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ORIGINAL ARTICLE

Improvement of climacteric symptoms with a novel sublingual product containing *trans*-resveratrol

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Summary. *Objectives:* To assess the improvement of climacteric symptoms, especially hot flushes, evaluated analyzing the total score of Menopause Rating Scale, after supplementation with a new sublingual spray formulation of resveratrol (Talitha® PH&T SpA) able to bypass gastro-enteric tract entering directly the systemic circulation. *Materials and Methods*: 30 women with symptoms suggestive of climacteric syndrome present for at least one month, with or without associated amenorrhea, and evaluated according to the standardized Menopause Rating Scale (MRS) were enrolled in an open, uncontrolled study. The Sublingual Spray was administered: 4 puffs 2 times/day for 3 months. *Results:* Menopause Rating Scale total score: this reduction was statistically significant at 0.01 level. Hot flushes mean score: this reduction was statistically significant at the 0.01 level. MRS Single items total score: the following items showed a statistically significant reduction ($p<0.05$): heart discomfort; sleep problems; depression mood; irritability; physical and mental discomfort; joint and muscular discomfort. Moreover no patient experienced any side effects and compliance was optimal. *Discussion:* resveratrol is a powerful phytoestrogen that can be used as an alternative to hormone replacement therapy. The novel product is formulated as a sublingual spray emulsion, by which resveratrol is rapidly absorbed through the sublingual mucosa reaching the systemic circulation, without being metabolized and thus inactivated by the liver. *Conclusions:* The results of this study show that the novel sublingual product produces a statistically significant reduction of the main symptoms associated with menopause when measured with a validated method.

Key words: Menopause, hot flushes, resveratrol

«Miglioramento dei sintomi del climaterio con un nuovo prodotto sublinguale contenente *trans*-resveratrolo»

Riassunto. *Obiettivi:* Valutare il miglioramento dei sintomi del climaterio, soprattutto le vampate di calore, analizzando il punteggio totale della Menopause Rating Scale (MRS) dopo supplementazione con una nuova formulazione di resveratrolo in spray sublinguale (Talitha® PH&T SpA), che permette al resveratrolo di bypassare il tratto gastro-enterico entrando direttamente nella circolazione sistemica. *Materiali e Metodi:* 30 donne con sintomatologia di sindrome climaterica presente da almeno un mese, con o senza amenorrea, sono state arruolate in uno studio in aperto non controllato, e valutate mediante una scala standardizzata, la Menopause Rating Scale (MRS). Lo spray sublinguale è stato somministrato in 4 spruzzi 2 volte/die per 3 mesi. *Risultati:* Punteggio totale Menopause Rating Scale: Si è riscontrata una riduzione statisticamente significativa al livello di 0,01. Punteggio medio delle vampate di calore: Si è riscontrata una riduzione statisticamente significativa al livello di 0,01. Punteggio dei singoli item della MRS. I seguenti sintomi hanno mostrato una riduzione statisticamente significativa ($p<0,05$): disturbi cardiaci; disturbi del sonno; disturbi dell'umore; irritabilità; stanchezza fisica e mentale; disturbi muscolari e articolari. Inoltre, nessuna paziente ha manifestato effetti collaterali e la compliance è stata ottima. *Discussione:* Il resveratrolo è un potente fitoestrogeno

che può essere utilizzato come alternativa alla terapia ormonale sostitutiva. Il nuovo prodotto è formulato in emulsione spray per somministrazione sublinguale, che permette al resveratrolo di essere assorbito rapidamente attraverso la mucosa sublinguale e di raggiungere direttamente la circolazione sistemica, senza essere metabolizzato e quindi inattivato dal fegato. *Conclusioni*: I risultati di questo studio dimostrano che il nuovo prodotto sublinguale produce una riduzione statisticamente significativa dei principali sintomi associati alla menopausa, valutati con un metodo convalidato.

Parole chiave: Menopausa, vampate di calore, resveratrolo

Introduction

The cessation of ovarian function at the time of menopause and resulting hormonal changes are associated with specific health conditions that are unrelated to those typically attributed to aging. Estrogen deficiency plays a major role in menopausal hot flushes, vaginal epithelium atrophy (1, 2) and until recently menopausal symptoms had been primarily managed with hormone replacement therapy.

