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Review Article

Phytomedicines for menopause

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Abstract

Concerns regarding the safety of hormone replacement therapy are causing women to seek out alternative treatments, particularly botanicals. Of these botanicals, black cohosh appears to be the most promising; however, reports of hepatotoxicity have reached high enough numbers that the FDA has decided to take the action of posting warning labels on products containing the herb. Soy and red clover are also popular phytotherapies for menopause despite the fact that their efficacy has yet to be proven. Although the hops plant contains the potent phytoestrogen 8-prenylnaringenin, it has only been tested in two clinical trials as a therapy for menopause. Based on positive results in these two trials, further studies on hops are warranted. Other herbs, such as dong quai, licorice, ginseng, kava, chasteberry and St. John's wort, are marketed as therapies for menopause; however, there is no evidence that they have any effect on the vasomotor symptoms associated with menopause. This review is focused on the relevant clinical trials, chemistry and pharmacology of these phytomedicines.

Introduction

For many years, hormone replacement therapy (HRT) was the gold standard for the symptomatic treatment of menopause (1, 2). However, in light of the results of the Women's Health Initiative (WHI), many women are searching for safer alternative treatments to manage their menopausal symptoms (3, 4).

Menopause is defined as the point in time following 12 consecutive months of amenorrhea, and occurs in response to normal physiological changes in the hypothalamic-pituitary-ovarian axis (5). During the perimenopausal period, occurring 2-8 years prior to the last menstrual period, and for the last 12 months of amenorrhea preceding menopause, fewer ovarian follicles develop in each menstrual cycle. In addition, the ovaries produce less estradiol, progesterone and androgens, resulting in irregular menstrual cycles, heavier or lighter flow, periods of amenorrhea and worsening or newly developing premenstrual symptoms. Eventually, ovarian follicle production stops and menstruation ceases. The postmenopausal period refers to the first 5 years or so following menopause when hormonal fluctuations are still present (5).

Understanding the onset of this transition, as well as the development of novel therapeutic alternatives for the treatment of menopause-related symptoms, has become increasingly important, particularly in light of 21st century age demographics. It is estimated that by the year 2030, there will be more than 60 million postmenopausal women in the United States, and 1.2 billion postmenopausal women worldwide (6, 7). Women in developed countries will spend approximately one-third of their lives in the postmenopausal state (8).

Due to the decline in estrogen and progesterone production and the increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), women (approximately 55-75% of American women) experience vasomotor symptoms (hot flashes and sweating) or other symptoms such as depression, mood swings, sleep disorders, vaginal dryness and joint pain (9, 10). Although most women experience symptoms acutely for only the first 4-5 years, 10% have severe symptoms, which may persist for more than 10 years. Between 10% and 25% of women will suffer such severe symptoms that they will seek treatment from their healthcare provider (9). In addition, the incidence of chronic diseases, such as cardiovascular disease, osteoporosis, urogenital atrophy, incontinence and dementia, dramatically increases in the postmenopausal period (11-13).

Until 2002, HRT was widely recommended for the prevention of cardiovascular disease irrespective of age, especially for high-risk women, such as those with exist-

ing coronary heart disease (14). Numerous studies have found HRT (estrogen alone or estrogen plus progestin) to be the most effective therapy for hot flashes and sleep disturbances, reducing symptoms by 80-90%, while other therapies, such as vitamins, clonidine and antidepressants, reduce symptoms by only 30-60% (2). While additional benefits have also been observed, such as decreased vaginal dryness, stress incontinence and urinary tract infections, and increased skin elasticity and thickness, HRT is no longer feasible as a treatment of choice due to significant concerns about safety and efficacy (15). The WHI, one of several studies exploring the risks and benefits of HRT use in postmenopausal women, has displaced the common belief in the protective effects provided by HRT (16). In fact, data from this randomized trial revealed an increased risk of heart disease (29%), breast cancer (26%) and events such as strokes (41%). On the other hand, HRT demonstrated a protective effect against colon cancer (37%) and hip fractures (34%) secondary to osteoporosis (16). The WHI results, in combination with clinical contraindications and a generalized fear of HRT, may leave some women with the opinion that HRT is inadequate or inappropriate for the treatment of menopausal symptoms.

