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Red Clover and Menopause

By David Kiefer, MD

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RECENT REPORTS OF HORMONE REPLACEMENT RISKS AREN'T MAKing menopause any easier. Many women suffering from hot flushes, insomnia, loss of libido and memory, and other problems related to menopause, now find themselves in the lurch, unsure what safe treatments are available to them. Clinical trials have been performed that focus on herbal medicines and their effects on symptoms of menopause such as black cohosh (*Actaea racemosa*) and soy (*Glycine max*). This review will add another plant, red clover (*Trifolium pratense*), to our knowledge base on the subject. Read on to find out that red clover has more relevance to our lives than just searching for the four-leaved clover in a field of wildflowers.

History and Traditional Use

Red clover has a long history of traditional use throughout the world, most commonly for its respiratory and purported anticancer effects.[1] In North America, the Cherokee, Ute, and Iroquois documented many medicinal uses for red clover,[1] while in Ayurvedic medicine it is used to decrease excessive pitta and kapha doshas while heavily increasing the vata dosha.[2] In traditional Chinese medicine, red clover is utilized for its effects on the liver, heart, and lung meridians.[3]

Modern herbalists use red clover for childhood eczema, psoriasis, coughs, bronchitis, and whooping cough.[4] The herb has also been shown to be helpful with pharyngeal inflammation and salivary congestion, and may have antibacterial activities, in addition to being part of the Hoxsey anticancer formula.[4,5]

The estrogenic effects of red clover, and its isoflavones, began to be investigated after observations of breeding effects and changes in the estrous cycles of livestock known to be grazing on large amounts of red clover.[1]

Botany and Pharmacology

Red clover (*Trifolium pratense*) is in the bean family (Fabaceae) and was named by Carolus Linnaeus in 1753; pratense translates from Latin to "found in meadows." This species of *Trifolium* is native to Northwest Africa, Europe, and Western Asia, and is a herbaceous perennial, growing to approximately 1-3 feet in height. The leaves consist of three leaflets ("three-leaved clover"); it is most commonly the pale violet-colored flowers that are used medicinally.

Red clover contains many phytochemicals, but especially relevant to menopause are the isoflavones, flavones, and flavonols.[1,6] Red clover contains the same isoflavones as soy, though in different concentrations; it contains a higher concentration of biochanin A and formononetin than genistein and daidzein, the reverse of the proportion of these compounds found in soy.[1,7,8] In addition to the fact that red clover supplements do not contain the proteins present in soy products, these unique phytochemical profiles are the main difference between the two plants with respect to menopausal effects.[1]

There are other constituents in red clover that may have physiological effects. For example, the polysaccharides present may provide antitumor activity by increasing the chemotactic markers that signal granulocytic leukocytes.[4] Red clover also contains coumarins, volatile oils (furfural), clovamides, and other flavonoids including pectolinarin and kaempferol.[4]

Mechanism of Action

There are numerous postulated mechanisms for the method by which red clover might improve hot flushes and other symptoms of menopause. The exact mechanism of action of the isoflavone phytoestrogens in red clover is still being elucidated but appears to involve, like soy, a combination of agonism and antagonism with respect to estrogen receptors.[9,10] There is also some evidence for a direct central estrogenic effect on hypothalmic thermoregulators, further supported by lower serum follicle-stimulating hormone (FSH) levels correlating with fewer hot flushes in some studies.[11] Related to these purported effects, there are conflicting data in the medical literature regarding the effect of phytoestrogens on serum estrogen and gonadotrophin levels; some results show increases, others decreases or no changes.[12]

Clinical Trials

There are numerous reviews that have examined herbal medicines, including red clover, being used for menopause.[9,10,13,-15] For example, a review through March 2007 of numerous non-hormonal therapies for menopause found six studies for red clover.[10] The researchers concluded that there was an inadequate number of Level 1 studies, the effects were inconsistent when compared with placebo groups, and long-term safety was unknown.

