

Improvement in menopausal symptoms with a nutritional product containing evening primrose oil, hop extract, saffron, tryptophan, vitamins B6, D3, K2, B12, and B9

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Abstract. – OBJECTIVE: Safety concerns or contraindications in the use of hormones have resulted in a rise in the use of nutritional medicinal products for the management of menopausal symptoms. The aim of the present study was to demonstrate the efficacy and safety of Exelvit Menopause®.

PATIENTS AND METHODS: A prospective, open, observational, and multicentre study was performed, including 156 menopausal women. The patients received the nutritional product containing evening primrose oil 50 mg; hop extract 0.127-0.212 mg; saffron Stigmas Extract 0.6 mg; tryptophan 71.25 mg, vitamins B6, D3, K2, B12, and B9 once per day for 12 weeks. The validated menopausal rating score (MRS) was used for recording symptoms.

RESULTS: A decrease in the MRS of all menopausal symptoms was observed after 12 weeks compared to baseline ($p < 0.0001$).

Overall, hot flashes were reduced by 48.15%, heart discomfort by 33.3%, sleep disturbance by 46.2%, joint and muscular discomfort by 27.8%, depressive mood by 45.0%, irritability by 47.6%, anxiety by 44.4%, physical problems by 36.4%, sexual problems by 30.0%, bladder problems 31.3%, and vaginal dryness by 33.3%.

CONCLUSIONS: The nutritional product Exelvit Menopause® significantly reduced menopausal symptoms.

Key Words:

Menopause, Nutritional product, Menopausal rating scale.

Introduction

According to the International Menopause Society, menopausal hormone therapy (MHT) is the

most effective treatment of vasomotor symptoms in menopause. The basis of this treatment is the application of estrogens alone or in combination with progestogens. Importantly, many women still have contraindications to these hormones or prefer a non-hormonal approach for the management of these vasomotor symptoms. Safety issues also play an important role in the management of this disorder, which affects up to 70% of the women entering menopause¹. Upon others, antidepressants, phytoestrogens, acupuncture, or traditional Chinese medicine have been used as non-hormonal methods against vasomotor symptoms², although the North American Menopause Society³ position statement of 2015 described the data situation of herbal therapies as insufficient regarding clinical data. Nevertheless, pollen extracts and vitamin E were mentioned in this report³, adding the fact that more data should be generated.

Intensity and frequency of hot flashes and night sweating are directly related to sleep disturbance and emotional instability, leading to stress which again re-increases sensitivity to hot flashes⁴. Although MHT is considered the most effective treatment for these problems, a constant decrease in the number of users of hormones has been registered following the publications of the Women's Health Initiative (WHI) study⁵ in 2002. In the United States⁶, the use of MHT fell from 38.3% in 2000 to 6.7% in 2010 within the age group 50-59 years. In addition to the consumers' fears, MHT is contraindicated for women with breast cancer, cardiovascular diseases like thrombotic events or strokes in their clinical history or hepatic diseases⁷. However, even phytoestrogens with a low efficacy activate estrogen receptors

creating safety concerns in regard to its mode of action, especially for women with breast cancer in their history⁸. Daidzein and genistein in high concentration stimulate the growth of breast cancer cells⁹. Selective serotonin reuptake inhibitors (SSRI) inhibit the activity of the enzyme CYP2D6 and thus reduce the conversion of the prodrug tamoxifen to the biological drug endoxifen^{10,11}; even if those anti-depressants are commonly used by women with breast cancer.

Hence, nutritional products play an increasingly important role in the management of menopausal symptoms. Some of these nutritional products have been previously studied in the literature. New approaches with a combination of different herbal substances and vitamins D, K, B9, and B12, hop extract, saffron, L-tryptophan and evening primrose oil have been developed and studied clinically. Here we present the first clinical data in menopausal women with this combination to demonstrate the efficacy and safety of this product. The results of this study will contribute to increasing menopausal women's quality of life.

Patients and Methods

A prospective, open, observational, and multicenter study in Spain and Romania was performed on 156 menopausal women to measure the improvement of menopausal symptoms. Before participating in the study, informed consent was obtained from the patients. Ethical approval was obtained from the Ethics Committee of the Hospital Universitario La Princesa, Madrid, Spain, number: CEIm NÚMERO 18/20, 10-09-20. The study has been registered at the German Clinical Trials Register with the ID DRKS00029349 (<https://drks.de/search/en/trial/DRKS00029349>).

