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Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study

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ABSTRACT

Objective: To investigate the effect of an oral soy isoflavone extract (Phytosoya) on hot flushes in menopausal women.

Design: The study was conducted on outpatients according to a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. A total of 75 patients in natural or surgical menopause suffering from at least seven hot flushes per day were randomized to receive during 4 months either soy isoflavone extract (total of 70 mg genistin and daidzin per day) or placebo.

Results: There is evidence to suggest that 16 weeks of treatment with soy extract can help reduce the mean number of hot flushes per 24 hours in menopausal women. Withdrawals during this trial made it difficult to obtain an unbiased estimate of the true treatment effect, but numerous sensitivity analyses lend support to the suggestion that taking soy extract can be beneficial in the treatment of hot flushes. In particular, women taking soy extract had a 38% reduction in the mean number of hot flushes by week 4 and a 51% reduction by week 8. By the end of week 16, patients taking soy extract had a 61% reduction in their daily hot flushes versus a 21% reduction obtained with the placebo. "Responders" (defined as patients whose hot flushes were reduced by at least 50% at the end of treatment period) were 65.8% in the soy extract group and 34.2% in the placebo group ($p < 0.005$).

Conclusion: Soy isoflavone extract may help to reduce the frequency of hot flushes in climacteric women and provides an attractive addition to the choices available for relief of hot flushes.

Key words: Hormone replacement therapy – Hot flush – Isoflavone – Menopause – Soy.

Hormone replacement therapy (HRT) is recognized as the most effective treatment for relief of the short-term symptoms of menopause.[1,2] However, in certain clinical settings, the use of estrogen in some women is undesirable or contraindicated. Other women may have a resolution of symptoms with estrogen replacement, but side effects — such as vaginal bleeding, breast tenderness, and bloating — result in discontinuation of therapy.[3,4] Despite clinical benefits attributed to the use of HRT in postmenopausal women, compliance ranges from 10% to 50%.[5] Therefore, alternative therapies are needed for women who refuse, are not compliant, or have contraindications for HRT.

Epidemiological data indicate that fewer than 25% of Japanese and 18% of Chinese climacteric women[6,7] complain of hot flushes compared with 85% of North American women[8] and 70% to 80% of European women.[9] Furthermore, Asian women have a low incidence of estrogen-dependent cancers, cardiovascular disease, and osteoporosis compared with Western women.[10,11] Many theories have been proposed to explain these differences, including cultural perceptions, attitudes toward aging and menopause, diet, physical activity, body mass, and the use of herbs and supplements containing phytoestrogens.

Several classes of phytoestrogens exist. When considering health effects, the major types of phytoestrogens of current interest are the lignans and isoflavones. The isoflavones include the biochemicals genistein, daidzein, glycitein, biochanin A, and formononetin. Genistein and daidzein are found in rich supply in soybeans and soy products as well as in red clover.[12–14]

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The structure of the isoflavone molecule resembles those of many estrogenic compounds, including the physiologic estrogen 17β-estradiol and the synthetic antiestrogen tamoxifen, prompting investigation of its mechanisms of action according to estrogenic and antiestrogenic activities.[15–18] The isoflavones have a common phenolic structure that seems to be a prerequisite for binding to estrogen receptors (ERs). Isoflavones seem to have more binding affinity for ERβ than for ERα.[19] Therefore, given the different tissue distribution of the α and β receptors, there is a clear potential that isoflavones could exhibit tissue-selective effects.

Isoflavones may exert a weak antagonistic effect on the ER,[20] thereby having an antiestrogenic effect on uterine and breast tissue,[21] where excess estrogen may stimulate synthesis. Alternatively, isoflavones may combine with the ER, albeit with lower affinity than 17β-estradiol,[22] and stimulate estrogen activity, thus having an estrogenic effect on bone[20] and blood vessels.[23]

Studies have been reported in which isoflavone-rich foodstuffs, such as soy, produce a moderate decrease in the incidence and severity of hot flushes when added to the diet of menopausal women. Some contradictory results could be due to the large chemical heterogeneity of soy derivatives used. To test the hypothesis that dietary intake of isoflavones may have a therapeutic benefit, a double-blind, placebo-controlled trial was conducted in menopausal women in which the test group received supplementation of dietary isoflavone intake provided as a semipurified isoflavone extract in capsule form.