In addition to HRT, selective serotonin reuptake inhibitors (SSRIs) have also shown promise for the symptomatic treatment of menopause. Clinical trials of SSRIs have provided evidence of efficacy; however, their effects are less pronounced than those of estrogen (17). Few trials have been published and many have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be useful for highly symptomatic women who cannot take estrogen, but are not optimal choices for most women (17). As a consequence, many women are actively seeking alternative treatments for menopausal symptoms, such as botanical dietary supplements for the relief of fatigue, hot flashes, joint pain and insomnia, as well as depression, anxiety and fatigue (3, 4).

A 2002 survey of 500 peri- and menopausal women at the University of Illinois at Chicago reported that 79% of women aged 40-65 attending clinics were using botanicals, with 65% of these women using botanical dietary supplements to treat symptoms associated with the menopausal period (3). In the United States, women use a variety of herbs for the treatment of menopause, including black cohosh (*Actaea racemosa* syn. *Cimcifuga racemosa*), dong quai (*Angelica sinensis*), ginseng (*Panax ginseng*), evening primrose oil (*Oenethera biennis*), soy (*Glycine max*) and red clover (*Trifolium pratense*) (18). This review will focus on plants for which there are clinical data supporting efficacy for the treatment of menopausal symptoms, as well as information on the relevant chemistry and pharmacology of these plants.

Black cohosh

Black cohosh is a perennial herb native to the eastern United States and Canada. Historically, black cohosh rhizomes (roots) were routinely used as a medicine by the Native American Indians (Penobscot, Winnebago and Dakota) for the treatment of coughs, colds, constipation, fatigue and rheumatism, as well as to increase breast milk production. In 1832, a tincture of black cohosh rhizome was reportedly used for the treatment of pain and inflammation associated with endometriosis, rheumatism, neuralgia and dysmenorrhea (19). More recently, extracts of black cohosh have been marketed worldwide for the management of menopausal symptoms.

A review of recently published randomized clinical trials suggests that treatment with a standardized black cohosh extract may be of some benefit for the management of menopausal symptoms, and further indicate that 40 mg/day of a black cohosh extract is sufficient for symptom reduction (4). Prior to 2003, there were at least 25 published studies supporting the use of black cohosh for the treatment of various gynecological ailments and for the management of symptoms such as anxiety, hot flashes, profuse sweating, insomnia and vaginal atrophy. Between 2003 and 2005, at least 10 new clinical studies were published, with all but 2 supporting the use of black cohosh for the management of menopausal symptoms (20-29). The 2 negative studies included the 2006 Herbal Alternatives for Menopause Trial (HALT), in which 351 women aged 45-55 were treated with black cohosh, a multibotanical, hormone therapy or placebo. No improvement in hot flash frequency or intensity was reported in the group treated with black cohosh (160 mg/day) or the multibotanical (200 mg/day) compared to placebo (23). In addition, a double-blind, randomized, placebo-controlled, crossover phase III trial of black cohosh for the management of hot flashes failed to provide any evidence that black cohosh reduced hot flashes compared with placebo (30).

In a pilot study, treatment of breast cancer survivors with a black cohosh product reduced the mean daily hot flash frequency by 50% and patients reported less trouble with sleep, less fatigue and a reduction in abnormal sweating (25). In another study in women with hot flashes due to tamoxifen administration, comparisons of the standard care group with the tamoxifen/black cohosh group showed a reduction in the number and severity of hot flashes in those patients treated with black cohosh (21).

It was previously thought that black cohosh extracts might reduce the symptoms of menopause through a mechanism that involves estrogen modulation. However, review of the evidence from numerous *in vitro* and *in vivo* studies, including one clinical trial, does not support this hypothesis, and an estrogenic mechanism of action for black cohosh does not appear plausible (31, 32). *In vitro* studies have instead demonstrated the ability of black cohosh extracts to bind to serotonin (5-HT) receptors, suggesting a possible serotonergic rather than an estrogenic mechanism (33). Presumably, the effects of black cohosh are mediated by its binding to 5-HT receptors expressed in the hypothalamus, a brain region known to be responsible for thermoregulation.