Overall, 156 patients with menopausal symptoms were included in the study. The patients received the nutritional product Exelvit Menopause® (Exeltis Healthcare, Guadalajara, Spain) containing evening primrose oil (10% GLA) 50 mg; hop extract [0.15-0.25% 8-prenylnaringenin (8-PN)] 0.127-0.212 mg; saffron stigmas extract (2% Safranal) 0.6 mg; tryptophan 71.25 mg, vitamins B6 (2.1 mg), D3 (5 µg), K2 (32 µg), B12 (2.5 µg), and B9 (200 µg) in a capsule taken once per day over three months. The primary study objective was the improvement in the visual analogue scale (VAS) score of

menopausal symptoms using the Menopausal Rating Scale.

The improvement of menopausal symptoms was recorded using the validated menopausal rating score (MRS) from Heinemann et al¹². The patients recorded the intensity of their symptoms at baseline as well as at the end of each month. The score ranges from 0 to 4 points (0 points = no menopausal symptoms, 1 point = moderate menopausal symptoms, 2 points = medium menopausal symptoms, 3 points = strong menopausal symptoms, 4 points = very strong menopausal symptoms).

Besides this, demographic data, medical history with the recording of menopausal symptoms, and possible medications or adverse events (AE) were documented. Data were collected during the single visit and documented in the source data and the validated CRF. This data was then transferred from the doctor to the CRF.

Adverse events (AEs) and serious adverse events (SAEs) were collected and documented on-site as part of safety reporting. An AE/SAE form had to be completed and sent to the sponsor within 24 hours of confirmation.

Statistical Analysis

Quantitative values are represented as mean and standard deviation, minimum and maximum, and quartiles. 95 % confidence intervals are calculated for the mean values of the primary endpoints to evaluate the accuracy of the estimates. All tests are performed on two sides with a significance level of 5%. Due to the mainly descriptive nature of the present study, alpha adjustments are not provided for multiple tests. A p -value < 0.05 was considered statistically significant. Furthermore, *a priori*, a sample size of at least $n = 150$ menopausal patients was defined to be sufficient for this exploratory study and to perform descriptive statistics.

Results

A significant global decrease of all menopausal symptoms was observed between baseline and after 12 weeks on the MRS ($p < 0.0001$) (see Figures 1 and 2).

Hot flashes were reduced by 48.15%, heart discomfort by 33.3%, sleep disturbance by 46.2%, joint and muscular discomfort by 27.8%, depressive mood by 45.0%, irritability by 47.6%, anxiety by 44.4%, physical problems by 36.4%, sexual problems by 30.0%, bladder problems 31.3%, and vaginal dryness by 33.3% ($p < 0.005$).