Many women experience vasomotor symptoms at or around the time of menopause. Hot flushes and night sweats are considered primary menopausal symptoms that may also be associated with sleep and mood disturbances, as well as decreased cognitive function. All of these symptoms may lead to social impairment and work-related difficulties that significantly decrease overall quality of life. The belief that products containing "natural" estrogens would provide most of the benefits but none of the risks of prescription hormones has resulted in a vast increase in the use of herbal products containing phytoestrogens by women seeking to alleviate menopausal symptoms (1).

Resveratrol is a natural substance extracted from the root of *Polygonum cuspidatum*, the richest natural source of resveratrol (3, 4). Resveratrol is a stilbene, one of the main classes of phytoestrogens, with a powerful estrogen-like action (3, 5). *trans*-Resveratrol has a broader spectrum of action of other phytoestrogens because it acts both on alpha- and beta-estrogenic receptors (6, 7). Because of its mechanism of action, it is considered particularly useful in the climacteric and menopause, to compensate the hormonal deficiencies that occur in these phases of life. Resveratrol is claimed to tackle many of the derangements associated with climacteric syndrome, including vasomotor symptoms and osteoporosis and is thus used to reduce postmenopausal health risks. The synergistic effects of resveratrol with vitamin D_3 may be effective in reducing bone loss and weight gain during menopause (8). Vitamin E protects against oxidation and it is active in the health protection.

A unique sublingual spray (Talitha® PH&T SpA) containing *trans*-resveratrol, vitamin E and vitamin D_3 has been formulated (9). The sublingual formulation allows a high bioavailability of *trans*-resveratrol because it bypasses the first-pass hepatic metabolism entering directly the systemic circulation (10, 11).

This study was design to establish the effectiveness of the supplementation of this novel nutraceutical product in sparing multiple symptoms associated with declining estrogen levels in post-menopausal women.

Materials and methods

30 women with symptoms suggestive of climacteric syndrome present for at least one month, with or without associated amenorrhea, and evaluated according to the *Menopause Rating Scale* (MRS) were recruited in an open, uncontrolled clinical study with the following inclusion and exclusion criteria:

- *Inclusion criteria:*
  - Patients in climacteric (regardless of age) with MRS greater than 8.
  - Patients who signed the informed consent.
- *Exclusion criteria*:
  - Patients receiving HRT at recruitment or suspended for less than 12 months (including therapy with topical estradiol).

- Patients treated with phytoestrogens at recruitment or suspended from less than 2 months.
- Patients who are allergic to the active substance or its excipients.
- Patients with psychiatric syndromes.

The aims of the MRS were essentially to compare severity of symptoms over time, and to measure changes pre- and post-treatment (12).

Study endpoints

The *Primary end point* was the statistically significant improvement of climacteric symptoms, especially hot flashes, evaluated analyzing the total score of *Menopause Rating Scale* and the score for the single item *hot flushes*.

Tolerability was also evaluated recording the occurrence of any adverse event.

Patients were asked to take the sublingual spray of *trans*-resveratrol, vitamin E and vitamin D_3 according to the following schedule: 4-5 puffs 2 times/day for 3 months.

Evaluation parameters

The patients at the time of enrollment (T_0) and at the end of the study (T_{final}–3 months) were evaluated for:

- medical history;
- gynecological, urogynecological and clinical breast examination.

All the patients filled in the *Menopause Rating Scale* at T_0 and at the end of the study.

Statistical methods

The results were analyzed by descriptive statistics (means, standard deviation and percentages) using the Student t-test with a significance value of $p<0.05$.

The assessment was made on the score for the single item "hot flushes" and the total score of the *Menopause Rating Scale*.

Results

Out of the 30 patients enrolled, one patient withdrew from the study for inefficacy after 49 days of use, and her data are included in the *Intention-to-Treat Analysis*.

