Dietary supplements containing red clover extracts were no better than placebo for hot flashes in menopause

Tice JA, Ettinger B, Ensrud K, et al. **Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial.** JAMA. 2003;290:207-14.

QUESTION

Are 2 dietary supplements derived from red clover effective and safe for reducing hot flashes and improving menopausal quality of life in symptomatic postmenopausal women?

DESIGN

Randomized (allocation concealed*), blinded {patients, clinicians, data collectors, and outcome assessors}†,* placebo-controlled trial with follow-up at 12 weeks (Isoflavone Clover Extract [ICE] study).

SETTING

3 academic clinical research sites in California, Minnesota, and Iowa, USA.

PATIENTS

252 women who were 45 to 60 years of age (mean age 52 y) and had ≥ 35 hot flashes per week; a follicle-stimulating hormone (FSH) level ≥ 30 mIU/mL; either bilateral oophorectomy or ≥ 2 consecutive months of amenorrhea; and ≥ 6 months of amenorrhea in the previous year. Exclusion criteria were vegetarian diet; regular use of dietary supplements containing isoflavones; allergy to red clover; consumption of soy products more than once per week; use of medications affecting isoflavone absorption or use of hormone preparations in the previous 3 months; consumption of > 2 alcoholic beverages per day; or gastrointestinal disease. 98% of women completed the study.

INTERVENTION

Women who were ≥ 80% compliant during a 2-week run-in phase of placebo were allocated to Promensil (Novogen Ltd, Sydney, Australia), 2 tablets once daily (average of 41.0 mg total isoflavones per tablet) ($n = 84$), Rimostil (Sigma Pharmaceuticals, South Croydon, Australia) (average of 28.6 mg total isoflavones per tablet) ($n = 83$), or placebo (< 0.04 mg total isoflavones per tablet) ($n = 85$).

MAIN OUTCOME MEASURES

Change in the number of hot flashes, menopausal quality of life (Greene Climacteric scale), and adverse events.

MAIN RESULTS

Analysis was by intention to treat. The Promensil and Rimostil groups did not differ from placebo for reduction in hot flashes at 12 weeks (Table). The reduction in hot flashes was faster in women who received Promensil than in those who received placebo. The 3 groups did not differ for any of the Greene symptom scale scores or for any adverse events ($P = 0.80$), including cold or upper respiratory tract infection, headache, myalgia, nausea, arthralgia, and diarrhea.

CONCLUSIONS

In symptomatic postmenopausal women, 2 dietary supplements derived from red clover extract (Promensil and Rimostil) did not differ from placebo for reducing hot flashes or improving menopausal quality of life. The groups did not differ for adverse events.

Source of funding: Novogen Inc.

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*See Glossary.

Promensil or Rimostil vs placebo in symptomatic postmenopausal women†

Outcomes at 12 wk	Promensil	Rimostil	Placebo
Mean number of hot flashes per d (95% CI)	5.1 (4.2 to 6.0)	5.4 (4.4 to 6.3)	5.0 (4.3 to 5.8)
Percent reduction in hot flashes from baseline to 12 wk (CI)	41% (29 to 51)	34% (22 to 46)	36% (26 to 45)

†CI defined in Glossary. Treatment groups were not significantly different from placebo.

COMMENTARY

The use of estrogen, even to treat hot flashes, has been called into question in light of recent studies. Alternatives to estrogen, such as isoflavones, are increasingly touted. Found in soy and red clover, isoflavones are especially alluring, possessing a chemical structure that allows selective binding to estrogen receptors in a manner similar to that of selective estrogen receptor modulators. Several published studies suggest a beneficial effect of soy isoflavones on hot flashes (1).

The well-designed study by Tice and colleagues assessed the effectiveness of 2 slightly different formulations of isoflavones in treating hot flashes. The authors found that isoflavones were no better than placebo, adding to the findings of other studies that have found little benefit (2, 3).

In addition to the lack of effectiveness, another concern with the use of "natural" products is the potential adverse effects. Characterization of the properties of isoflavone properties is not complete, and the findings of both human and animal studies are inconclusive regarding the effect of isoflavone on such estrogen-sensitive tissue as the breast and endometrium (4). Furthermore, most trials assessing "natural" products for treatment of hot flashes have been done over short periods—that is, ≤ 24 weeks. This length of time is not long enough to detect the development of major complications, such as cardiovascular disease or breast cancer.

Women continue to look for ways to control the discomfort of hot flashes, and "natural" products may yet play a role. However, more studies are needed to provide clinicians with a basis to discuss alternatives with conviction rather than guesswork.

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