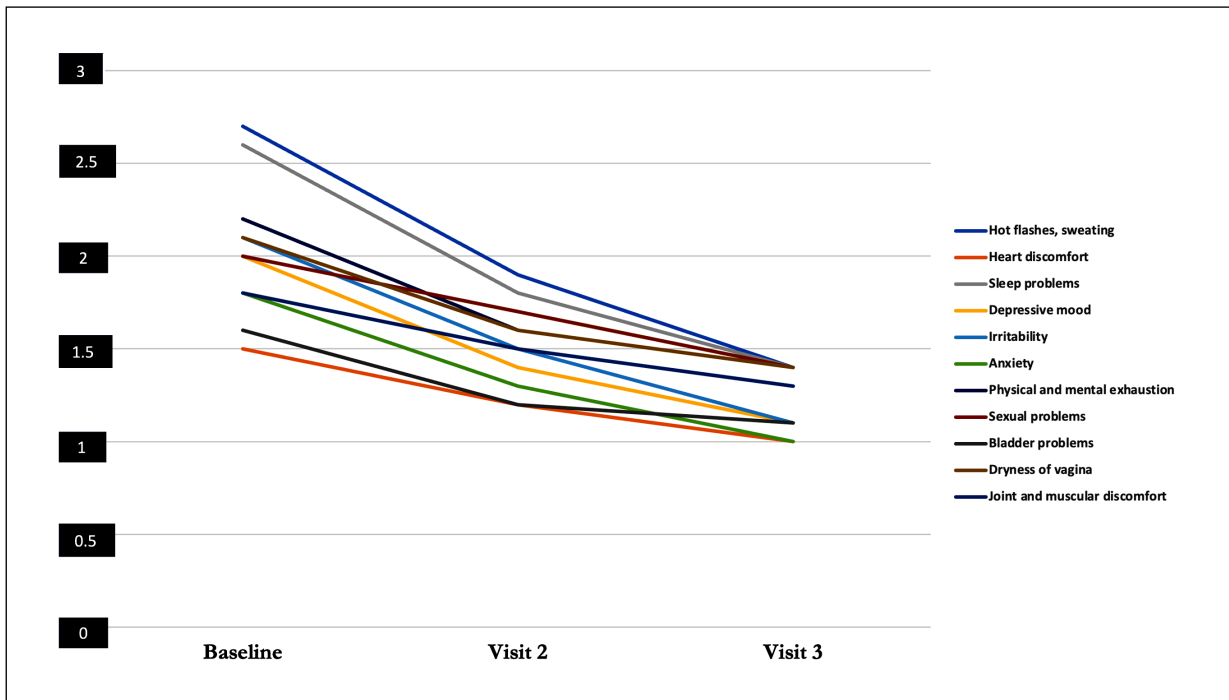


Figure 1. Evolution of the means of the individual questions throughout the study.

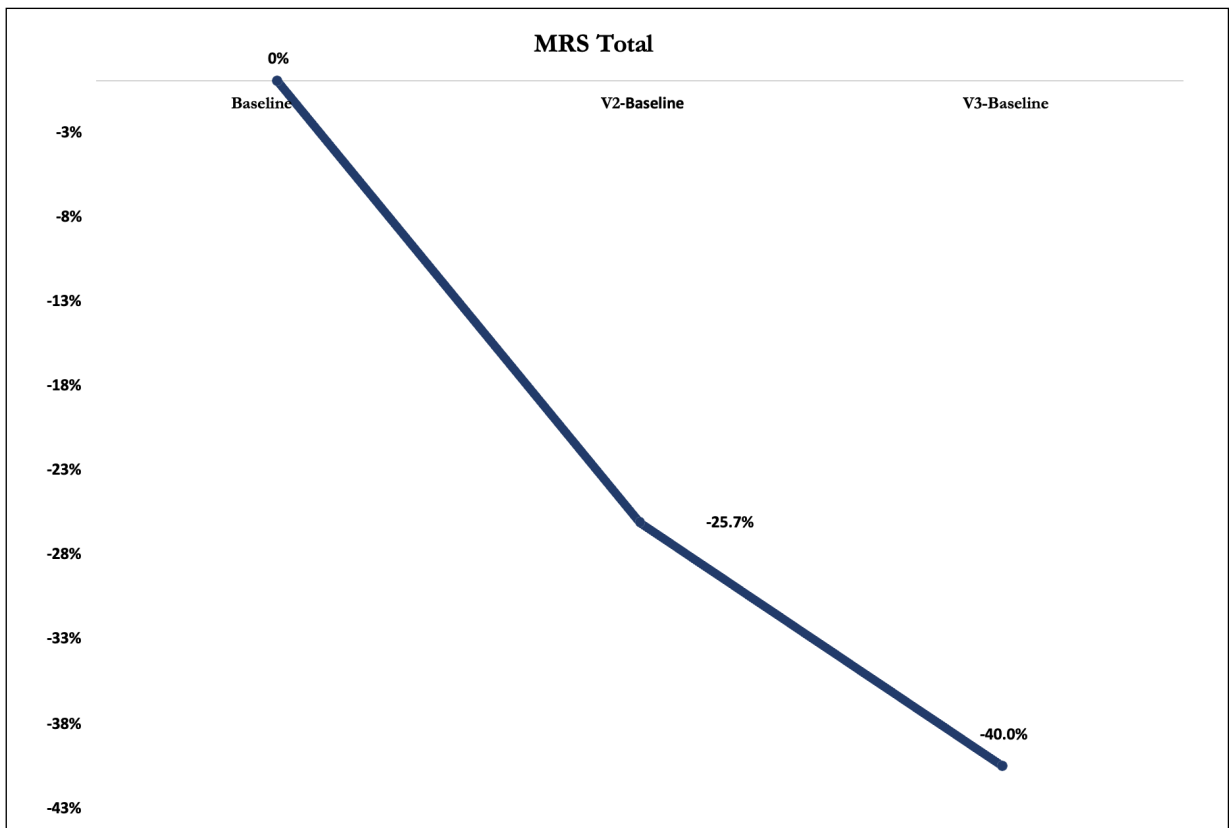


Figure 2. Evolution of the menopausal rating score (MRS) differences (%).

Improvement in menopausal symptoms with a nutritional product

Table I. Means of the different questionnaire items and the overall MRS score, by visit.