The characteristic chemical constituents of the roots and rhizomes of black cohosh include cycloartenol-type

triterpenoids, such as actein, 23-epi-27-deoxyactein and cimicifugoside (see Table I), as well as cinnamic acid derivatives (*i.e.,* ferulic acid, isoferulic acid and piscidic and fukiic acid esters) (3, 34). Although black cohosh was previously thought to contain the estrogenic isoflavone formononetin, more recent studies have shown this not to be the case (35, 36).

Safety data from previously published postmarketing surveillance studies, clinical trials and reviews have generally found very few serious adverse events associated with the ingestion of black cohosh products (31, 32). However, since 2003, a number of adverse event reports have been published, raising concern about the safety profile of black cohosh (37, 38). The number of purported cases of autoimmune or drug-induced hepatotoxicity associated with the ingestion of black cohosh has escalated to over 150 worldwide. While many of the cases were poorly described and the occurrence appears to be rare considering the millions of doses of black cohosh sold per year, there are now a sufficient number of cases to cause concern. A recent workshop by the Office of Dietary Supplements concluded that the reports of hepatotoxicity require a thorough investigation and that warning labels should be affixed to packaging of products containing black cohosh (39). Preclinical toxicological studies are needed to try to address this serious issue. In the meantime, it appears prudent to advise menopausal women with underlying liver disease, autoimmune diseases or taking medications that may impact liver function not to use products containing black cohosh until this issue has been scientifically investigated. Since black cohosh appears to be one of the only herbal supplements to date that may have some efficacy for menopause, it is critical that preclinical testing be performed to identify any safety issues that need to be addressed.

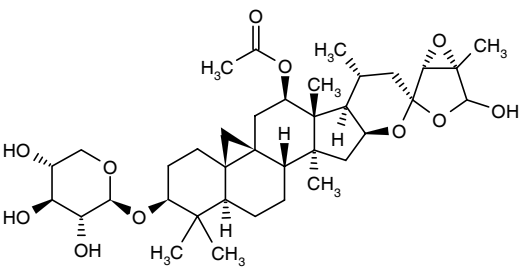
Red clover

Interest in the estrogenicity of red clover was sparked by reports of fertility disorders in cattle fed with silage containing the herb in the 1970s and early 1980s (40, 41). Although there are no published records of red clover

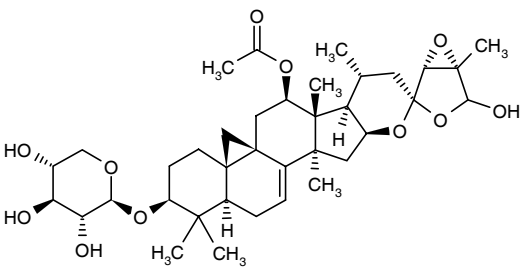
Table I: Chemical structures of active constituents from black cohosh, red clover, soy and hops.

Black cohosh

Triterpene glycosides
1. Actein
2. Cimicifugoside



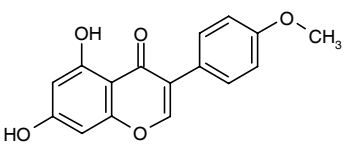
(**1**)



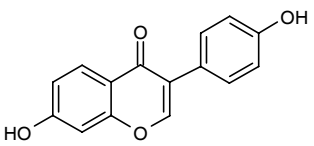
(**2**)

Soy, red clover

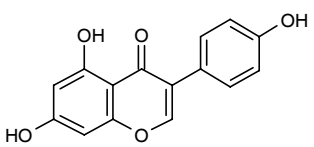
Isoflavonoids
3. Biochanin-A
4. Daidzein
5. Genistein
6. Formononetin