In addition, a group of clinical trials have examined the efficacy of herbal products containing more than one herb to treat symptoms of menopause.[16] Results from this research are interesting from the standpoint that it is helpful to know whether a specific product works and/or is safe, but it remains then to figure out which individual component or combination of components is actually responsible for the effect(s).

Other papers[1,17] have reviewed some of the existing clinical trials on red clover for symptoms of menopause;[12,18-22] the main clinical outcomes examined were the number and severity of hot flushes. A meta-analysis of five of these trials (all using the proprietary extract Promensil®) found that the red clover groups had 1.45 fewer hot flushes per day than the placebo groups ($P < 0.05$).[17] In the other review, of seven clinical trials examined, four found no changes in hot flushes.[1] The trials, again using Promensil, varied with respect to length of study (2-12 months), total isoflavone content used (40-160 mg daily), and numbers of women included in the study (30-252). One example of the "positive" studies randomized 30 women with at least five hot flushes daily to either 80 mg isoflavones per day (Promensil) or placebo for 12 weeks, after a four-week placebo run-in period, and showed a 44% decrease in

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Summary Points

- Red clover (*Trifolium pretense*) has a long history of use worldwide for many conditions, including respiratory disease, cancer, childhood eczema, psoriasis, coughs, bronchitis, whooping cough, pharyngeal inflammation, salivary congestion-and as an anti-bacterial.
- After observing breeding effects and changes in the estrous cycle of livestock grazing on large amounts of red clover, scientists began investigating whether red clover and its isoflavones might relieve menopausal symptoms.
- Clinical trials of red clover for relief of menopausal symptoms have showed mixed results, with many trials showing no benefits compared to placebo. Positive effects may not appear before eight weeks of treatment and may require more than the 40 mg/d dosage.

hot flush frequency ($P < 0.001$).[22] The authors point to the higher isoflavone dose, the more severe hot flush entry criteria, and the run-in period as reasons why a significant effect was seen in this study but not other Promensil trials.

Red clover researchers have commented that positive effects of red clover in menopausal symptoms may not appear before eight weeks of treatment and may require more than the 40 mg daily total isoflavones used in many studies.[1] Furthermore, future research should take into account the contribution of other important variables, such as the isoflavones in the background diets of study subjects, to more accurately comment on the effects of phytoestrogen supplements.

Other Effects

Other women's health effects have been documented in clinical trials of red clover. For example, research has examined the effects of red clover on characteristics of the vaginal mucosa, overall sexual health, and hormone levels.[7,11,22] One randomized trial compared 109 women receiving either two capsules of a standardized red clover extract (MM11RCE, 80 mg of isoflavones) to placebo for three months, and found that the red clover group had increased serum testosterone ($P < 0.001$), decreased endometrium thickness ($P < 0.001$), and no change in serum estradiol.[7] Also, a crossover trial randomized 60 postmenopausal women to receive either red clover (the proprietary extract Menoflavon, 80 mg isoflavones daily) or placebo for three months.[11] Only 49 women completed the trial that resulted in a statistically significant drop in the total Kupperman index (a compilation of numerous menopausal symptoms each rated from 0 [not present] to 3 [severe]) from a baseline of 27.2 to 5.9 in the isoflavone group vs 20.9 in the placebo group ($P < 0.05$). In addition, the red clover group had positive effects on vaginal cytology, and a slightly lower serum triglyceride level. Finally, an extract of red clover (MF11RCE, 80 mg of isoflavones daily) over 90 days helped 53 postmenopausal women with vaginal and sexual health issues by improving the vaginal cells' karyopyknotic, cornification, and basal cell maturation indices, decreasing vaginal dryness, decreasing dyspareunia, and improving libido.[22]