Questionnaire	Baseline Mean ± SD	Visit 2 Mean ± SD	Visit 2 - Baseline Mean ± SD	% Decrease V2 - Baseline	Visit 3 Mean ± SD	Visit 3 - Visit 2 Mean ± SD	% Decrease V3 - V2	V3 - Baseline Mean ± SD	% Decrease V3 - Baseline
Hot Flashes	2.7 ± 0.9	1.9 ± 0.9	-0.7 ± 0.8	-30%	1.4 ± 0.9	-0.5 ± 0.8	-26%	-1.2 ± 1	-48%
Heart discomfort	1.5 ± 1.1	1.2 ± 0.9	-0.3 ± 0.7	-20%	1 ± 0.8	-0.2 ± 0.6	-17%	-0.5 ± 0.9	-33%
Sleep problems	2.6 ± 1.1	1.8 ± 0.9	-0.8 ± 0.8	-31%	1.4 ± 1	-0.4 ± 0.9	-22%	-1.3 ± 1.1	-46%
Joint and muscular discomfort	1.8 ± 1.2	1.5 ± 1.0	-0.3 ± 0.7	-17%	1.3 ± 0.9	-0.2 ± 0.7	-13%	-0.5 ± 0.9	-28%
Depressive mood	2.0 ± 1.2	1.4 ± 0.9	-0.6 ± 0.9	-30%	1.1 ± 0.8	-0.3 ± 0.7	-21%	-0.9 ± 1.1	-45%
Irritability	2.1 ± 1.2	1.5 ± 0.9	-0.6 ± 0.9	-29%	1.1 ± 0.8	-0.4 ± 0.8	-27%	-1 ± 1	-48%
Anxiety	1.8 ± 1.2	1.3 ± 0.9	-0.5 ± 0.9	-28%	1 ± 0.8	-0.3 ± 0.7	-23%	-0.8 ± 1.1	-44%
Physical and mental exhaustion	2.2 ± 1.1	1.6 ± 0.9	-0.6 ± 0.8	-27%	1.4 ± 0.9	-0.3 ± 0.8	-13%	-0.9 ± 1.1	-36%
Sexual problems	2.0 ± 1.2	1.7 ± 1.0	-0.4 ± 0.8	-15%	1.4 ± 1	-0.2 ± 0.7	-18%	-0.7 ± 1.0	-30%
Bladder problems	1.6 ± 1.1	1.2 ± 0.9	-0.4 ± 0.7	-25%	1.1 ± 0.8	-0.1 ± 0.6	-8%	-0.5 ± 0.8	-31%
Vaginal dryness	2.1 ± 1.2	1.6 ± 0.1	-0.5 ± 0.7	-24%	1.4 ± 0.9	-0.2 ± 0.6	-13%	-0.8 ± 0.9	-33%

Table II. Means of the different questionnaire items by clinical subgroups and menopausal rating score (MRS), by visit.

Questionnaire	Baseline Mean ± SD	Visit 2 Mean ± SD	Visit 2 - Baseline Mean ± SD	% Decrease V2 - Baseline	Visit 3 Mean ± SD	Visit 3 - Visit 2 Mean ± SD	% Decrease V3 - V2	V3 - Baseline Mean ± SD	% Decrease V3 - Baseline
Somato-vegetative	8.6 ± 3	6.4 ± 2.5	-2.2 ± 1.8	-25%	5.1 ± 2.5	-1.3 ± 1.8	-21%	-3.5 ± 2.3	-41%
Psychological	8.2 ± 3.9	5.9 ± 2.9	-2.3 ± 2.6	-28%	4.51 ± 2.6	-1.3 ± 2	-22%	-3.6 ± 3.2	-44%
Urogenital	5.7 ± 2.8	4.4 ± 2	-1.3 ± 1.8	-23%	3.9 ± 2	-0.5 ± 1.3	-12%	-1.9 ± 1.9	-32%
MRS TOTAL SCORE	22.5 ± 8.1	16.7 ± 6.3	-5.9 ± 5.0	-26%	13.6 ± 6	-3.3 ± 4.3	-19%	-9.2 ± 6.1	-40%