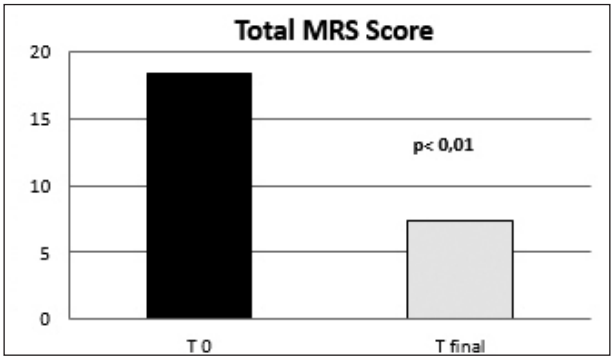

Figure 1. Means of MRS total score at baseline (before therapy) and at end of observation (after therapy)

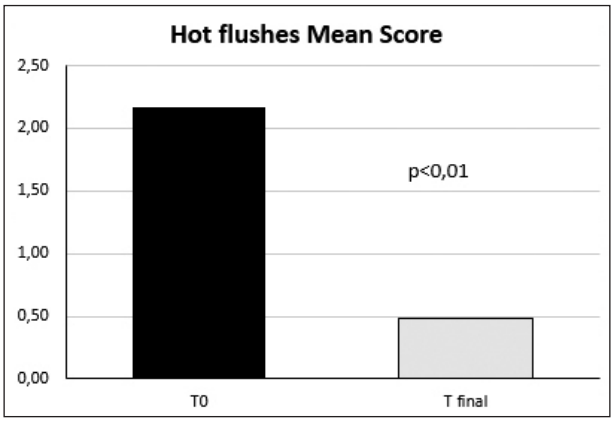

Figure 2. Item hot flushes average score: changing from baseline (before therapy) to the end of observation (after therapy)

Primary efficacy results

At baseline, the mean *Menopause Rating Scale* total score was 18.23 (SD:±6.20). By three months, a reduction was observed in all the patients, with a mean value of 7.37 (SD:±4.57).

This reduction was statistically significant at $p<0.01$ (Fig. 1) as per the clinical study protocol.

At baseline, the item *hot flushes* mean total score was 2.20 (SD:±1.12). By three months, a reduction was observed in all the patients, with a mean value of 0.57 (SD:±0.86).

This reduction was statistically significant at $p<0.01$ (Fig. 2).

A further analysis was performed also on each single items of the MRS (Fig. 3) showing a statistically significant reduction ($p<0.05$) in the following:

- Heart discomfort.
- Sleep problems.