Dosage and Administration

Promensil is one product used in clinical trials, often dosed as a 40-80 mg tablet daily, providing 3.24-6.48 mg of isoflavones daily; Rimostil, on the other hand, is usually dosed 57 mg daily, providing 13.11 mg isoflavones daily.[1,6] As a comparison, the USP reference dose is a 50 mg tablet containing 6.60 mg of isoflavones;[6] of note, most clinical trials (see "Clinical Trials" section) refer to the tablet-mg amounts as "isoflavones," a different quantity from the laboratory-extracted amount.[6]

There is a wide variety in isoflavone content in both the products available for purchase and those that have been studied in research trials. Researchers have found a range of daily doses being recommended that correspond to daily isoflavone intakes of 4-43 mg, which may or may not correspond with what laboratory testing actually determines is present in the product.[1,6] There can also be varying ratios of the four main isoflavones and different plant parts (flowers, above-ground parts, leaves, and/or whole plant) used to make the extracts.[1,6]

Adverse Effects and Drug Interactions

Some references are made to adverse effects in clinical trials. In one review, only three of 17 articles mentioned adverse effects, all of which were mild (such as headache, thrush, upper respiratory tract infection, nausea, and diarrhea).[17] Other reviews and clinical trials list a variety of similar mild, self-limiting complaints.

Many researchers have explored a possible increased breast cancer risk with the use of phytoestrogens. There seems to be a mix of enhanced proliferation, anti-proliferation, tumor prevention, and complicated estrogen and progesterone-receptor binding at work, depending on the specific phytoestrogen being tested and the type of in

vitro and in vivo model.[14] Some clinical trials have actually demonstrated decreased endometrial thickness in the red clover treatment groups,[1,7] though a five-year study of 376 women using 150 mg of soy isoflavones or placebo daily demonstrated less endometrial atrophy (70% vs 81% in the placebo group) and 3.8% had endometrial hyperplasia (vs 0% in the placebo group; $P < 0.05$).[23] Examining possible effects on breast tissue, one research group randomized 205 women to one tablet of Promensil or placebo daily for one year, showing no significant differences between the groups with respect to mammographic appearance (i.e., breast density) of breast tissue.[12] In addition, in the latter study, red clover did not significantly affect serum estradiol, FSH, or luteinizing hormone.

Red clover has been shown to cause in vivo inhibition of thyroid peroxidase, and the liver cytochromes, CYP1A1, CYP1B1, and CYP2C9, though no clinically significant adverse effects related to any of these has yet been observed.[1]

Conclusion

Red clover, a member of the bean family, has been a medicinal favorite across the centuries and across the continents. It is most well known now for its isoflavones, especially biochanin A and formononetin, and resulting phytoestrogenic effects and, therefore, potential benefits for symptoms of menopause. The exact physiological effect of these phytoestrogens is complicated and still being determined, but seems to have both agonist and antagonist effects on central hypothalamic and distal estrogen receptors. Result of clinical trials have been mixed, with many showing no benefits when compared to placebo; it is possible that doses on the higher end (for example, > 6 mg isoflavones daily), and for at least eight weeks, are more likely to be effective at lowering the number of hot flushes daily or other menopausal symptoms. Recommended doses vary; each proprietary extract contains certain plant parts in certain concentrations, invariably changing the phytochemical profile. It may be best to aim for doses comparable to the USP standard of 50 mg of red clover containing 6 mg isoflavones daily. Adverse effects are generally mild as noted in clinical trials, and other, more severe adverse effects, such as increased breast tissue density and resulting risk of breast cancer or endometrial hyperplasia, appear to be primarily theoretical in nature. Definitive, large clinical trials remain to be done to answer these questions for sure.