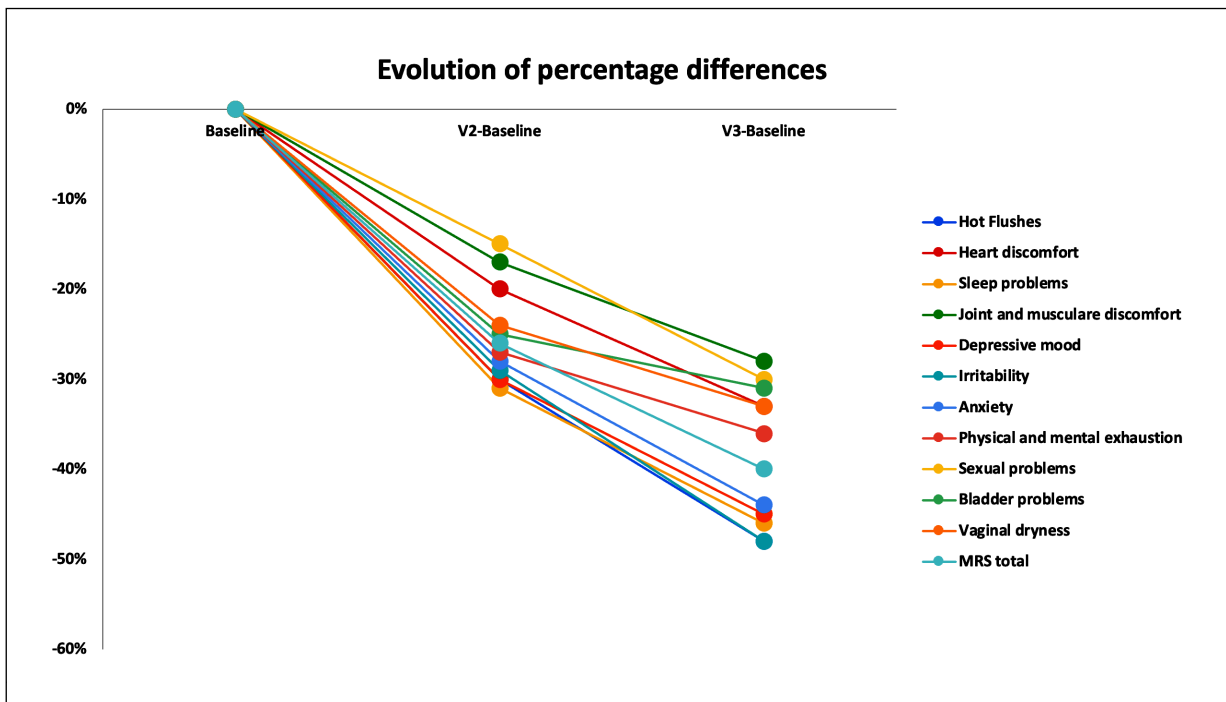


Figure 3. Evolution of the percentage differences for each one of the individual menopausal rating scores (MRS) questionnaire items. Differences between visit 2 and 3 with the baseline.

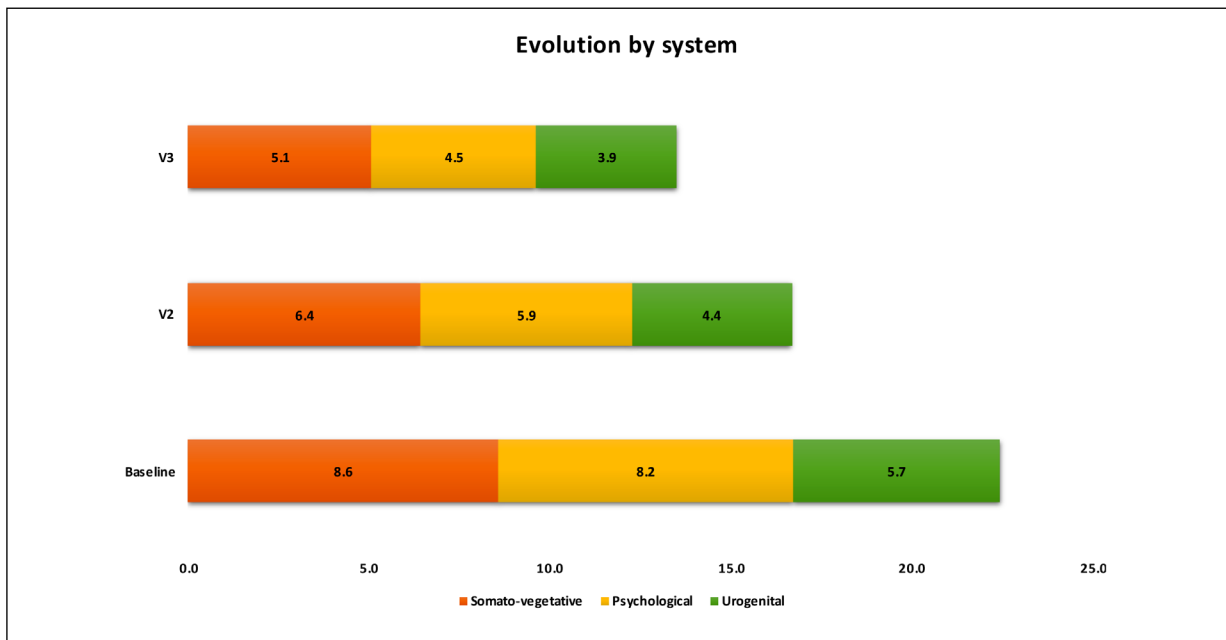


Figure 4. Overall score by domain.