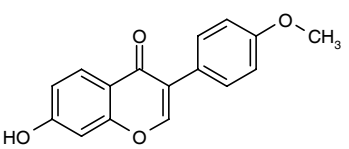
(**3**)



(**4**)



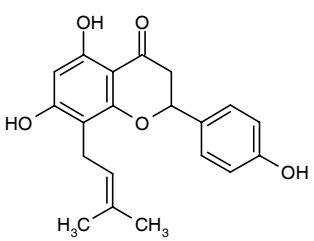
(**5**)



(**6**)

Hops

Prenylated flavonoids
7. 8-Prenylnaringenin



(**7**)

being used in traditional medicine for women's health conditions, it is known to have been used as a topical treatment for dermatological disorders such as psoriasis and eczema, as well as orally for the treatment of asthma and cough (42, 43).

Red clover is a common, low-growing, perennial herb native to Europe. Rich in isoflavonoids, the major active constituents are biochanin-A, formononetin, daidzein and genistein (42, 44-46) (see Table I). Alone and as part of a crude alcoholic extract, these red clover isoflavones have proven to be significantly estrogenic in both *in vitro* and *in vivo* assays (47-49). However, clinical trials have reported contradictory and overall inconclusive results regarding the efficacy of red clover for the treatment of vasomotor symptoms in menopausal women. Nonetheless, red clover remains one of the most widely marketed dietary supplements throughout the world for the management of menopausal symptoms and postmenopausal health (43).

In a recently published review, all randomized controlled trials of orally administered red clover for the treatment of hot flashes in menopausal women were included in a meta-analysis (50). Of five trials using 40-80 mg/day of a standardized preparation (Promensil©), two showed a significant decrease in the number of hot flashes (51, 52), while the other three showed no ability of red clover to improve symptoms compared to placebo (53-55). The result of the meta-analysis, however, was a mean overall reduction of 1.6 hot flashes/day as compared with placebo (50). A previous review did not come to this conclusion, but rather it was found that when comparing only the mean number of hot flashes between red clover and placebo, and not taking into consideration baseline data, red clover had no significant effect on hot flash frequency (56).

Six trials have assessed the effects of red clover isoflavones on total cholesterol and lipid levels (53, 57-61). Of these studies, only one reported a significant effect. This study demonstrated that oral administration of an isoflavone combination extracted from red clover was associated with a significant increase in high-density lipoprotein (HDL) cholesterol, a significant fall in apolipoprotein B (Apo B), and a small but significant increase in the predominantly cortical bone of the proximal radius and ulna after 6 months of treatment (60). Another study measuring the effect of red clover isoflavones on lumbar spine bone mineral content (BMC) and bone mineral density (BMD) in peri- and postmenopausal women reported significantly less reduction in BMC and BMD for the perimenopausal group, but not the postmenopausal group (62). No differences in BMD of the hip or significant changes in markers of bone turnover were seen in any of the groups (62). Similarly, Schult *et al.* (61) reported no statistically significant differences among treatment groups for bone turnover markers in a study of the standardized red clover preparations Promensil© and Rimostil©.

Ingestion of large amounts of clover in animal feed has been associated with a number of adverse effects in cattle and sheep. A description of "clover disease" was published and included symptoms of infertility, abnormal lactation, dystocia and prolapsed uterus in Australian sheep, all of which were hypothetically attributed to the estrogenic effects of isoflavones (63). However, none of the controlled clinical trials has reported adverse effects at doses up to 160 mg/day of isoflavones. *T. pratense* does not contain coumarins and therefore concerns about blood coagulation are unfounded (64, 65).