METHODS

Patients

The patients were all postmenopausal women requesting treatment for hot flushes. In all cases, at least 6 months had passed since the last menstrual period. To be eligible for the study, participants must have had a minimum of seven moderate to severe hot flushes (including night sweats) per 24 hours during the 2 weeks of the prestudy period. Moderate hot flushes were defined as a warm sensation associated with sweating that left the patient able to continue her daily activity. Severe hot flushes were defined as a hot sensation associated with sweating so intense that the patient had to stop her activity.

Patients also were required to have a baseline follicle-stimulating hormone concentration greater than 40 IU/L and a serum estradiol concentration less than 35 pg/mL. HRT or any other drug used for the treatment of climacteric symptoms, such as vitamin E or clonidine, was not allowed throughout the study period. Patients who had received HRT in the past had to have stopped treatment at least 6 weeks before the prestudy period.

All participants signed an informed consent at the beginning of the study, and the study was approved by the Ethical Committee of the Nîmes hospital.

Test substances

Phytosoya is a standardized isoflavone supplement prepared from soy extract in 325-mg capsule form containing 17.5 mg per capsule of total isoflavones and containing the four primary isoflavones: genistein, daidzein, and their methylated precursors biochanin and formononetin. A placebo capsule was formulated with a similar appearance and taste. The placebo capsule contained cellulose microcrystalline and sodium magnesium stearic in the same amount as the soy capsules.

The patients were either given 2 × 2 capsules of soy extract a day or a placebo capsule.

Study design

This was a 16-week, double-blind, randomized, multicenter, parallel trial. The patients were first seen at the screening visit and were then assessed 2 weeks later, before randomization, and then again at treatment weeks 4, 8, and 16. For the entire study period, including the prestudy period, each participant filled out a special card daily to evaluate the number of moderate to severe hot flushes (including night sweats) and brought it to each visit.

Adverse events were collected at each visit. For each event, the nature, duration, severity, outcome, and causal link with the study treatment as evaluated by the investigator were recorded in the case report form. Overall safety assessments by the patient and investigator were recorded.

A sample size of 60 patients (30 per treatment arm) was required to detect, with 90% power, a treatment difference of 3 hot flushes per 24 hours, assuming a standard deviation of 3.8 hot flushes per day. The test was performed two-sided at a significance level of $\alpha = 0.05$. The primary efficacy criterion was the mean change from baseline of the number of daily moderate and severe hot flushes (including night sweats) in each month of treatment. The primary analysis was based on the two-way repeated measures analysis of variance model, including the following factors: treatment effect, time effect, and treatment by time interaction.

TABLE 1. *Demographic data (mean ± standard deviation)*

	Soy group (n = 39)	Placebo group (n = 36)
Age (y)	53.0 ± 5.6	53.9 ± 4.1
Weight (kg)	66.2 ± 10.8	64.9 ± 9.8
Body mass index (kg/m^2)	24.9 ± 3.9	24.9 ± 3.5
Number of hot flushes per 24 h	10.1 ± 6.4	9.4 ± 3.4

Data were analyzed using both an intention to treat (ITT) and a per protocol (PP) approach. For the ITT analysis, the last recorded treatment value was used in accordance with the "last observation carried forward" (LOCF)[24] principle and, therefore, included patients who withdrew prematurely from the trial. For the PP analysis, only data observed at the 16-week endpoint were analyzed and, therefore, this analysis disregarded patients who withdrew prematurely.

Responders were classified as patients whose number of hot flushes had been reduced by at least 50% at the end of the treatment period.

RESULTS

A total of 75 postmenopausal women were randomized in this study (39 in the soy extract group and 36 in the placebo group). These patients were well balanced with respect to baseline characteristics, and there was no statistically significant difference between baseline values in the two groups (Table 1). At baseline, the median number of hot flushes (mean ± standard deviation) was 10.1 ± 6.4 for the group taking soy extract and 9.4 ± 3.4 for the placebo group.