The differences in the individual symptoms with a reduction of $\geq 45\%$ are described in more detail in the following chapters. All values are depicted in Tables I and II and Figures 3 and 4.

Hot Flashes

The overall reduction in the subgroup with an MRS value of 4 was 17.4%. The number of patients at baseline with this score was 20.4% and it de-

clined to 3.3% after the 3-month treatment ($p < 0.005$). In the subgroup with a value of 3, the difference was 28.3%. 34.8% of the women had a value of 3 at baseline, and after 90 days of treatment, only 6.5% had this value. The differences in the group with a value of 2 were between 34.8% at the beginning and 32.0% after 3 months.

In contrast, the group of patients with a value of 0 increased from 3.2% to 11.1% during the treatment, and the number of women with a value of 1 increased from 8.5% to 47.1%, which corresponds to a change of 38.7%.

Sleep Disturbance

The change in the subgroup with an MRS value of 4 was 3.9% at the end of the study. The number of patients at baseline with this score was 3.9% and it declined to 0% after the 3-month treatment ($p < 0.005$). In the subgroup with a value of 3, the difference was 12.2%. 14.8% of the women had a value of 3, while only 2.6% scored this value at the end of treatment.

In contrast, the percentage of patients with a value of 0 increased from 23.2% to 32.7% during the treatment and the number of women with a value of 1 from 30.3% to 39.8%. This was a change of 38.7%. The differences in the group with a value of 2 were between 24.5% at the beginning and 27.5% after 3 months.

Depressive Mood

The decrease in the subgroup with an MRS value of 4 was 10.3%. At baseline, 11.0% had this score and it declined to 0.7% after the 3-month treatment ($p < 0.005$). In the subgroup with a value of 3, the difference was 21.7%. Here at the beginning, 28.4% of the women had a value of 3, and after 90 days of treatment it was 1.3%.

The group of patients with a value of 0 increased from 11.6% to 24.8% during the treatment, while the number of women with a value of 1 increased from 27.1% to 44.4%, i.e., a change of 17.3%. The differences in the group with a value of 2 were between 21.9% at the beginning and 28.8% after 3 months.

Irritability

The reduction in the subgroup with an MRS value of 4 was -13.6%. The number of patients at baseline with this score was 13.6% and it declined to 0% after the 3-month treatment ($p < 0.005$). In the subgroup with a value of 3, the difference was 23.2%. Here at the beginning, 25.8% of the women had a value of 3 and after 90 days of treatment, it was 2.6%.

The percentage of patients with a value of 0 increased from 10.3% to 22.2% during the treatment and the percentage of those with a value of 1 increased from 24.5% to 49.0%. This corresponds to a change of 24.5%. The differences in the group with a value of 2 were between 25.8% at the beginning and 26.1% after 3 months.

Adverse Events

Regarding the safety of the nutritional product, only 1 woman (1.8% of the 54 women in the Spanish cohort that took at least one dose of the investigational product) experienced adverse events during the 3 months of treatment. She reported 3 different symptoms (weakness, palpitations, and dizziness) that started and finished at the same time, which points to a unique process causing the 3 symptoms.

Discussion

One of the main reasons of menopausal women receiving a hormonal replacement treatment (HRT) is to relieve such diverse climacteric symptoms like hot flush, vaginal dryness, joint pain, etc. It is well established that hormone replacement therapy is effective for climacteric vasomotor symptoms and other subjective problems like insomnia, night sweats, memory loss or depressive condition. These treatments were introduced in the early 90s of the last century¹³. This therapy has been used in clinical areas for a long period of time. However, since the publication of the WHI study in 2002 and the one million study¹⁴ afterward, estrogen replacement therapy has been associated with a wide range of possible side effects like a higher risk of developing breast cancer or coronary artery disease. Though HRT is still the most effective treatment option for the management of the clinical symptoms in menopause and is recommended e.g., by the North American Menopause Society, a broad spectrum of alternative nutritional products trying to alleviate the symptoms of menopause have been introduced into the market.

