

The effects of isoflavones derived from red clover on vasomotor symptoms and endometrial thickness

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SUMMARY

There is a great demand for safe, effective alternatives to estrogen in the treatment of symptoms related to estrogen deficiency. Isoflavones are biologically active substances and have been studied for the relief of menopausal symptoms, based on favorable epidemiological evidence from Asian countries with isoflavone-rich diets (1). This is the first U.S. study to evaluate the safety and efficacy of red clover-derived isoflavone dietary supplement, Promensil™ [Novogen]. The symptoms of 23 postmenopausal women were monitored and estrogenicity was evaluated by measuring serum levels of estradiol, follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG) and by using transvaginal ultrasound to indicate endometrial thickness. All measurements were taken at baseline and after 2 months of isoflavone supplementation of 40 mg daily.

INTRODUCTION

Menopausal symptoms are a common complaint and a normal if unpleasant part of the aging process. At least 85 percent of American women



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suffer from vasomotor flushes, night sweats, insomnia, memory loss and vaginal dryness as well as other symptoms related to declining circulating estrogen concentrations (2, 3). By the beginning of the 21st century, an estimated 50 million American women will be menopausal, and considering the use of some form of estrogen or hormone replacement therapy (HRT: estrogen plus a progestin or naturally occurring estrogens). While studies indicate HRT is 90 percent effective in relieving menopausal symptoms, the noncompliance rate among users is high. 70 percent non-compliance is commonly reported(4). Side effects, such as bloating, irritability, breast tenderness and intermittent bleeding (largely due to the progestin component of HRT) as well as the fear of breast cancer promotion (5, 6) may contribute to this low utilization rate. Additionally, approximately 10 percent of women have conditions that are a contraindication to estrogen therapy, including a history of estrogen dependent malignancy, liver disease, thrombo-embolic disorders, and severe migraine (7). Given these concerns, both women and their physicians are increasingly interested in treatments that offer the benefits of HRT without the associated discomforts or risks.

Isoflavones have been studied regarding the relief of menopausal symptoms as well as potential use in protection from cancer, cardiovascular protection and influence on bone and mineral metabolism based on epidemiological evidence from Asian populations. The typical U.S. diet contains less than one fifth of the isoflavones of the typical Japanese diet (8). While any dietary affect is likely to be multifactorial, isoflavone-rich diets are associated with a lower incidence of hormone-related cancer and of menopausal symptoms (9). In addition, *in vitro* studies have shown that isoflavones behave as selective estrogen receptor modulators (SERMs), having a greater affinity for beta estrogen receptors than for alpha estrogen receptors (7). Interest in the estrogenic properties of red clover isoflavones, the most abundant source of the four main dietary isoflavones, stemmed from observations of effects in sheep grazing on clover in Australia (10)

MATERIALS AND METHODS

Dietary supplement

To study the effects of isoflavone supplementation in women with menopausal symptoms, PromensilTM [Novogen] was used. This isoflavone dietary supplement is prepared from a extract of red clover and is standardized to 40 mg of total isoflavones, including specific ratios of biochanin, formononetin, genistein and daidzein, the four main dietary isoflavones. These isoflavones are present as hydrolyzed agylcones.

Study population

Twenty three symptomatic menopausal women, aged 40 to 65 years (mean age 53.5 years), were selected for the study. All met the inclusion criteria of at least 5 vasomotor flushes per day (averaged over 7 days); an FSH of greater than 40 IU/L; amenorrhea for at least 12 months or ovaries removed; a normal mammogram within 6 months prior to study entry.

Subjects were excluded if they had used a form of HRT in the previous 12 months; had an endometrial thickness greater than 6 mm; were vegetarians or regular soy users; had serious mental illness; or had taken one or more of the following drugs within the previous 12 weeks: aspirin, H2 antagonists, anticonvulsants, phenothiazines, benzodiazepines, ergots, beta blockers, clonidine or any natural substance with estrogenic activity (black cohosh, dong quai, isoflavone supplements).