Table 2 shows that 6 (15%) patients withdrew from the soy extract group [4 (10%) due to treatment inefficacy] and 14 (39%) withdrew from the placebo group [11 (28%) due to treatment inefficacy]. In addition, three patients presented outlying data. These problems have been addressed by running sensitivity analyses to obtain a sensible estimate of the treatment effect.

The absolute mean number of hot flushes for soy extract and placebo at all time points are provided in Table 3 for LOCF data and in Table 4 for observed data. From baseline to week 16 (LOCF values), the mean numbers of hot flushes (mean ± standard error of the mean) decreased to −6.4 ± 1.0 and 2.2 ± 1.2 in participants who were taking soy extract and placebo, respectively.

In the ITT analysis, repeated measures analysis of variance testing differences between treatment groups indicated treatment effect (p = 0.01) on the change in frequency of hot flushes, whereas time (p = 0.33) had no significant effect on hot flushes frequency (Table 5).

TABLE 2. *Premature study termination*

Reasons	Soy extract group (%)	Placebo group (%)
Inefficacy	4 (10)	11 (31)
Adverse drug reaction	0 (0)	2 (6)
Lost to follow up	1 (3)	1 (3)
Others	1 (3)	0 (0)

TABLE 3. *Last observation carried forward data for mean number of hot flushes at the given week*

	Week 4	Week 8	Week 16
Raw			
Phytosoya			
n	38	38	38
Mean (SEM)	6.1 (0.9)	4.7 (0.6)	3.9 (0.7)
Placebo			
n	35	35	35
Mean (SEM)	7.1 (0.9)	6.6 (1.0)	7.0 (1.2)
Change from BL			
Phytosoya			
n	38	38	38
Mean (SEM)	−4.2 (0.8)	−5.6 (0.9)	−6.4 (1.0)
Placebo			
n	34	34	34
Mean (SEM)	−2.2 (0.8)	−2.7 (0.7)	−2.2 (1.2)
% change from BL			
Phytosoya			
n	38	38	38
Mean (SEM)	−38.8 (6.1)	−51.1 (5.7)	−61.2 (5.9)
Placebo			
n	34	34	34
Mean (SEM)	−24.8 (6.4)	−32.9 (6.6)	−20.8 (16.9)

BL, baseline; SEM, standard error of the mean.

The p values from the PP analyses that only take into account the observed data at the 16-week endpoint are not significant, but the 95% confidence intervals estimating the treatment effect are supportive of the findings for the ITT/LOCF analysis (Table 5). The fact that there were a substantial number of withdrawals in this trial (Table 2), and that they occurred disproportionately, complicates the unbiased estimation of the true treatment effect. Indeed, it is difficult to say which statistical analysis is the most appropriate (ie, including or excluding outliers, using ITT/LOCF data or PP/observed data). However, one can remark that all results from the various analyses and the corresponding 95% confidence intervals estimating the treatment effect remain consistent in their suggestion that treatment with soy extract has a positive effect in the reduction of hot flushes for menopausal women (Table 5).

Figure 1 shows the variation of hot flushes during the 16 weeks of treatment in the two groups. Using the criteria of ≥50% reduction in number of hot flushes from baseline as evidence of a clinically relevant response, 65.8% of patients treated with soy extract were classi-

TABLE 4. *Observed data for mean number of hot flushes at the given week*

	Baseline	Week 4	Week 8	Week 16
Raw				
Phytosoya				
n	39	38	36	32
Mean (SEM)	10.1 (1.0)	6.1 (0.9)	4.8 (0.6)	3.3 (0.7)
Placebo				
n	35	35	32	22
Mean (SEM)	9.4 (0.6)	7.1 (0.9)	6.5 (1.0)	5.8 (1.6)
Change from BL				
Phytosoya				
n	NA	38	36	32
Mean (SEM)		−4.2 (0.8)	−5.4 (0.9)	−6.5 (1.1)
Placebo				
n		34	31	21
Mean (SEM)		−2.2 (0.8)	−3.0 (0.7)	−3.3 (1.8)
% change from BL				
Phytosoya				
n	NA	38	36	32
Mean (SEM)		−38.8 (6.1)	−50.7 (6.0)	−66.6 (6.2)
Placebo				
n		34	31	21
Mean (SEM)		−24.8 (6.4)	−37.2 (6.6)	−27.9 (26.7)

NA, Nonapplicant; BL, baseline; SEM, standard error of the mean.

fied as responders, compared with 32.4% of patients on placebo.