Soy

The hypothesis that soy would reduce menopausal symptoms originated from epidemiological data suggesting that hot flashes occur much less frequently in Asian women than in Western women (66, 67). For example, a 2001 cohort study of Japanese women revealed an inverse relationship between soy intake and hot flashes (67). However, reviews of clinical trials assessing the effects of soy are difficult to perform due to variations in the products used (soy foods to purified isoflavones), dose, scoring systems for symptoms of hot flashes and the menopausal status of patients (18). Studies have also been of short treatment duration, and only 3 of 8 studies with treatment phases that lasted for more than 6 weeks showed significant improvement in hot flashes at the end of the study, and most benefits disappeared after 6 weeks (68). The longest study to date showed no benefit for hot flashes (or other symptoms) at 24 weeks (69). Of interest was the observation that in a few studies, menopausal symptoms decreased in all groups —often as much as 50-60% in both placebo and treatment groups. In contrast, 2 trials have reported a significant reduction in hot flashes in the soy-treated group compared with placebo (68, 70). Hot flash frequency was reduced by 45% and 28% compared with placebo, although the dose used and the modes of administration were not well defined (18).

Reports of adverse events associated with soy intake have been few. However, in 2004 Unfer *et al.* (71) reported the results of a 5-year randomized, double-blind, placebo-controlled clinical trial that assessed the endometrial effects of soy isoflavones in postmenopausal women. The primary outcomes measured were the results of endometrial histology from biopsies obtained at baseline, 30 months and 5 years after the beginning of the treatment. Two hundred and ninety-eight women completed the 5-year treatment. No cases of malignancy were detected during biopsy. Seventy percent of women undergoing treatment with soy phytoestrogens had an endometrium classified as atrophic or nonassessable *versus* 81% receiving placebo. The occurrence of endometrial hyperplasia was significantly higher in the soy group at the 5-year mark (3.37% *vs.* 0%; a total of 4 cases of hyperplasia at 5 years). No cases of hyperplasia were observed at 30 months. The endometrial hyperplasia was first detected after 5 years and most of the cases had simple hyperplasia, which indicates a weak estrogenic effect of isoflavones on the endometrium.

At least 8 clinical trials and numerous other pharmacological investigations have assessed the effects of soy

on menopausal symptoms (53, 70, 72-78). None of these investigations have reported endometrial hyperplasia as an adverse event after treatment with soy isoflavones or protein. In the Unfer study (71), only 3.37% of those treated with the soy isoflavones developed hyperplasia (a total of 4 women), which is actually lower than the percentage observed in the general population. Furthermore, hyperplasia was not observed until after 5 years of therapy. The two primary differences in this investigation were the very high dose of isoflavones (150 mg/day) and the treatment period of 5 years, which was significantly longer than any other previously published study. Considering that the average recommended dose of isoflavones in the United States is 40-80 mg/day, the dose used in the Unfer study is 2-3 times higher. This dose was much higher than that used in other clinical studies and there are no clinical trials supporting the use of this dose for any therapeutic indication. Thus, the dose used in the Unfer study was atypical. Review of the clinical and pharmacological data suggests that soy isoflavones do not cause endometrial hyperplasia when used at normal therapeutic doses. In fact, for premenopausal women, the data actually suggest that soy ingestion may protect against endometrial hyperplasia and cancer, as in the presence of estrogen soy isoflavones appear to act as antiestrogens (67).

The biologically active components of soy are isoflavones comprised primarily of the glucosides genistin and daidzin and their respective aglycones genistein (4',5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroxyisoflavone) (79) (see Table I). Soy isoflavones interact with the mammalian estrogen receptor and appear to have both estrogen-agonist and -antagonist effects on mammalian physiology, depending on the tissue involved and the concentration or dose used (79-89).

Evidence for the antiestrogenic effects of soy were published by Nagata *et al.* (67), who found that, in a study in 50 young, regularly cycling Asian women, the intake of soy products was inversely correlated with serum estrone and estradiol levels. Premenopausal Japanese women were randomly assigned to receive either a soymilk-supplemented diet (n=31) or a normal (control) diet (n=29). At the end of the study period, estrone and estradiol levels were decreased by 23% and 27%, respectively, in the soymilk-supplemented group and were increased by 0.6% and 4%, respectively, in the control group (67). These data suggest that regular consumption of soymilk may actually protect against estrogen-induced cancers by reducing the serum estrogen levels over the lifetime of premenopausal women.

