after conducting the outcome-specific Bonferroni or BKY procedure. The results are shown in Table 4.

**Table 3.** Metabolic and inflammatory biomarkers in postmenopausal women at baseline (Visit 1) and Visit 5.

| Parameters | 2-capsule | | 1-capsule | | Placebo | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 5 | Visit 1 | Visit 5 | Visit 1 | Visit 5 |
| HbA1c (%) | 6.69 ± 0.56 | 6.04 ± 0.47 | 6.47 ± 0.42 | 6.22 ± 0.46 | 6.81 ± 0.76 | 6.77 ± 0.70 |
| RBG (mg/dL) | 168.8 ± 24.12 | 107.9 ± 10.67 | 169 ± 27.00 | 128.8 ± 17.22 | 174.4 ± 18.88 | 147.6 ± 20.13 |
| ESR (mm/h) | 24.08 ± 5.14 | 22.46 ± 7.83 | 24 ± 6.61 | 23.69 ± 7.63 | 21.46 ± 2.37 | 22.46 ± 2.50 |
| Estrogen (pg/mL) | 15.69 ± 4.97 | 14.15 ± 3.89 | 16.38 ± 4.09 | 14.62 ± 3.71 | 18.77 ± 3.94 | 16.23 ± 4.13 |
| Calcium (mg/dL) | 7.81 ± 0.43 | 8.42 ± 1.48 | 7.69 ± 0.61 | 7.62 ± 0.81 | 7.75 ± 0.77 | 7.49 ± 0.75 |
| Iron (µg/dL) | 96.92 ± 16.53 | 99.77 ± 17.6 | 93.41 ± 15.25 | 96.23 ± 17.34 | 103.2 ± 10.24 | 104.5 ± 9.35 |
| Vitamin D (ng/mL) | 20.62 ± 3.55 | 22.68 ± 2.36 | 19.54 ± 2.79 | 25.15 ± 19.36 | 21.23 ± 2.98 | 22 ± 2.27 |
| Hemoglobin (g/dL) | 13.03 ± 0.80 | 13.31 ± 0.60 | 13.22 ± 0.28 | 13.35 ± 0.75 | 13.13 ± 0.45 | 13.11 ± 0.23 |
| Values are expressed as mean ± SD. | | | | | | |

**Table 4.** Metabolic and inflammatory biomarkers in perimenopausal women at baseline (Visit 1) and Visit 5.

| Parameters | 2-capsule | | 1-capsule | | Placebo | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 5 | Visit 1 | Visit 5 | Visit 1 | Visit 5 |
| HbA1c (%) | 5.57 ± 0.37 | 5.57 ± 0.48 | 5.86 ± 1.52 | 5.93 ± 1.54 | 5.54 ± 0.54 | 5.53 ± 0.49 |
| RBG (mg/dL) | 112.8 ± 17.95 | 113 ± 13.93 | 137.6 ± 62.9 | 123.7 ± 44.25 | 113.4 ± 14.96 | 111.8 ± 14.28 |
| ESR (mm/h) | 15.38 ± 7.78 | 14.85 ± 7.02 | 21.15 ± 9.78 | 21.77 ± 10.31 | 14.23 ± 7.42 | 15.22 ± 7.75 |
| Estrogen (pg/mL) | 153.6 ± 75.76 | 156.1 ± 75.39 | 185.2 ± 52.38 | 183.9 ± 55.11 | 200.6 ± 103 | 204.2 ± 101.3 |
| Calcium (mg/dL) | 9.36 ± 0.45 | 9.62 ± 0.90 | 9.53 ± 0.38 | 9.63 ± 0.53 | 9.42 ± 0.33 | 9.4 ± 0.37 |
| Iron (µg/dL) | 67.09 ± 6.95 | 66.62 ± 7.16 | 66.27 ± 9.38 | 66.68 ± 8.19 | 69.83 ± 13.07 | 70.68 ± 13.6 |
| Vitamin D (ng/mL) | 33.2 ± 9.78 | 33.04 ± 10.65 | 29.41 ± 10.8 | 30.16 ± 11.03 | 33.06 ± 9.42 | 32.31 ± 9.46 |
| Hemoglobin (g/dL) | 12.17 ± 0.91 | 12.12 ± 1.13 | 12.05 ± 1.5 | 12.08 ± 1.64 | 12.12 ± 1.11 | 12.27 ± 1.05 |
| Values are expressed as mean ± SD. | | | | | | |

### 3.4 Safety and Tolerability

No treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) were reported in any participant across either subpopulation or any treatment arm throughout the six-month observation period. Study compliance was high across the entire enrolled population: 88% of participants demonstrated complete adherence to the prescribed dosing regimen (100% dose compliance), 8% maintained approximately 90% compliance, and 4% demonstrated approximately 85% compliance.

### 3.5 Discussion

Previous reviews have pointed out that women's health is largely affected during the perimenopausal and postmenopausal periods. Menopausal symptoms involve changes in ovarian hormone production and thermoregulation, and most of the symptoms are influenced by several physiological and psychological factors (Monteleone et al., 2018). The effects of the individual ingredients are not established, as this study was only conducted on the combined formulation. The results from the study are consistent with the established role of AKBA-containing Boswellia serrata extracts in inhibiting 5-lipoxygenase-mediated leukotriene biosynthesis, a pathway associated with inflammation (Sengupta et al., 2008). Fenugreek is reported to have biological activity in women's health. Bromelain, magnesium, and vitamin K2-7 may have contributed to the overall effects of the multi-ingredient formulation. The improvements seen are biologically reasonable and fit with the growing evidence supporting multi-component non-hormonal treatments for women who cannot or do not want to undergo menopausal hormone therapy (MHT).