Recommendation

There are many unknowns about the use of red clover for menopause. Its efficacy in clinical trials is variable, and each proprietary extract varies in the spectrum of isoflavones. Furthermore, there are concerns, just as with conventional hormone therapy, about the risk of breast and endometrial cancer; there are some preliminary results for red clover that are reassuring, but these need to be replicated. Provided that a woman is not at high risk for breast cancer nor a breast cancer survivor, red clover could be considered as one option for the treatment of hot flushes and other symptoms of menopause; if so, doses on the higher end for proprietary extracts used in clinical trials (for example, Promensil 80 mg daily or Rimostil 57 mg daily) should be used for at least 8 weeks. ❖

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Here Comes the Sun: Phototherapy and SAD

By Dónal P. O'Mathúna, PhD

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Source: Horowitz S. Shedding light on seasonal affective disorder. *Altern Complement Ther* 2008;14:282-287.

HIPPOCRATES, THE NOTED GREEK PHYSICIAN, ONCE said: "It is chiefly the changes of the seasons which produce diseases." And modern scientists also recognize this. Commonly known as winter depression, seasonal affective disorder (SAD) is classified as a mood disorder with a seasonally recurrent pattern. The well-known seasonal symptoms of depressed mood, low energy levels, disturbed sleep, overeating, and weight gain were first described in clinical terms in the early 1980s. This article discusses the prevalence, diagnosis, treatment options, and etiology of this disorder.

■ COMMENTARY

January brings a sense of relief in Ireland as the days are finally starting to lengthen. Things can get gloomy on those days when daylight is limited to six or seven hours. People living in more northern latitudes get even less daylight. For some, the lack of daylight is not just a nuisance but can trigger such severe changes in mood, energy, and appetite that they are diagnosed with seasonal affective disorder (SAD). This condition can include depression, lack of energy, disturbed sleep, loss of libido, overeating, and weight gain.[1] To be characterized as SAD, the symptoms must develop during the fall and winter, decrease as the days lengthen, and be absent in the spring and summer. The symptoms have a wide range of severity.

The incidence of SAD is much higher in women than men. Various studies put the incidence at 3-4 times higher in women than men. However, both genders experience the same range of symptoms and appear to respond similarly to different therapies.[2] The overall prevalence of SAD in the general population ranges from 4% to 10%. For unknown reasons, SAD is more prevalent in the northern hemisphere than the southern hemisphere.[1] There may be some genetic component to the condition. For example, people of Icelandic descent living in Canada had a significantly lower incidence of SAD compared to people living in the same area of non-Icelandic descent.[1]

The Horowitz article focused primarily on reviewing the evidence available for therapies commonly used to treat SAD. The standard approach currently is bright light therapy using a light box with white fluorescent lights of 10,000 lux. This is about 20 times more intense than ordinary indoor lighting. Other practitioners recommend less intense light and there is some debate as to whether the intensity of the light impacts effectiveness.[1] With the intense light, ultraviolet filters are usually attached to avoid harm to eyes or skin. People typically sit exposed to the light for 30 minutes each morning, increasing to twice daily as daylight shortens. Side effects rarely develop, but can include headaches, eye strain, irritation, insomnia, and other mild symptoms, which decrease as exposure is reduced. The review mentioned that light therapy was clinically validated, but only a few clinical studies were briefly described. A

more complete description of the available studies and a critical appraisal of their findings would have been more beneficial.

A number of dietary supplements are also used during the treatment of SAD. These include vitamin D, melatonin, L-tryptophan, and 5-hydroxytryptophan. The review provided a very brief overview of some of the evidence available for their use, which appears to be inconclusive. In spite of this, the review cited various authorities who recommend the use of different supplements. A variety of pharmaceutical antidepressants have been used to treat SAD, either with or without concurrent light therapy. The review referenced clinical trials that have been conducted using these drugs for SAD, but did not critically appraise the primary literature.

Other approaches to SAD therapy include psychotherapy and lifestyle factors. Among the former, cognitive behavioral therapy has shown promise in some controlled trials. Patients had significantly better outcomes when cognitive behavioral therapy was used in addition to light therapy compared to light therapy alone. As would be expected, other lifestyle factors can impact people's mood. Approaches to treating SAD generally recommend regular exercise (in the outdoors if possible to increase light exposure), developing support through friends and family or a more structured support group, and using an activity diary to determine if other factors influence symptoms. The review did not discuss whether these approaches have been evaluated in studies.