Protocol

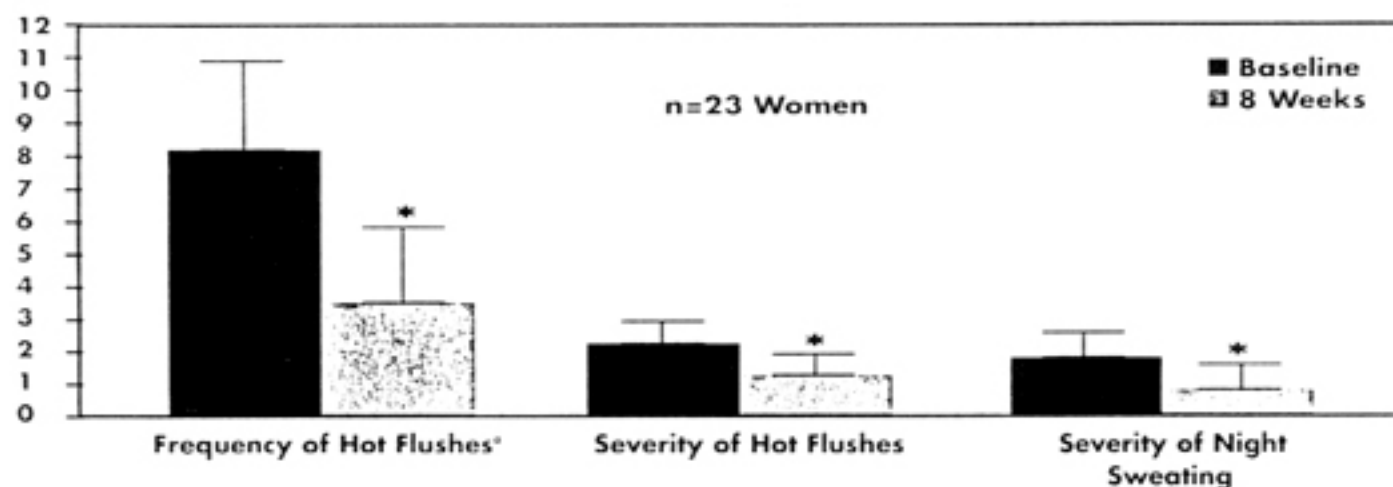
All subjects who met the inclusion criteria were given 40mg of Promensil daily (1 tablet) for two months. All subjects were asked to record the occurrence and severity of menopausal symptoms daily for at least one week prior to taking the dietary supplement and for at least 8 weeks while receiving Promensil™, using a Green Score Questionnaire. Subjects were asked to rate the severity of their symptoms according to the following scale: 0 = Absent (no symptom); 1 = Mild (symptom did not interfere with usual activity); 2 = Moderate (symptom interfered with usual activity); or 3 = Severe (symptom prevented usual activity).

At baseline and after 8 weeks, blood was analyzed for concentrations of FSH, estradiol, fasting lipid concentrations, DHEAS and SHBG.



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^a Mean number of hot flashes per 24 hours averaged over 1 week

* $P < 0.001$ two-tailed t-test, baseline compared to 8 weeks

Menopausal Symptoms

	Mean at Baseline	Mean at Week 8	% Change	P	N
Frequency of Hot Flashes ^a	8.1	3.6	-56%	< .001	23
Severity of Hot Flashes ^b	2.1	1.2	-43%	< .001	23
Severity of Night Sweating ^b	1.9	.89	-52%	< .001	23

^a Mean number of hot flashes per 24 hours averaged over 1 week

^b Rated on scale from 0 (lowest intensity) to 3 (highest intensity)

Note: Mean age 53.5 years (range 48-62)

Figure 1:

Significant positive changes in women's menopausal symptoms after using Promensil™



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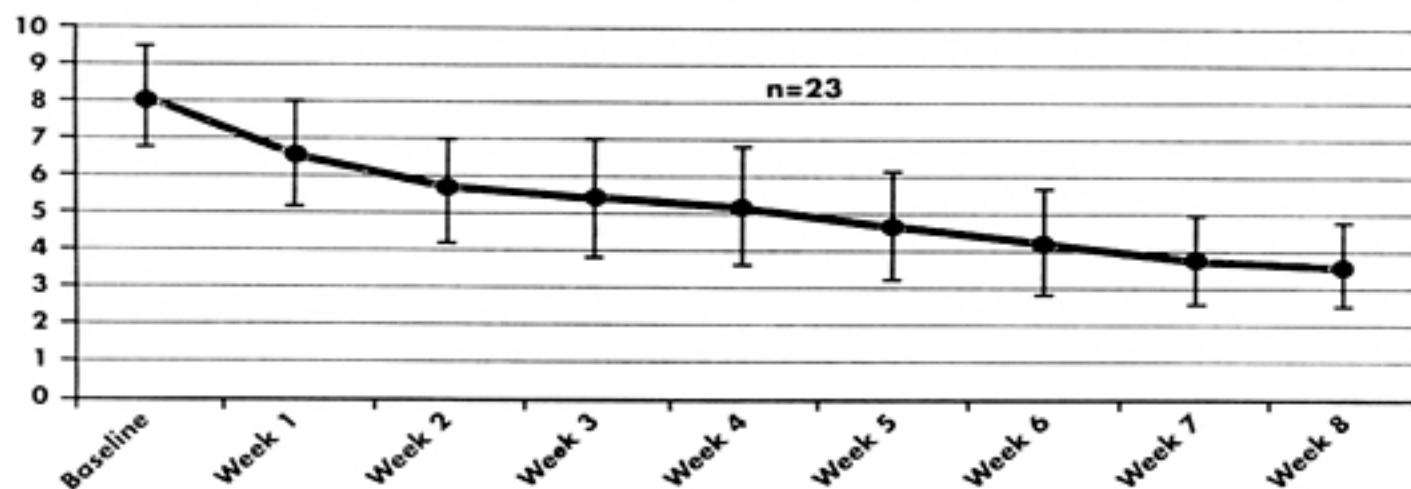
Every 4 weeks, safety monitoring included the following blood tests: a full blood count (CBC); chemistries (including BUN, creatinine, potassium, chloride, bicarbonate, sodium and glucose); as well as liver function tests (LFTs). A transvaginal ultrasound was performed to measure endometrial thickness and to exclude underlying pathology at baseline and again at 8 weeks.