The standardized soy extract did not modify any other menopausal symptoms (data not shown). No significant changes in systolic and diastolic blood pressure were observed in either treatment group. There was a low incidence of medication-related adverse experiences in both groups. No patient in the soy extract group and two patients in the placebo group withdrew prematurely because of an adverse event (vertigo and weight gain) from the study.

DISCUSSION

The results of this study are consistent with our hypothesis that soy protein rich in isoflavones would reduce hot flush frequency in postmenopausal women. Several published studies report improvements in menopausal symptoms with soy protein, soy foods, or soy extract. Washburn et al.[25] investigated the effect of three dietary supplements: placebo, 34 mg of isoflavones consumed once daily, and 34 mg of isoflavones split into two equal doses consumed twice daily. They concluded that a significant improvement was observed for the severity of vasomotor symptoms and for hypoestrogenic symptoms in the twice-daily group compared with the placebo group. Although similar effects were noted in the single dose and the split-dose soy supplementation diets, the effect on vasomotor symptoms was greater on the split-dose diet. This may suggest that having more consistent circulating levels of phytoestrogens may be more efficacious than a higher single dose.

Brzezinski et al.[26] investigated the effects of short-term dietary intervention with phytoestrogen-rich diet on menopausal symptoms in 145 women. The total score of menopausal symptomatology was reduced significantly in both groups. There seemed to be an overall greater improvement in the phytoestrogen diet group than in the control group, but this difference did not reach statistical significance. However, when analyzed separately, the reductions in hot flushes and vaginal dryness scores were more significant ($p = 0.004$ and 0.005 respectively) in the women assigned a phytoestrogen-rich diet than in the controls.

Albertazzi et al.[27] assessed the effects of 60 g isolated soy protein (containing 76 mg isoflavones in the aglycone form). Soy was significantly superior to placebo ($p < 0.01$) in reducing the mean number of hot flushes per 24 hours after 4, 8, and 12 weeks of treatment. By the end of the 12th week, patients taking soy had a 45% reduction in their daily hot flushes versus a 30% reduction obtained with the placebo ($p < 0.01$).

Scambia et al.[28] examined the effect of soy extract (50 mg isoflavones/day) compared with placebo on climacteric symptoms during the course of 6 weeks, after which estrogen replacement therapy was added to both groups. When compared with pretreatment data on week 6 of the study, a significant ($p < 0.01$) reduction in the mean number of hot flushes per week was observed in participants who received the standardized soy extract, whereas a more marked relief was observed in both soy and placebo groups during estrogen replacement therapy administration. Concurrently, the severity of hot flushes, assessed by means of the Greene climacteric scale, was also reduced in the soy group participants.

The most recently published study by Upmalis et al.[29] examined the efficacy of an oral soy isoflavone extract (50 mg genistin and daidzin per day). Decreases in the incidence and severity of hot flushes occurred in as soon as 2 weeks in the soy group, whereas the placebo group experienced no relief for the first 4 weeks. Differences between women evaluated in both groups were statistically significant over 6 weeks ($p = 0.03$). Over 12 weeks, between-group differences approached significance ($p = 0.08$).

Several other studies investigating the effects of isoflavones showed no statistically significant changes in the frequency of hot flushes between active and control groups.

