Phytoestrogen Supplements for the Treatment of Hot Flashes: The Isoflavone Clover Extract (ICE) Study
A Randomized Controlled Trial

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Context Clinical trials demonstrating increased risk of cardiovascular disease and breast cancer among women randomized to hormone replacement therapy have increased interest in other therapies for menopausal symptoms. Dietary supplements containing isoflavones are widely used as alternatives to hormonal therapies for hot flashes, but there is a paucity of data supporting their efficacy.

Objective To compare the efficacy and safety of 2 dietary supplements derived from red clover with placebo in symptomatic menopausal women.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of menopausal women, aged 45 to 60 years, who were experiencing at least 35 hot flashes per week. The study was conducted between November 1999 and March 2001 at 3 US medical centers and included women who were recently postmenopausal (mean [SD], 3.3 [4.5] years since menopause) experiencing 8.1 hot flashes per day. Women were excluded if they were vegetarians, consumed soy products more than once per week, or took medications affecting isoflavone absorption.

Intervention After a 2-week placebo run-in, 252 participants were randomly assigned to Promensil (82 mg of total isoflavones per day), Rimostil (57 mg of total isoflavones per day), or an identical placebo, and followed-up for 12 weeks.

Main Outcome Measure The primary outcome measure was the change in frequency of hot flashes measured by participant daily diaries. Secondary outcome measures included changes in quality of life and adverse events.

Results Of 252 participants, 246 (98%) completed the 12-week protocol. The reductions in mean daily hot flash count at 12 weeks were similar for the Promensil (5.1), Rimostil (5.4), and placebo (5.0) groups. In comparison with the placebo group, participants in the Promensil group (41%; 95% confidence interval [CI], 29%-51%; P = .03), but not in the Rimostil group (34%; 95% CI, 22%-46%; P = .74) reduced hot flashes more rapidly. Quality-of-life improvements and adverse events were comparable in the 3 groups.

Conclusion Although the study provides some evidence for a biological effect of Promensil, neither supplement had a clinically important effect on hot flashes or other symptoms of menopause.

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finity for estrogen-receptor $\beta$ than for estrogen-receptor $\alpha$.$^{10-12}$ Dietary supplements containing isoflavones from soy or red clover are widely marketed for menopausal symptoms and are increasingly being used by women in the United States as an alternative to estrogen.$^{11-16}$ Most published studies of isoflavones for relief of menopausal symptoms have investigated the effectiveness of soy products.$^{17-28}$ Dietary supplements derived from red clover contain additional isoflavones (biochanin A, formononetin) not found in soy, which may have additional biological activity. On the other hand, red clover lacks components of soy that may contribute to soy’s biological effects. There are few published data$^{29-33}$ and no published large clinical trials on the effects of these compounds on menopausal symptoms and quality of life. Furthermore, many clinicians and the public have expressed concern about the safety of dietary supplements.

We initiated the Isoflavone Clover Extract study to investigate whether 2 dietary supplements derived from red clover were safe and more effective than placebo at reducing hot flashes and improving menopausal symptoms and quality of life in symptomatic postmenopausal women.

METHODS

Participants

Women were recruited at 3 academic clinical research sites located in Oakland, Calif; Minneapolis, Minn; and Iowa City, Iowa. The study was administered through a coordinating center at the University of California, San Francisco. The institutional review boards at each clinical site and at the coordinating center approved the study protocol. All participants gave written informed consent.

Women were recruited from the general population through newspaper and radio advertising, flyers posted in clinics and at health fairs, and directed mailings. Participants were enrolled between November 1999 and November 2000. All participants were aged 45 to 60 years, experiencing at least 35 hot flashes per week, and had a follicle-stimulating hormone (FSH) level of 30 mIU/mL. Eligible women had either documented unilateral oophorectomy or at least 2 consecutive months of amenorrhea prior to enrollment with at least 6 months of amenorrhea in the year prior to entry. Women were excluded from the study if they were vegetarian, consumed soy products more than once per week, took medications affecting isoflavone absorption (antibiotics, antacids) or hormonal preparations during the 3 months prior to enrollment, had significant gastrointestinal disease, drank more than 2 alcoholic beverages per day, were allergic to red clover, were regular users of dietary supplements containing isoflavones, or consumed less than 80% of the expected study tablets during the 2-week placebo run-in period.