The Horowitz review provides a useful introduction to SAD and the variety of approaches to its treatment. However, it suffers from the limitations of any narrative review as compared to a systematic review. No details are given as to why the cited studies were chosen over others, and the quality and details of the studies were not examined. The conclusions of practitioners and authorities in the field were cited without explaining how they evaluated the contradictory evidence often available from clinical studies. The article also would have benefitted from further examination of the diagnosis of SAD, and especially how it can be distinguished from other conditions with similar symptoms. The review should only be used as an introduction to the field. Further examination of the literature would be needed to provide the evidence necessary to influence practice in this area. ❖

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News Briefs

NIHSeniorHealth Web Site Adds CAM Information

Visitors to NIHSeniorHealth, the National Institutes of Health (NIH) web site designed especially for older adults, now have the opportunity to learn about complementary and alternative medicine (CAM).

Older adults who go to http://nihseniorhealth.gov/cam/toc.html will find easy-to-understand information on the basics of CAM, as well as useful tips on how to be an informed consumer, choose a CAM practitioner, and talk candidly with their doctor about CAM use.

NIHSeniorHealth is a joint effort of the National Institute on Aging (NIA) and the National Library of Medicine (NLM). The site is based on the latest research on cognition and aging. It features short, easy-to-read segments of information that can be accessed in a number of formats, including various large-print type sizes, open-captioned videos, and an audio version. Topics coming soon to the site include dry eye and substance abuse among older adults. ❖

CAM Conference to Be Held May 12-15 in Minneapolis

The North American Research Conference on Complementary & Integrative Medicine will be held in Minneapolis, MN, May 12-15, 2009. This conference is sponsored by the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), which consists of 42 leading academic medical centers from across North America. This is a follow-up to the first conference presented in Edmonton, Alberta, in May 2006, which was itself the third in a series of international meetings initially co-sponsored by Harvard Medical School and the University of California, San Francisco.

The North American Research Conference on Complementary & Integrative Medicine is international in scope and invites and encourages the submission of scientific abstracts and proposals for sessions from corporate scientists, academic researchers, educators, and health care providers worldwide.

The conference will showcase original scientific complementary, alternative, and integrative medical research (CAIM) through keynote and plenary presentations, oral and poster presentations, and innovative scientific sessions. Areas of CAIM research presented and discussed at this conference will include: research in basic science, clinical research, methodological research, health services research, and education research.

The goal of the directors of this conference is to provide a single event that attracts a critical mass of cutting-edge, peer-reviewed science and discussion in the broad field of complementary and integrative medical research, organizers say. "The conference invites and benefits enormously from collaboration with many major professional organizations, publishers, and granting agencies, which focus on aspects of the CAIM field. Events throughout the four-day meeting are designed to foster the development of new collaborations and to strengthen existing partnerships." ❖

FDA Warning Expands to Include 69 Weight-loss Products

The FDA expanded an alert to consumers about weight-loss supplements that contain undeclared pharmaceutical ingredients and/or natural or herbal ingredients. Many of the weight-loss products analyzed contain potentially harmful ingredients that are not listed on product labels or in promotional materials. On Dec. 22, 2008, FDA warned consumers about 28 weight-loss products. Since that time, FDA analysis identified 41 additional tainted weight-loss products that may jeopardize consumers' health. A list of these products can be found at: www.fda.gov/bbs/topics/NEWS/2008/NEW01933.html. The recent analysis found that the following active pharmaceutical ingredients, often in amounts far exceeding FDA recommended levels, were present in some of these products:

- **Sibutramine**, a controlled substance that can cause

CME Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. Upon receipt of your evaluation, a certificate will be mailed.