In a recent double-blind, crossover trial of 149 breast cancer survivors with hot flushes using 50 mg of iso-

TABLE 5. *Results from repeated measures models presenting least square means (adjusted means) and their estimated 95% confidence intervals at the specified endpoint*

Model	Treatment effect	Time effect	Treatment *time interaction	Adjusted mean and 95% confidence interval of estimated treatment effect (Phytosoya-placebo) at 16-week endpoint
Repeated measures intention to treat analysis using 16-week LOCF[a] data	0.0103	0.3324	0.3085	−3.6 (−6.2; −0.9)
Repeated measures intention to treat analysis using 16-week LOCF data (after removing outliers)[b]	0.0141	0.4500	0.5178	−2.7 (−4.7; −0.7)
Repeated measures per protocol analysis using 16-week observed data[c]	0.1251	0.3748	0.3978	−2.8 (−6.0; 0.5)
Repeated measures per protocol analysis using 16-week observed data (after removing outliers)	0.2525	0.4758	0.8389	−1.1 (−2.6; 0.5)

LOCF, last observation carried forward.
[a]LOCF is imputed data using the last known value on treatment.
[b]Outliers were #1502 (placebo), who increased from 5 to 31 hot flushes per 24 hours; #1904 (Phytosoya), who increased from 17 to 21 hot flushes per 24 hours; and #3703 (placebo), who increased from 15 to 23 hot flushes per 24 hours.
[c]Observed data at 16 weeks uses only data actually recorded at the 16-week visit and does not therefore take into account study withdrawals.

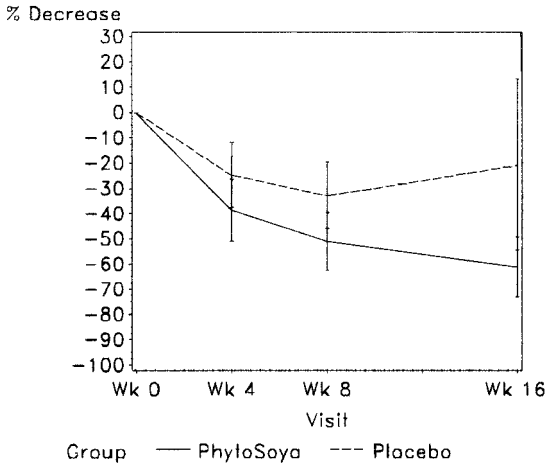

FIG. 1. Percentage decrease from baseline of hot flushes. Results presented as mean ± 2 standard error of mean [LOCF (last observation carried forward) data].

flavones in soy extract tablets, the effects of isoflavones on the frequency and severity of hot flushes were evaluated.[30] The soy tablet in this trial was not more effective than the placebo in reducing hot flushes. Another study examined the change in menopausal symptoms in response to 24 weeks of isoflavone-rich (80.4 mg/day) and isoflavone-poor (4.4 mg/day) soy protein isolate treatment in perimenopausal women.[31] At the completion of the study, no treatment effect was founded on frequency or severity of hot flushes.

Data are often conflicting and difficult to analyze because of variations in the populations studied, duration of dietary soy exposure, study design and variability in responsiveness of some postmenopausal women to phytoestrogen supplementation. But the discrepancies between the negative and positive studies may be related mainly to the specific source of phytoestrogens. Treatments studied have varied from unmodified soy products or phytoestrogen-rich food diets[26] to soy bread (containing soy grits), soy flour, soy protein powder with different doses of isoflavones,[25,27] and tablets containing concentrated subfractions.[28–30] To make direct comparisons between naturally occurring, plant-derived substances and pharmaceutical preparations may be inappropriate. Furthermore, phytoestrogens' metabolite concentration may vary widely between individuals, even with administration of a controlled quantity of isoflavones.

The present study emphasizes many of the problems with pharmaceutical-style intervention studies using naturally occurring dietary compounds. A high withdrawal rate complicated the estimation of the treatment effect, although sensitivity analyses provided support to the suggestion that soy extract taken twice daily can help in the reduction of hot flushes. There is a need for further large studies investigating the areas of clinical effectiveness of isoflavone supplementation in the treatment of menopausal symptoms.

CONCLUSION

In conclusion, on the basis of the results obtained in this pilot short-term trial, this standardized soy extract

(Phytosoya) has a good efficacy on vasomotor symptoms, decreasing hot flushes and night sweats, and it may be safely and effectively used by women who experience vasomotor symptoms and who choose not to take estrogens for personal or medical reasons.

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