Study Supplements and Randomization

The 2 study supplements, Promensil and Rimostil, and identical placebo were prepared by the manufacturer (Novogen Ltd, Sydney, Australia) and sent to a central research pharmacy for packaging and labeling. The central pharmacy was not involved in the study design or participant monitoring. Promensil contains a higher proportion of biochanin A and genistein. Rimostil contains a higher proportion of formononetin and daidzein. An independent laboratory (Sigma Pharmaceuticals, South Croydon, Australia) verified the contents of the study tablets. Placebo tablets contained less than 0.04 mg of total isoflavones per tablet; Promensil tablets contained an average of 41.0 mg of total isoflavones (range, 37.0-43.0 mg); and Rimostil tablets contained an average of 28.6 mg of total isoflavones (range, 25.6-31.4 mg). Participants were instructed to take 2 tablets once daily.

The randomization schedule was prepared by the central pharmacy using computer-generated randomization in blocks of 6, stratified by clinical site. The allocation schedule was maintained at the pharmacy. Each site received numbered containers and distributed them sequentially at randomization. The clinical center principal investigators, their staff, the participants, and the coordinating center principal investigator and staff were all blinded to treatment allocation until the last participant completed her close-out visit and the data clean-up was finished.

Measurements

Staff from each of the clinical sites attended a training session organized by the coordinating center to ensure standard administration of the study protocol and to certify staff on measurement techniques. Participant eligibility, according to the selection criteria previously described, was assessed at an initial screening telephone call and 2 clinic visits. At the first clinic visit, weight, height, pulse, and blood pressure were measured according to a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Demographics, reproductive history, smoking, and alcohol consumption were assessed by participant self-report. A supply of placebo tablets was distributed for a 2-week run-in phase. The participants were informed that the run-in tablets were placebos and were the same as those that were to be used in the main study. At the end of the run-in phase, baseline questionnaires and physical examination were completed. A 24-hour urine sample was collected and willing participants, who were at least 80% compliant with the run-in regimen, were randomized to receive a dietary supplement or placebo.

Participants were contacted by telephone at 1, 4, and 8 weeks to encourage compliance, assess adverse effects, verify concurrent medications, and obtain follow-up information on hot flashes and other symptoms. At 12 weeks, the trial participants returned to the clinic sites for a full evaluation including repeat of the quality-of-life measures, physical examination, blood draw, and 24-hour urine collection. Compliance was assessed by pill count.
Women participating in the study were given hot flash diary cards to record the number of hot flashes and night sweats they experienced on a daily basis. Hot flash counts were averaged for each week. If more than 3 days during a week had missing data, the average for that week of the study was treated as missing.

Changes in quality of life were assessed using the Greene Climacteric Scale, a validated instrument for women experiencing symptoms attributed to menopause. This instrument has 6 subscales specifically designed to assess menopausal symptoms. The Greene questionnaire was completed at randomization and at 1, 4, 8, and 12 weeks after randomization.

Fasting serum, 24-hour urine collections, and second morning void urine specimens were collected prior to randomization and at study closeout. All specimens were aliquoted at the clinical sites, frozen at -80°C, and sent to a central laboratory for storage (Esoterix Inc, Calabas Hills, Calif). Paired 24-hour urine specimens were analyzed for isoflavone excretion (genistein, daidzein, biochanin A, formononetin, o-desmethyl-angolensin, and equol) by laboratory personnel blinded to treatment allocation (Australian Government Analytical Laboratories, Canberra). Total isoflavone excretion was calculated as the sum of the individual isoflavone excretion amounts.

Statistical Considerations
We hypothesized that the isoflavone supplements would be more effective than placebo in reducing hot flashes. The study was designed to have 90% power to detect at least a 15% greater reduction in hot flash frequency in the active treatment arms compared with the placebo arm. We assumed that women taking placebo would have a 25% decrease in the number of weekly hot flashes.

We analyzed differences in rate of change of weekly hot flash counts over the 12-week treatment period using a random coefficients regression model with a quadratic effect for each treatment through time. Each participant had her own random intercept and slope. Separate analyses were done comparing each phytoestrogen supplement with placebo. No analysis combining the 2 active treatment arms was planned or performed. The primary analysis was an intention-to-treat analysis that included all patients who were randomized. No adjustment for baseline covariates was planned for the primary analysis. Models were also analyzed including covariates known to be associated with hot flashes. A secondary per protocol analysis was performed, which included only participants who had hot flash count data available for the 12th week after randomization, who had at least 80% compliance with study tablets by pill count, and whose total isoflavone excretion was less than 1 mg/24 hours at baseline and remained less than 1 mg/24 hours at closeout (placebo group) or was more than 1 mg/24 hours (phytoestrogen groups). The remaining prespecified subgroups were time since menopause (5 years vs >5 years), BMI (median vs >median), and FSH level (median vs >median). They were analyzed to identify women who might particularly benefit from either phytoestrogen supplements. Because isoflavone excretion was not normally distributed, Spearman correlation was used to assess the association of change in urinary isoflavone excretion.