In this clinical trial a new formulation of a nutritional product containing evening primrose oil (10% GLA) 50 mg; hop extract (0.15-0.25% 8-PN) 0.127-0.212 mg; saffron stigmas extract (2% Safranal) 0.6 mg; tryptophan 71.25 mg, vitamins B6 (2.1 mg), D3 (5 µg), K2 (32 µg), B12 (2.5 µg), and B9 (200 µg) for the management of menopausal symptoms was tested.

Evening primrose oil (EPO) is a rich source of gamma-linolenic acid (a precursor of prostaglandin E), popularly believed to suppress menopausal flushing. EPO is obtained from the seeds of *Oenothera biennis*, a biennial plant. Moreover, EPO may decrease the severity of menopausal hot flashes¹⁵. It is recognized as a potential source of unsaturated fatty acids. In one study¹⁵, patients took evening primrose compared to placebo for 6 weeks. The percentage of improvement in hot flash frequency, severity and duration were 39, 42 and 19% in the evening primrose group and 32, 32 and 18% in the placebo group, respectively.

The Hop (*Humulus lupulus L.*) in Cannabaceae family has been used as a bitter constituent of beer worldwide. Notably, hop extracts contain diverse phytoestrogen compounds that were the highest in the extracts from female flowers of the Hop plant. Prenylflavonoids, including 8-prenylnaringenin (8-PN), isoxanthohumol, and xanthohumol have been demonstrated to be active components (phytoestrogens) of the Hop plant, in which 8-PN was the most potent ingredient with binding affinity to estrogen receptors¹⁶. The estrogenic activity of 8-PN was found to be higher than that of well-established phytoestrogens such as coumestrol, genistein, and daidzein¹⁷.

Since phytoestrogens can produce stronger estrogenic effects in the absence of adequate estrogen, they can compensate for the reduced levels of endogenous 17 β -oestradiol during menopause. Substantial amounts of 8-PN, the strongest known phytoestrogen capable of binding to both estrogen receptors in the human body, are found in *Humulus lupulus* (commonly known as Hop).

Owing to its potent phytoestrogen compounds and humulene, tannin, β -myrcene, pectin, potassium, and flavonoid contents, along with its ability to create estrogenic, sedative, hypnotic, antipyretic, anti-inflammatory, and antiseptic effects^{18,19}, *H. lupulus* has found wide medicinal and industrial applications. The presence of estrogenic compounds, such as isoxanthohumol, progesteron xanthohumol, and 8-PN, in the Hop, has also made it an appropriate herbal medicine for the treatment of menopausal symptoms²⁰. Heyerick et al²¹ examined the efficacy of a hop extract enriched in 8-PN on the relief of menopausal symptoms. They showed that daily intake of a hop extract has favorable effects on vasomotor symptoms. Rosic et al²² noticed significant improvements in the physical, psychological, and genitourinary symptoms of menopause following the

administration of phytoestrogens. In this regard, another study²³ observed that Hop effectively reduced vasomotor symptoms. Likewise, a clinical trial by Mohammad Alizadeh-Charandabi et al²⁴ showed significantly that Hop can reduce early menopausal symptoms.

Crocus sativus (saffron), the dried stigma of the plant *Crocus sativus L.*, has been used as a medicinal plant in traditional medicine²⁵. Three major constituents, including crocin, picrocrocin, and safranal, have been found in saffron²⁶. Different clinical trials²⁷⁻²⁹ show that saffron is effective in the treatment of depression. Akhondzadeh et al³⁰ showed that with the use of saffron in fifty-six patients, the general linear model repeated measures demonstrated a significant effect for time \times treatment interaction on the Hot Flash-Related Daily Interference Scale (HFRDIS), [F (3.162) = 10.41, $p = 0.0001$] and the Hamilton Depression Rating Scale (HDRS) [F (3.162) = 5.48, $p = 0.001$]. The frequency of adverse events was not significantly different between the two groups.

A work conducted by Freedman and Krell³¹ has shown that hot flashes are triggered by small elevations in core body temperature acting within a reduced thermoneutral zone. Thus, women with hot flashes both sweat and shiver more readily than women without them. The reduction in the thermoneutral zone is caused, in part, by elevated brain norepinephrine³². This is supported by works^{33,34} showing that clonidine, an α 2-adrenergic agonist, reduces brain norepinephrine and hot flash occurrence. Conversely, yohimbine, an α 2-adrenergic antagonist, elevates brain norepinephrine and provokes hot flashes^{33,35}. Animal studies³² have shown that serotonin in the brain generally works in the opposite fashion to norepinephrine, suggesting that elevation of brain serotonin should ameliorate hot flashes. Indeed, recent studies^{36,37} of SSRIs, which increase the amount of serotonin in the synaptic gap, have demonstrated amelioration of hot flashes. For example, a double-blind study³⁶ of 151 women with hot flashes showed that paroxetine 10 mg/day reduced hot flash frequency by 40.6% compared to 13.7% for placebo and that paroxetine 20 mg reduced hot flash frequency by 51.7% compared to 26.6% for placebo. Another double-blind study³⁷ of 707 women found that desvenlafaxine succinate 100 mg/day reduced hot flash frequency by 64% compared with 29% for placebo.