The bone health findings revealed significant differences between the groups at Visit 5. The progressive decline in estrogen during the menopausal transition promotes osteoclast-mediated bone resorption while suppressing osteoblast-mediated bone formation, culminating in net bone loss and progressive reduction in BMD (Cauley, 2015). For postmenopausal women, a T-score of $\leq$ -2.5 indicates osteoporosis, a T-score between -1.0 and -2.5 denotes osteopenia, and a T-score > -1.0 is considered normal (Kanis et al., 1994). The mean baseline T-score in the postmenopausal two-capsule active regimen group was -3.12 $\pm$ 0.72, which is within the osteoporotic range. Following six months of supplementation, the mean T-score improved and was within the normal range. Vitamin K2-7 serves as a cofactor for the gamma-carboxylation of osteocalcin and matrix Gla protein (Huang et al., 2015; Sato et al., 2020). Magnesium has established roles in osteoblast differentiation and parathyroid hormone regulation (Rondanelli et al., 2021).

Random blood glucose at Visit 5 was lower with both active regimens than with placebo in postmenopausal women. A mean baseline RBG of 168.8 mg/dL in the postmenopausal two-capsule active regimen group was elevated. The decline to a mean of 107.9 mg/dL at Visit 5 represents a large reduction in RBG during the study period. Fenugreek fiber has been shown to attenuate postprandial glycemia through delayed gastric emptying and competitive inhibition of intestinal disaccharidases (Neelakantan et al., 2014). The concurrent decline in HbA1c of 0.65 $\pm$ 0.35% further supports a change in glycemic parameters over the study period.

ESR did not differ significantly from placebo after BKY adjustment in either subpopulation. The non-significant reductions in ESR in postmenopausal active-arm participants may indicate a change in inflammatory status during the course of the study period (Brien et al., 2004; Rathnavelu et al., 2016; Safayhi et al., 1992; Sengupta et al., 2008). Chronic low-grade inflammation contributes to musculoskeletal pain. Reducing systemic inflammation may therefore be a key factor behind the improvement noted across various areas in this study.

The marked improvements in sleep quality seen in the active treatment groups are noteworthy since sleep issues are common and persistent during menopause. Current evidence shows that menopausal insomnia is due to various factors, including vasomotor symptoms, nighttime awakening, chronic pain, mood changes, and a shift in body temperature regulation, rather than just sleep disorders (Baker et al., 2018). Thus, the improvement in sleep quality observed might be due to the improvement of these factors. This perspective aligns with modern reviews that emphasize the close connection between sleep quality, pain, inflammation, and overall menopausal symptom load. The BMIS scores for both active regimens did not differ significantly from placebo at Visit 5 in either subpopulation. Longer follow-up periods and multi-instrument mood assessments may be required to characterize this domain more definitively.

During the six-month observation period, no treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) were reported in either subpopulation or in any of the treatment arms. Compliance with the study was high, since 88% of the participants achieved 100% dose compliance, 8% had about 90% compliance, and 4% had about 85% compliance. The positive

safety profile also matches previous clinical studies that show generally good tolerance for the individual ingredients, such as Boswellia serrata extract, vitamin K2-7, magnesium, bromelain, and fenugreek, when taken at recommended doses. Since long-term commitment is crucial for treatments targeting persistent menopausal symptoms and bone health, the high compliance seen in this study further supports the practical use of this formulation.

## 4. LIMITATIONS

The sample sizes per arm were relatively small in both the postmenopausal and perimenopausal subgroups (13 per arm), limiting statistical power to detect smaller effects. The separate analysis of postmenopausal and perimenopausal women was conducted post hoc and should be interpreted as exploratory. Visit 5 comparisons were unadjusted for baseline. Multiplicity adjustments were outcome-specific. The study was also limited by its six-month follow-up period and single-center design. Future adequately powered multicenter trials with longer follow-up and pre-specified subpopulation analyses are needed to confirm and extend these findings.

## 5. CONCLUSIONS

In this six-month randomized, double-blind, placebo-controlled trial, FemHealQA™ showed significant between-group differences in menopausal symptom severity, bone mineral density, and sleep quality at Visit 5 in both perimenopausal and postmenopausal women, with additional differences in joint function observed in selected treatment groups when compared with the placebo. Significantly lower HbA1c and RBG at Visit 5 were observed with both active regimens compared with placebo in postmenopausal women. There were no significant treatment-related differences observed for most other laboratory parameters following multiplicity adjustment. Overall, these findings support the potential of FemHealQA™ as a well-tolerated, non-hormonal nutritional intervention for supporting multiple aspects of women's health during the menopausal transition and postmenopausal period.

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## AUTHORS CONTRIBUTION

All authors contributed significantly to the study's conception and design, data collection and analysis, and manuscript preparation. They all reviewed the manuscript carefully and approved the final version for publication.

## HUMAN AND ANIMAL RIGHTS

All procedures involving human participants were conducted in accordance with the Declaration of Helsinki. No animals were used in the study.

## AVAILABILITY OF DATA AND MATERIALS

The data will be made available from the corresponding author upon reasonable request.

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## DISCLAIMER

The complete details of the AKBA-QA processing methods are proprietary. However, additional information can be made available upon reasonable request.

## CONFLICT OF INTEREST

Hirehal Greenspace Herbs Pvt. Ltd., Bengaluru, India, funded the study. Tahira HS and Debjit Ghosh are affiliated with Hirehal Greenspace Herbs Pvt. Ltd., Bengaluru, India, as Chief of Research and Development and Research Consultant, respectively. The authors declare no additional competing interests.

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