Scores for the subscales of the Greene Climacteric Scale were calculated using the standard method described by Greene. Data are reported using the last observation carried forward. Alternative strategies for imputation of missing values did not affect the results nor did per protocol (secondary) analyses.

Baseline characteristics were summarized by treatment group. For continuous variables, means were compared using analysis of variance for normally distributed variables and the Kruskal-Wallis test for variables with skewed distributions. Categorical variables were compared using the χ² test. For all primary and secondary outcomes, outliers were included in the principal analysis. Secondary analyses excluding participants with values higher than 3 SDs from the mean did not alter the results and have not been presented in this article. Safety data was tabulated according to initial randomization assignment. We reported all adverse events occurring in at least 3% of the women and those that differed across arms (P = .05). The Fisher exact test was used to examine the differences in rates of occurrence between the 3 groups.

RESULTS
Participants
Among 1191 women screened by telephone (FIGURE 1), 870 were ineligible. The principal reasons for ineligibility included too few hot flashes (n=223), not interested in participation (n=205), medical conditions and medications (n=192), dietary exclusions (n=104), and not being menopausal (n=94). Of the 321 women who were invited to the clinic for blood tests and a 2-week placebo run-in, 69 were ineligible. The principal reasons for ineligibility included too few hot flashes (n=28), FSH level of less than 30 mIU/mL (n=18), and not interested in participation (n=11). Only 3 women were ineligible for randomization due to inadequate adherence during the run-in. Participants were randomized to Promensil (n=84), Rimostil (n=83), or placebo (n=85). All participants received treatment as allocated. Two participants in each arm did not complete the 12-week active phase of the study.

At baseline, the participants did not differ across groups by age, demographic characteristics, reproductive factors, or FSH level (TABLE 1; all P>.05). On average, the women were recently postmenopausal, experiencing about 8 hot flashes per day, and were white.

Compliance
Ninety-eight percent (246/252) of the women completed the full 12 weeks of the study. The participants took 97%
of the expected number of tablets by count of the returned tablets, and 98% of the participants took at least 80% of the tablets. Compliance did not differ across groups \((P = .21)\). Only 1 woman dropped out because of an adverse event (nausea in a participant randomized to Rimostil).

**Hot Flashes**

The reduction in mean hot flash count at 12 weeks was 41% (95% confidence interval [CI], 29%-51%) for the Promensil group, 34% (95% CI, 22%-46%) for the Rimostil group, and 36% (95% CI, 26%-45%) for the placebo group (TABLE 2). The change in hot flash counts from randomization to closeout was significant for all 3 groups \((P < .001)\). However, the hot flash reductions in the phytoestrogen groups were not statistically different from placebo \((P = .20)\). The reduction in hot flashes was faster for Promensil compared with placebo (FIGURE 2; \(P = .03\)). The comparable analysis for Rimostil vs placebo found that the rate of reduction in hot flashes was similar for the 2 groups \((P = .74)\). Adjusting for baseline covariates including study site, season, FSH level, age at randomization, age at menopause, and time since menopause did not change the results. On average, women in all 3 groups were still experiencing more than 5 hot flashes per day at the end of the 12-week study period.

Per protocol results \((n = 197)\) were similar to the intention-to-treat analyses. There was some evidence that the benefit of the phytoestrogen supplements in reducing hot flash frequency was most pronounced for women above the median BMI. For Promensil, the reduction in hot flashes over 12 weeks was 49% (95% CI, 35%-63%) for women above the median BMI (25.1) and 30% (95% CI, 16%-44%) for thinner women (BMI <25) \((P = .09)\). For Rimostil, the reduction in hot flashes over 12 weeks was 45% (95% CI, 32%-59%) for overweight women and 22% (95% CI, 7%-37%) for thinner women \((P = .02)\). For women in the placebo group, the reduction in hot flashes over 12 weeks was 32% (95% CI, 21%-42%) for overweight women and 40% (95% CI, 26%-55%) for thinner women. There were no significant interactions for the subgroups defined by FSH level or years since menopause.