RESULTS

Subjects experienced significant decreases in both severity and number of vasomotor incidents. The frequency of hot flushes decreased by 56% from a mean of 8.1 vasomotor flushes/day during the baseline week to a mean of 3.6 vasomotor flushes/day during the 8th week on the supplement ($P < 0.001$). Using a 0-3 scale of severity, self-rated intensity of hot flushes decreased 43%, from 2.1 to 1.2 and night sweats declined 52%, from 1.9 to 0.89 respectively ($P < 0.001$) from baseline compared to 2 months. [Figure 1] The rate of decrease in frequency of flushing was highest in the initial two weeks while taking PromensilTM [Figure 2]

There were no significant changes in the ultrasound and laboratory results of subjects during the course of the study. There were no significant changes in FSH (79.3 IU/L baseline, 87.0 IU/L at 8 weeks, $P = 0.13$) or estradiol levels (31.4 pg/ml baseline, 29.4 pg/ml at 8 weeks, $P = 0.71$). [Figure 3] Lipid profiles remained statistically unchanged, in terms of total cholesterol (222.8 ng/dl baseline, 220.7 ng/dl at 8 weeks, $P = 0.66$), HDL (62.6 ng/dl baseline, 62.8 at 8 weeks, $P = 0.94$), LDL (140.0 ng/dl baseline, 133.9 ng/dl at 8 weeks, $P = 0.09$), and triglycerides (97.5 ng/dl baseline, 111.6 at 8 weeks, $P = 0.21$).

Transvaginal ultrasound revealed no significant changes in endometrial thickness (2.4 mm at baseline, 2.8 mm at 8 weeks, $P = 0.25$). There were no significant changes found in glucose levels or in total



* Averaged over one week

Figure 2:

Vasomotor hot flushes decreased rapidly over two weeks and significantly in 6 weeks using PromensilTM

	Mean at Baseline	Mean at Week 8	% Change	P	n
Endometrial Thickness (mm)	2.4	2.8	18.0%	0.25	20
Estradiol (pg/ml)	31.4	29.4	-2.1%	0.71	23
FSH (IU/L)	79.3	87.0	7.8%	0.13	26
Total Cholesterol (ng/dl)	222.8	220.7	-2.0%	0.66	25
HDL (ng/dl)	62.6	62.8	.2%	0.94	24
LDL (ng/dl)	140.0	133.9	-6.0%	0.09	24
Triglycerides (ng/dl)	97.5	111.6	14.0%	0.21	26
DHEAS (ug/dl)	78.6	74.2	-5.6%	0.66	24
SHBG (nMol/L)	65.6	64.0	-2.5%	0.67	24

Figure 3:

No change in laboratory and safety results in women using Promensil™

body weight. No abnormalities in the CBCs, liver function tests or electrolytes occurred. No change in FSH or estradiol levels was measured. No other adverse effects were reported by the participants.

CONCLUSIONS

In conclusion, 40 mg of red-clover derived isoflavones, in the form of Promensil™, is safe for short-term use. There were no adverse effects observed and the majority of subjects elected to continue taking Promensil™ after completion of the study. That the supplement did not affect FSH or estradiol levels is reassuring in terms of the potential use of the extract in women with active breast cancer or those with other contraindications to estrogen use. The lack of change in endometrial thickness reduced concern about the possibility of endometrial hyperplasia.

This was the first U.S. study to evaluate the safety and efficacy of the red-clover derived isoflavone, Promensil™. Admittedly the power of the study was limited as the participants acted as their own control. Menopausal women do experience spontaneous changes in symptoms over time. However, the reduction of hot flushes among supplement users was greater than that found in placebo users in other studies (54% vs. ≤ 30%) (11). The other limitation was the relative short duration of the study, especially in terms of lipid profiles. This study's findings do not rule out a potential long term effect of red clover isoflavones on lipoproteins. Other studies using isoflavones for example, have found heightened lipidemic effects in hypercholesterolemic women (12,13,14) Improvements in vascular compliance(not measured in this study) similar to those found using conventional estrogens in menopausal women have also been observed using this preparation (15)

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