Tryptophan is the amino acid precursor of serotonin. Once in the central nervous system, tryptophan is converted to 5-Hydroxytryp-

tophan (5-HTP) and then decarboxylated to serotonin. The levels of some neurotransmitters can be elevated by increasing the dietary supply of their precursors^{38,39}. Oral administration of L-tryptophan produces increases in serotonin synthesis and release in the brain.

Clinical trials in the literature about 5-HTP for depression and related disorders show that the mechanism for improvements in symptoms may be due to an increase in serotonin levels. Theoretically, 5-HTP supplementation would have the ability to increase the amount of serotonin available, thus producing a similar effect to the SSRIs without the potential drawbacks.

Overall, the results presented here showed a clear reduction in the severity of all the menopausal symptoms monitored throughout the study. The differences among the total MRS scores were statistically significant between baseline and visits 2 and 3, but not between visit 2 and visit 3. These results highlight a positive and rapid effect of the investigated nutritional product for menopausal symptoms that could lead to an improvement in the quality of life of menopausal women.

This prospective, open, multicenter study with a new herbal product, was able to reveal a significant reduction of menopausal symptoms like vasomotor symptoms, fatigue, irritability, depression, or vaginal dryness. In view of the very low estrogenic activity of the formulation, the therapy is suitable even for women for whom receiving estrogens are contraindicated or can be dangerous due to possible side effects.

Interestingly other nutritional supplementations are also being used for the management of menopausal symptoms. One interesting approach is the use of probiotics. A study by Szydłowska et al⁴⁰ showed that the use of a probiotic was associated with a reduction in follicle-stimulating hormone (FSH) values in peri and post menopause which subsequently is associated with a reduction in the cardiometabolic risk.

Also of crucial importance in menopause is physical activity. Cerulli et al⁴¹ described that physical inactivity in menopause led to a vitamin D deficiency and, hence, a higher risk of developing osteoporosis. This clearly shows the need to add to any nutritional supplementation an age-adapted physical activity.

Limitations

The limitations of this trial include that it was not a placebo-controlled one. However, if we as-

sume that a placebo effect can reach up to 33% of the baseline values⁴², especially in the reduction of vasomotor symptoms, the obtained results still exceed this and are in the range of the comparison of placebo with SSRI. Nevertheless, this nutritional product represents an effective approach to the treatment of climacteric symptoms without raising the fear of the use of hormones. Further studies, including placebo-controlled trials, should be performed to obtain more data in broader populations.

Conclusions

In summary, all individual MRS scores have been reduced compared to the baseline after the treatment with the nutritional product for 3 months, which indicates an alleviation of the menopausal symptoms. The decrease in most of the symptoms is more pronounced in the first month of treatment, which could indicate a rapid effect of the nutritional product. Thus, the results of the study indicate that the use of Exelvit Menopause® is safe in women over 50 years old with menopausal symptoms. However, further controlled studies, comparing the normal evolution of the menopausal symptoms with the effect of the investigational product would give consistency to the results observed and would confirm the effects of Exelvit Menopause® on the alleviation of the main menopausal symptoms and the quality of life of these women.

Funding

Insud Pharma funded the study.

Conflict of Interest

Santiago Palacios: Consultant for Exeltis.
Calin Mustata is an employee of Sunwave Pharma Romania.
Jose Miguel Rizo is an employee of Chemo Spain.
Pedro-Antonio Regidor is an employee of Exeltis Healthcare.

Authors' Contributions

SP: Conceptualization of the study.
CM: Data evaluation.
JMR: Study design.
PAR: Responsible for writing.

Ethics Approval

Ethics Committee of the Hospital Universitario La Princesa, Madrid, Spain, number: CEIm NÚMERO 18/20, 10-09-20.

Clinical Trial Registry

DRKS00029349.

Data Availability

Data are available from the corresponding author upon reasonable request.

Informed Consent

All patients were informed of the study characteristics and approved to be enrolled in the study.

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