

The Use of an Isoflavone Supplement to Relieve Hot Flushes

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The incidence of menopausal symptoms is low in Asian countries, associated in part with the high levels of dietary isoflavones and lignans present in the soybean products that constitute much of the Asian diet.¹ Numerous studies have demonstrated that dietary supplementation with foods high in isoflavones reduces hot flushes in up to 66% of women.² According to 1999 estimates from the Peruvian Menopause Society, 70% to 80% of menopausal Peruvian women report the occurrence of hot flushes, but fewer than 3% of this population uses conventional hormone replacement therapy (HRT).

Most studies of dietary isoflavones have focused on soy legumes (ie, soybeans), which contain genistein and daidzein—only two of the isoflavones known to have significant estrogenic properties. Red clover (*Trifolium pratense*), also a legume, contains these compounds plus two additional isoflavones, formononetin and biochanin, which have been shown to bind to estrogen receptors to produce estrogen-like effects.³ This study was undertaken to evaluate the effectiveness of Promensil™, an isoflavone supplement derived from red clover, in relieving the frequency and severity of hot flushes in postmenopausal women. Promensil was selected for this study because it contains the key isoflavones commonly found in soy foods and is widely available as a consumer product. Evaluation of potential heart disease prevention, favorable lipid influences, and preservation of bone strength was beyond the scope and duration of this study.

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MATERIALS AND METHODS

This 16-week, randomized, double-blind prospective study selected 30 healthy, nonvegetarian women who had been postmenopausal for more than 1 year, using nonprobabilistic sampling and randomly dividing them into two groups of 15. Eligibility criteria required that subjects be younger than age 60, have follicle-stimulating hormone (FSH) levels of more than 30 mIU/mL, experience at least five hot flushes daily (averaged for more than 1 week), and not use HRT, antidepressants or other medications, or soy or other estrogen-active plant products for the previous 16 weeks. The median age was 52 ± 0.7 years for the treatment group, and 51 ± 0.8 years for the control group. All participants were Hispanic, with a middle-class income and good education. There were no statistically significant differences between the two groups with respect to demographics or eligibility criteria. Before starting the study, both groups were asked to rate the severity of their symptoms on a scale of 0 (no symptoms) to 3 (severe, interfering with normal activities).

The 15 treatment-group subjects were given a single daily tablet of Promensil containing 40 mg of standardized isoflavones (genistein, daidzein, formononetin, and biochanin). The 15 control-group subjects received 1 placebo tablet per day, identical in appearance to the active tablets. All subjects were asked to record incidence and severity of hot flushes at the beginning and end of the study. Data were statistically analyzed using the Student *t* test and χ^2 -square test to evaluate the significance of mean differences between the treatment and placebo groups.

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The Use of Isoflavone Supplement

TABLE 1. Frequency of Hot Flushes

	Treatment Group	Control Group
Baseline (no./day)	7.0 + 0.5	5.7 + 0.4
16 weeks	3.6 + 0.3	5.1 + 0.3
Mean % reduction	48.5 + 7.2	10.5 + 9.6

RESULT

At the end of the 16-week study, a reduction in both frequency and severity of hot flushes was reported by women in the treatment group (Tables 1 and 2). The treatment group reported a statistically significant reduction of 48.5% (7.0 ± 0.5 to 3.6 ± 0.3) in the frequency of hot flushes per day compared with 10.5% (5.7 ± 0.4 to 5.1 ± 0.3) in the control group. -Square analysis for proportional differences of frequency of hot flushes revealed that the reduction in the treatment group was statistically significant ($\chi^2 = 25.25$, $P < 0.001$). The severity index for the Promensil group showed a statistically significant reduction from 2.53 to 1.33 (47% reduction), whereas there was no change in the placebo group ($t = 3.67$, $P < 0.001$). There was a shift for the participants in the active group from severe hot flushes ($n = 8$) at baseline to light ($n = 10$) at the study's end.

Mean FSH levels decreased in 14 Promensil-group women from 59.27 ± 4.22 IU/mL to 48.60 ± 3.93 IU/mL, but increased in nine control-group women from 51.47 ± 3.96 IU/mL at baseline to 54.60 ± 3.62 IU/mL at 16 weeks. Although the decrease in FSH values in the treatment-group women was statistically significant ($t = 4.39$, $P < 0.001$), the absolute levels remained above the 30-IU/mL threshold—ie, the level at which ovarian estrogen production is considered to have ceased. There was no observed correlation between FSH levels and frequency of hot flushes or between age and frequency of hot flushes at baseline.

DISCUSSION

Most Peruvian women avoid HRT because they fear that it may lead to breast or uterine cancer, vaginal bleeding, and weight gain,⁴ and often they are reluctant to interact with the medical system to obtain medications.

TABLE 2. Severity of Hot Flushes

Severity Score	No. of subjects reporting each severity score			
	Treatment Group		Control Group	
	Baseline	16 weeks	Baseline	16 weeks
0 (none)	0	0	0	0
1 (light)	0	10	3	3
2 (moderate)	7	5	9	9
3 (severe)	8	0	3	3
Severity Index*	2.53	1.33	2.00	2.00

*Severity Index = No. of subjects reporting each symptom score X symptom score

Total no. of subjects per group

This study demonstrates that dietary supplementation with red clover-derived isoflavones is an effective alternative for relief of vasomotor symptoms in postmenopausal women, reducing both the average daily frequency and severity of hot flushes. A previous study using the same red clover isoflavone supplement failed to demonstrate a statistically significant effect on hot flushes, primarily due to the failure to control for isoflavone intake in the placebo group.⁵ However, that study showed a clear correlation between isoflavone excretion and hot flush reduction, and an 18% reduction in high-density lipoprotein levels—even in the absence of an effect on hot flushes. That study also demonstrated the safety of red clover isoflavones in that uterine thickness remained unchanged in the women using supplementation over a 12-week period.⁵

A recent study evaluating the bioavailability of commercial isoflavone supplements confirmed the manufacturer's statements regarding the composition of Promensil tablets. Under high-performance light chromatography, the product was shown to contain predominantly formononetin and biochanin A in the aglycone form, small amounts of their glycosides, and daidzein and genistein (Table 3). In a single subject who was given 1 tablet of Promensil, the plasma concentrations of daidzein and genistein rapidly rose to levels typically observed after the ingestion of soy-containing foods.⁶

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TABLE 3. Content of Four Isoflavones in Promensil⁶

Daidzein (µg/g)	1,532 + 163
Genistein (µg/g)	2,900 + 65
Formononetin (pg/g)	26,726 + 540
Biochanin A (µg/g)	44,330 + 1,072
Ratio of (daidzein + glycitein)-derived/ genistein	1.36 + 0.07
Aglycones (%)	99.9
Total isoflavones (mg/g)	78.15 + 1.61
Label content per capsule	40.0
Actual content per capsule	41.7

Based on the efficacy in hot-flush reduction reported here and findings of improved cardiovascular function, bone density, and safety reported elsewhere,^{3,5,7} red-clover isoflavone supplementation offers a useful alternative for women seeking relief from acute symptoms of menopause.

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