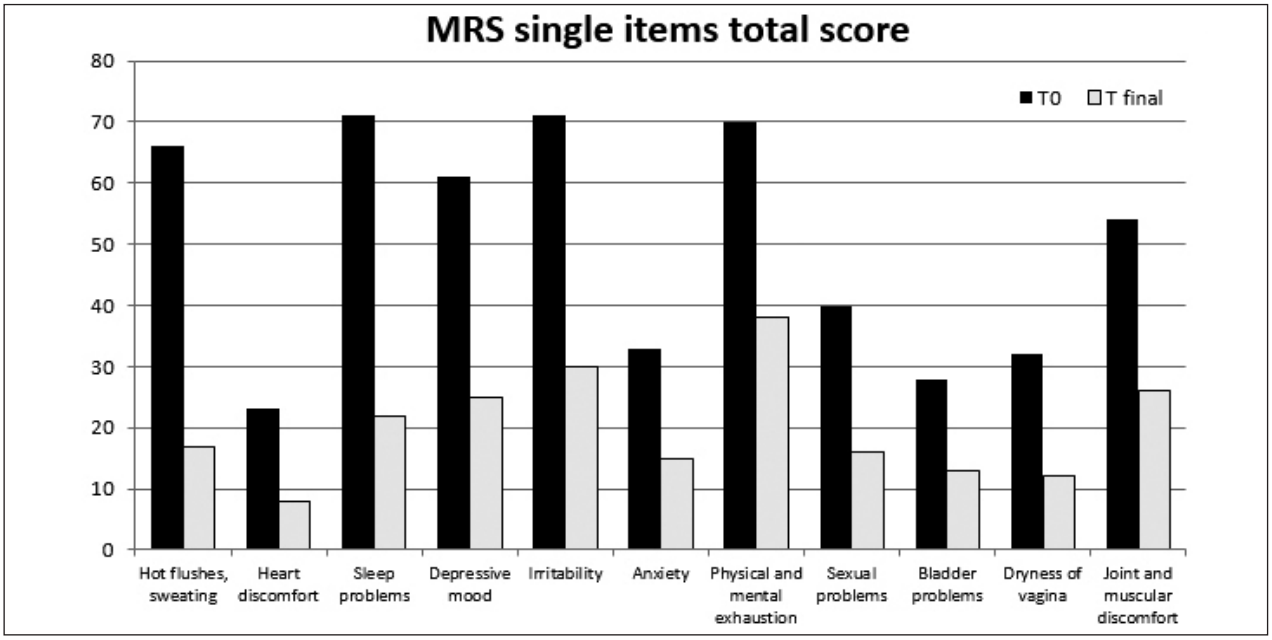

Figure 3. MRS single items total score: changing from baseline (before therapy) to the end of observation (after therapy)

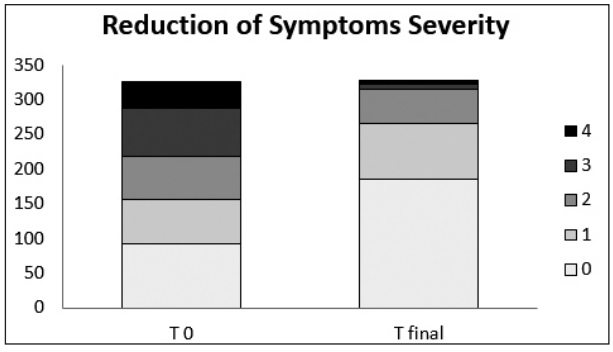

Figure 4. Reduction of the severity of the totality of symptoms from baseline to the end of use

- Depression mood.
- Irritability.
- Physical and mental discomfort.
- Joint and Muscular discomfort.

The scoring scheme of the MRS is simple, i.e. the score increases point by point with increasing severity of subjectively perceived symptoms in each of the 11 items, from severity 0 [no complaints] to severity 4 scoring points [very severe symptoms]. A reduction of the severity of the totality of symptoms from baseline to the end of use was observed in all patients (Fig. 4). No side effects were registered in the whole study.

Discussion

The results of this study, despite the small sample size, show that the novel *trans*-resveratrol-based sublingual spray produces a highly statistically significant reduction of the main symptoms associated with menopause. The tolerability has been proved to be high as no side effects have been recorded.

Phytoestrogen supplements are increasingly popular among women who expect these products to prevent symptoms associated with menopause without the side effects normally associated with Hormone Replacement Therapy. *trans*-Resveratrol has a powerful estrogen-like action with a broader activity spectrum of other phytoestrogens because it acts both on alpha- and beta-estrogenic receptors. It is also a potent free radical scavenger and is thus a strong antioxidant, acting both by preventing the formation of free radicals and by blocking their action; it promotes osteoblastic proliferation. Different clinical studies have shown that the antioxidant properties of resveratrol are higher to those of the vitamins alone (13). Published literature also shows that resveratrol has anti-inflammatory (14) and vasoprotective actions (15).

Vitamin D_3 (cholecalciferol) is a fat-soluble vitamin synthesized by man. It is a bone calcium me-

tabolism regulator (16). It stimulates the absorption of calcium and phosphorus in the intestine and regulates blood levels of calcium, maintaining adequate mineralization of the skeleton and encouraging the tropism of the bone tissue, especially in conjunction with the phenomena of decalcification and osteoporosis.

Vitamin E (tocopherol) is a fat-soluble vitamin that is found primarily in cold- pressed vegetable oils. It is a powerful antioxidant, vital in the fight against free radicals. Protects against oxidation and it is active in the health protection (17).

Moreover it has an anti-aging effect, allowing a correct use by the body of linoleic acid. Vitamin E enhances the anti-oxidant effect of resveratrol via synergic effect.

In conclusion, the clinical study results confirm that the sublingual formulation of *trans*-resveratrol is adequate in improving in a significant way the climacteric symptoms because it bypasses the first-pass hepatic metabolism. This is the first study done in human on the bioavailable supplementation of *trans*-resveratrol to improve quality of life in menopausal woman.

Future research should include a double-blinded, placebo-controlled trial to confirm results.

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