Among the 241 women with paired 24-hour urine results available, there was no statistically significant correlation of change in hot flash number with change in total isoflavone excretion \((P = .01; P = .84)\) or with change in the excretion of genistein, daidzein, bio-

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**Table 1. Clinical and Demographic Characteristics at Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Promensil ((n = 84))</th>
<th>Rimostil ((n = 83))</th>
<th>Placebo ((n = 85))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52.3 (2.8)</td>
<td>52.3 (3.0)</td>
<td>52.3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>49.1 (4.5)</td>
<td>48.6 (5.2)</td>
<td>49.5 (4.9)</td>
</tr>
<tr>
<td>Time since menopause</td>
<td>3.3 (4.3)</td>
<td>3.9 (6.1)</td>
<td>2.8 (4.1)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.3 (5.1)</td>
<td>25.6 (4.2)</td>
<td>26.5 (5.4)</td>
</tr>
<tr>
<td>FSH level, mIU/mL</td>
<td>80 (30)</td>
<td>85 (33)</td>
<td>81 (35)</td>
</tr>
<tr>
<td>Hot flashes per day</td>
<td>8.5 (4.8)</td>
<td>8.1 (3.0)</td>
<td>7.8 (2.4)</td>
</tr>
</tbody>
</table>

**No. (%)**

| Surgical menopause  | 6 (7)                   | 4 (5)                  | 6 (7)                |
|                     | >High school education  | 34 (40)                | 31 (37)              |
| Current smoker      | 14 (17)                 | 5 (6)                  | 10 (12)              |
| Race or ethnicity   | 71 (85)                 | 73 (88)                | 69 (81)              |
| White               | 10 (12)                 | 8 (10)                 | 7 (8)                |
| Black               | 3 (4)                   | 2 (2)                  | 9 (11)               |
chanin A, formononetin, o-desmethylangolensin, or equol.

**Greene Symptom Scales**

Compared with age- and sex-matched population normative data, women entering this study reported high levels of distress on the vasomotor scale (mean [SD], 3.6 [1.2]), but lower distress on the psychological (mean [SD], 6.0 [4.4]) and somatic (mean [SD], 2.8 [2.4]) scales. Over the 12-week treatment period, there were significant improvements from baseline in all 3 groups, but there were no statistically significant differences between groups on any of the Greene scales (TABLE 3).

**Adverse Events**

Adverse events occurring in at least 3% of the participants are shown in TABLE 4. There was no statistically significant association of either of the dietary supplements with adverse events; the only adverse event approaching statistical significance was headache ($P = .10$ for Rimostil vs placebo; $P = .12$ for Promensil vs placebo), which was more common among women randomized to placebo. There was no association with vaginal spotting (3.6% for Promensil group, 1.2% for Rimostil group, and 2.4% for placebo group) and there were no reports of breast tenderness, venous thrombosis, pulmonary embolism, myocardial infarction, stroke, fracture, or gallbladder disease. There were no treatment-related changes in weight, blood pressure, or heart rate ($P = .28$).

**COMMENT**

The Isoflavone Clover Extract study was a large, multicenter, randomized, placebo-controlled trial of red clover extracts in postmenopausal women reporting hot flashes. At the end of 12 weeks, the reduction in hot flashes was similar for the 3 groups. Promensil, but not Rimostil, reduced the frequency of hot flashes more rapidly than placebo. The reduction was modest (41% over 12 weeks), but similar in size to that found in other studies of phytoestrogen supplements. This suggests that women in all 3 arms experienced improvements in quality of life that were clinically important. The magnitude of the improvements in hot flashes and other menopausal symptoms in the placebo group highlight the importance of placebo-controlled clinical trials in evaluating the efficacy of potential therapies for menopausal symptoms.

The red clover extracts were well tolerated by the participants. We did not find any trend toward an association of these dietary supplements with adverse outcomes. However, the 12-week intervention period was too short to assess the risk for endometrial hyperplasia, breast cancer, venous throm-
Table 3. Change in the Greene Climacteric Subscales From Randomization to the End of Study

<table>
<thead>
<tr>
<th></th>
<th>Promensil (n = 83)</th>
<th>Promensil vs Placebo P Value*</th>
<th>Rimostil (n = 82)</th>
<th>Rimostil vs Placebo P Value*</th>
<th>Placebo (n = 84), Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.8 (−2.6 to −0.9)</td>
<td>.23</td>
<td>−1.2 (−2.0 to −0.3)</td>
<td>.77</td>
<td>−1.0 (−1.9 to 0.1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>−1.1 (−1.6 to 0.6)</td>
<td>.33</td>
<td>−0.8 (−1.3 to 0.3)</td>
<td>.80</td>
<td>−0.7 (−1.3 to 0.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>−0.7 (−1.1 to 0.2)</td>
<td>.23</td>
<td>−0.4 (−0.8 to −0.2)</td>
<td>.79</td>
<td>−0.3 (−0.7 to −0.2)</td>
</tr>
<tr>
<td>Somatic</td>
<td>−0.4 (−0.8 to −0.03)</td>
<td>.60</td>
<td>−0.6 (−1.1 to 0.2)</td>
<td>.82</td>
<td>−0.6 (−1.0 to 0.1)</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>−1.1 (−1.5 to 0.8)</td>
<td>.93</td>
<td>−0.9 (−1.3 to 0.6)</td>
<td>.36</td>
<td>−1.2 (−1.5 to 0.8)</td>
</tr>
<tr>
<td>Sexual desire</td>
<td>−0.1 (−0.2 to −0.1)</td>
<td>.23</td>
<td>−0.2 (−0.3 to −0.03)</td>
<td>.66</td>
<td>−0.2 (−0.4 to 0.02)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
* Test used (last observation carried forward analysis).

Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. (%) of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Promensil (n = 84)</td>
</tr>
<tr>
<td>Any</td>
<td>31 (37)</td>
</tr>
<tr>
<td>Cold or upper respiratory tract infection</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

The mechanism of action of these supplements is unclear but is thought to be primarily through estrogenlike effects of the isoflavones. Isoflavones are structurally similar to estradiol, binding to both estrogen-receptor α and estrogen-receptor β, and appear to have tissue-specific effects like selective estrogen-receptor modifiers.12 They have been shown to affect the catabolism of estrogens42 and may affect estrogen-receptor expression.43 Several nonhormonal mechanisms have been demonstrated for isoflavones including tyrosine kinase inhibition, antioxidant activity, and effects on ion transport.44

Given that the overall reduction in hot flashes was not different between the 3 treatment groups and that the effect of isoflavone supplementation on rate of reduction was seen only for Promensil and not Rimostil, it could be argued that the results are due to chance alone and not the biological effects of the isoflavones. Alternatively, the results may indicate that the biochanin A and genistein found in higher concentrations in Promensil are more effective for hot flash reduction than the formononetin and daidzein found in Rimostil. Genistein is also present in higher concentrations than daidzein in soy, which is the basis of the traditional Asian diet.45,46

We examined several subgroups to explore whether certain populations might receive greater benefit from isoflavones derived from red clover. Heavier women appeared to receive more benefit from the isoflavone supplements while the changes in the
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placebo group were similar to a placebo effect. This was contrary to our expectation and needs to be reproduced in other studies. Postmenopausal women with higher BMIs tend to have higher circulating estrogens due to conversion of androgens to estrogens by aromatase in adipocytes.\(^47\) We hypothesized that the isoflavones might have greater effects in an estrogen-poor environment, although the relationship between estrogen level and menopausal symptoms has been inconsistent.\(^48\) Several studies have reported a higher incidence of hot flashes in women with higher BMIs.\(^49,50\) This may be due to the insulating effects of body fat leading to a more rapid rise in core body temperature, which then triggers hot flashes.\(^51\) It is unclear why phytoestrogens would have greater efficacy in overweight women.

This study has several limitations. Most of the study participants were white and highly educated, which limits the generalizability of the results to other socioeconomic or racial groups. In addition, the women were all postmenopausal. Thus, the results may not apply to perimenopausal women, which is usually the period when women experience the most frequent and severe hot flashes. Furthermore, we required women to document at least 35 hot flashes per week to be eligible for this study; less symptomatic women may or may not benefit.

This study is the largest randomized clinical trial of red clover extracts in postmenopausal women. Compliance with therapy was exceptionally high (98%) and the drop-out rate was low (2%). We attempted to recruit from a broad cross-section of the population through media advertising and mailings to age-eligible women, rather than recruiting primarily from menopause clinics or referral centers.

In conclusion, the overall reduction in hot flashes after 12 weeks of treatment was modest and similar between women in all 3 groups. Promensil reduced hot flashes more rapidly than placebo. Although the study provides some evidence for a biological effect of Promensil, neither supplement had a clinically significant effect on hot flashes or other menopausal symptoms when compared with placebo.

Author Contributions: Study concept and design: Tice, Ettinger, Wallace, Cummings. Acquisition of data: Tice, Ettinger, Ensrud, Wallace. Analysis and interpretation of data: Tice, Ettinger, Ensrud, Wallace, Blackwell, Cummings. Drafting of the manuscript: Tice, Wallace, Blackwell. Critical revision of the manuscript for important intellectual content: Ettinger, Ensrud, Wallace. Statistical expertise: Blackwell. Obtained funding: Tice, Ensrud, Wallace.

Administrative, technical, or material support: Wallace.

Study supervision: Ettinger, Wallace, Cummings.


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In the practical use of our intellect, forgetting is as important as remembering.
—William James (1842-1910)