CME Questions

9. There are several phytochemicals in red clover that fall into the category of isoflavones and are thought to account for its effect(s) in relieving the symptoms of menopause. All of the following are such compounds *except*:

a, epigallocatechin gallate (EGCG).
b. genistein.
c. biochanin A.
d. daidzein.
e. formononetin.

10. The results of clinical trials using red clover extracts in menopause have been mixed. Which of the following do researchers think may improve the chance of efficacy in treating the symptoms of menopause?

a. Using red clover in women with more severe menopausal symptoms, such as at least five hot flushes daily
b. Using red clover in low-medium doses, where a plateau effect has been seen
c. Treating women daily for at least eight weeks
d. All of the above
e. Answers a and c are correct

Answers: 9. a, 10. e.

high blood pressure, seizures, tachycardia, palpitations, heart attack, or stroke;

- **Rimonabant**, a drug not approved for marketing in the United States; in Europe, the drug has been associated with increased risk of depression and suicidal thoughts;
- **Phenytoin**, an antiseizure medication;
- **Phenolphthalein**, a solution used in chemical experiments and a suspected cancer-causing agent;
- **Bumetanide**, a diuretic.

Many of the weight-loss supplements are promoted and sold on various web sites and in retail stores. Although some of the products claim to be "natural" or to contain only "herbal" ingredients, they actually contain potentially harmful ingredients not stated on the product labels or in promotional advertisements. The products are not FDA-approved and may be potentially harmful to unsuspecting consumers.

"These tainted weight-loss products pose a great risk to public health because they contain undeclared ingredients and, in some cases, contain prescription drugs in amounts that greatly exceed their maximum recommended dosages," said Janet Woodcock, M.D., director, Center for Drug Evaluation and Research, FDA. "Consumers have no way of knowing that these products contain powerful drugs that could cause serious health consequences. Therefore FDA is taking this action to protect the health of the American public."

FDA has inspected many of the companies associated with the sale of these illegal products, and currently is seeking product recalls *(see below)*. Based on the FDA's inspections and the companies' inadequate responses to recall requests, if necessary, FDA may take additional enforcement steps, such as issuing warning letters or initiating seizures, injunctions, or criminal charges.

Information for consumers can be found at: www.fda.gov/cder/consumerinfo/weight_loss_products.htm. ❖

FDA Warns Against Taking Venom HYPERDRIVE 3.0

The FDA is warning consumers not to take Venom HYPERDRIVE 3.0, a product sold as a dietary supplement and containing sibutramine. Sibutramine, a controlled substance with risks for abuse or addiction, poses potential safety risks. Sibutramine can substantially increase blood pressure and heart rate, and may present a significant risk for people with a history of heart disease, heart failure, irregular heart beats, or stroke, according to Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

Venom HYPERDRIVE 3.0 is marketed by Applied Lifescience Research Industries (ALR Industries), Oak View, CA. On Dec. 24, 2008, ALR Industries initiated a recall of all lots of Venom HYPERDRIVE 3.0 after the FDA laboratory analysis showed samples of the product contained undeclared sibutramine. Although ALR Industries claims on its web site that only "trace amounts" of sibutramine were found in this product, the FDA laboratory tests showed that Venom HYPERDRIVE 3.0 contains a significant amount of sibutramine per dosage unit.

The product was sold via distributors and in retail stores nationwide as well as in Canada, Poland, Sweden, Hungary, South Africa, the Netherlands, Australia, France, and the United Kingdom. The product was packaged in red plastic bottles containing 90 capsules each with the UPC# 094922534743.

Consumers who have this product should stop taking it immediately and contact their health care professional if they have experienced any adverse effects. Consumers can contact the company at legal@alrindustries.com to receive further instructions for returning the product and to ask any questions. Health care professionals and consumers may report serious adverse events or product quality problems with the use of this product to the FDA's MedWatch Adverse Event Reporting program either on-line: www.fda.gov/medwatch/report/hcp.htm; by fax: (800) FDA-1078; or by phone: (800) FDA-1088. ❖