Hops

Hops, the resinous inflorescences of the twining vine *Humulus lupulus*, are used today primarily for their bitter and aromatic properties in the manufacture of beer. Although most commercially available hop-derived preparations (often in combination with other plants, such as *Valeriana officinalis* and *Melissa officinalis*) are focused on the tranquilizing (sedative) effect of the plant, hops have been known to be estrogenic both from traditional medicine and from anecdotal reports (90). Hops are a rich source of prenylated flavonoids including 8-prenylnaringenin (8-PN) (see Table I). Comparison with well-known phytoestrogens, *e.g.*, coumestrol (from clover and/or alfalfa) and genistein and daidzein (from soy), showed that 8-PN is currently one of the most potent phytoestrogens (91-93).

To date, two clinical studies have investigated hops as a treatment for hot flashes in menopausal women and both reported a significantly positive effect. While one study (94) took place before the discovery of 8-PN and thus was not a standardized extract, a 2005 randomized, double-blind, placebo-controlled study of an extract standardized to 100 μg 8-PN showed pronounced improvement in symptoms by means of a modified Kupperman Index and patient questionnaires (95).

Due to the estrogenic nature of hops, further studies on its safety are needed. However, no adverse events associated with its use as a dietary supplement have been reported.

Other botanicals

Several other botanicals are widely marketed for the management of menopausal symptoms, including licorice root (*Glycyrrhiza glabra*), dong quai, chasteberry (*Vitex agnus castus*), wild yam (*Dioscorea villosa*), evening primrose, Ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), kava (*Piper methysticum*), valerian (*Valeriana officinalis*), motherwort (*Leonurus cardiaca*) and St. John's wort (*Hypericum perforatum*) (96). While herbs such as dong quai, chasteberry and wild yam have a history of use in issues related to women's health, there is little research showing efficacy for the treatment of vasomotor symptoms associated with menopuase. Furthermore, these herbs are often prepared in combination with other herbs, such as black cohosh and red clover, and so their contribution is difficult to assess. Ginkgo, ginseng, kava, valerian and St. John's wort have proven to be effective for sleep disturbances, nervousness, depression, mood swings and memory loss. While these disturbances are often associated with the menopausal transition, most of these products have been studied in the general population and not in menopausal women. Studies on the safety of products containing these herbs are also lacking. Licorice root, for example, is known to cause congestive heart failure at doses as low as 500 mg/day (96), and kava has also been the subject of concern due to hepatotoxicity associated with its use (97). St. John's wort interacts with drug-metabolizing enzymes, and so it is contraindicated in cases where patients are on other medications (98).

Conclusions

Menopausal symptoms, such as hot flashes, are the result of decreased production of estrogen in menopausal

women (5). For this reason, HRT has for a long time been the gold standard for treating menopausal symptoms and is the most effective therapeutic option (1, 2). However, women are now more than ever turning to alternative therapies, particularly botanicals, in response to the results of the WHI, which linked an increased risk of cancer and cardiovascular illness to HRT (3). While a wide variety of herbs are marketed alone and in combination for the treatment of menopausal symptoms, only a select few have been studied in reliable randomized, double-blind, placebo-controlled clinical trials in menopausal women. Furthermore, the results of these trials are often contradictory and studies on safety are lacking.

Two of the most popular herbs for the treatment of menopausal symptoms, red clover and soy, are rich in isoflavones, plant secondary metabolites that weakly mimic the effects of human estrogen. Despite the well-studied estrogenicity of these herbs in *in vitro* and *in vivo* animal models, there is little evidence to suggest that they are effective in reducing the number and intensity of hot flashes in menopausal women. Hops, on the other hand, contains the potent phytoestrogen 8-PN, and although only two clinical trials have been performed, the herb appears to be effective and worthy of future study.

Interestingly, one of the most promising therapeutic options, black cohosh, is not estrogenic, but rather may act as a 5-HT agonist (33). Taken as a whole, the results of clinical trials suggest that black cohosh is effective in reducing hot flashes, although further study is needed on safety and efficacy due to an ever-increasing number of reports of hepatotoxicity associated with its use.

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