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Botanical and Dietary Supplements for Menopausal Symptoms: What Works, What Doesn't

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Abstract

All women reach menopause and approximately two-thirds of women develop menopausal symptoms, primarily hot flashes. Hormone therapy long was considered the first line of treatment for vasomotor symptoms. However, given the results of the Women's Health Initiative, many women are reluctant use exogenous hormones for symptomatic treatment and are turning to botanicals and dietary supplement (BDS) products for relief. Despite the fact that there is limited scientific evidence describing efficacy and long term safety of such products, many women find these "natural treatments" appealing. Peri- and postmenopausal women are amongst the highest users of these products, but 70% of women do not tell their health care providers about their use. Compounding this issue is the fact that few clinicians ask their patients about use of BDS, largely because they have not been exposed to alternative medical practices in their training and are unfamiliar with these products. This paper reviews the botanicals and dietary supplements commonly used in menopause, (such as black cohosh, red clover, soy products, among others) as well as the available data on efficacy and safety. We searched the MEDLINE database from 1966 to December 2004 using terms related to botanical and dietary supplements and menopausal symptoms for peri- or postmenopausal women. Abstracts from relevant meetings as well as reference books and websites on herbal supplements were also searched. Randomized-controlled trials (RCTs) were used if available; open trials and comparison group studies were used when RCTs were not available. The evidence to date suggests that black cohosh is safe and effective for reducing menopausal symptoms, primarily hot flashes and possibly mood disorders. Phytoestrogen extracts, including soy foods and red clover appear to have at best only minimal effect on menopausal symptoms but have positive health effects on plasma lipid concentrations and may reduce heart disease. St. John's wort has been shown to improve mild to moderate depression in the general population and appears to show efficacy for mood disorders related to the menopausal transition. Other commonly used botanicals have limited evidence to demonstrate safety and efficacy for relief of symptoms related to menopause.

Keywords

Menopause; botanical supplements; dietary supplements

Introduction

Approximately two-thirds of perimenopausal women develop symptoms related to the menopausal transition. Of these, only 10–25% of women seek treatment from a traditional

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health care provider and many frequently resist or are dissatisfied with conventional medical recommendations for their symptoms.[1] Although hormone therapy is still considered the first line of treatment for vasomotor symptoms, given the published results of the Women's Health Initiative, many women are reluctant use exogenous hormones and are turning to botanical and dietary supplement (BDS) products for relief.[2, 3]

Botanicals are classified by the Dietary Supplement Health Education Act (DSHEA) as dietary supplements, not drugs, that are intended to either (1) supplement the diet, (2) contain one or more dietary ingredients (vitamins, minerals, herbs or other botanicals, or amino acids), (3) be taken by mouth as a pill, capsule, tablet, or liquid, and (4) be labeled as being a dietary supplement. Botanicals and dietary supplements are not intended for diagnosis, prevention, or treatment and are not regulated by the Food and Drug Administration (FDA). This fact results in considerable variability of content, standardization, dosage, purity, and possible contamination of available products in the United States (US). This is in contrast to Germany where dietary supplements are scrutinized for safety and efficacy by their Commission E, an agency similar to the FDA.[4]

The use of botanical and dietary supplements among menopausal women has increased in recent years in the US, with the largest increase in the use of so called "natural hormonal agents".[5–8] Most women report using such treatments largely because they find these alternatives to traditional medicine more congruent with their values, beliefs, and lifestyles.[9, 10] A recent survey of 500 peri- and postmenopausal women conducted at the University of Illinois Medical Center found that 70% of women between the ages of 40–60 reported using BDS to treat symptoms or diseases; however, fewer than 10% of users could actually verbalize the health benefits of these supplements.[11]

A particularly troubling fact is that while many women regularly use BDS, approximately 70% do not tell their clinicians about use of these products.[11] Many women appear to be under the misconception that herbal products are "natural" and therefore safe.[12] Compounding this problem is that many conventional practitioners do not ask their patients about use of alternative medicines.[13–16] One study which specifically examined knowledge, attitudes, and behaviors of 62 physicians and nurses who care for peri- and postmenopausal women regarding use of BDS found that knowledge about botanical therapies was quite low. Over two-thirds of clinicians reported they had limited or no knowledge about BDS, no formal training, and had not studied these supplements on their own.[16] The promising finding was that they were open to learning more about these modalities, were interested in additional training predominantly because of growing patient awareness and use and were open to using or referring for these therapies if they had adequate knowledge about efficacy and safety. These results suggest that the more information providers have about BDS the more likely they are to discuss these options with their patients.[17]

This paper reviews the scientific literature related to BDS for relief of menopausal symptoms including the available data on efficacy and safety focusing primarily on the most heavily utilized botanicals for menopause, black cohosh, soy products and red clover.

Methodology

The MEDLINE database from 1966 to December 2004 was searched using terms related to botanical and dietary supplements and menopausal symptoms. The following terms were used in the search strategy: dietary supplements, black cohosh, red clover, soy, isoflavones, medicinal plants, hot flashes, menopause, osteoporosis, bone mineral density, cognition, blood lipids. All articles related to the topic were reviewed and the bibliographies of clinical trials (randomized and open trials), other research studies, and review articles were searched for

other relevant studies. Finally, abstracts from the North American Menopause Society were searched by hand.

Studies were eligible for inclusion if study subjects were peri- or postmenopausal women and were related to menopausal symptoms or postmenopausal symptoms related to aging such as bone density, lipids, cognition, or psychological issues including sleep, anxiety, and memory problems. Randomized, placebo-controlled trials were used when available, although open trials and comparison group studies were also used to gain as much information as possible. More detail on study design for each trial is outlined in the tables and text.

Black Cohosh (*Cimicifuga racemosa*)

Black cohosh is a perennial plant native to North America and a member of the buttercup family. Black cohosh has been traditionally used primarily by American Indians for a variety of "female complaints" including menstrual problems and childbirth. At the turn-of-the-last century, black cohosh was part of Lydia E. Pinkham's vegetable compound used by women to ease "all those painful complaints and weaknesses so common to our best female population".[18–20] Next to soy, black cohosh is the most widely studied botanical for menopausal symptoms.

Black cohosh contains triterpine glycosides, flavonoids, aromatic acids, and numerous other constituents[21] but the exact mechanism of action of this botanical has not been clearly understood. Some of the older studies have suggested an estrogenic activity, however, new studies show no effect on serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, sex hormone binding globulin (SHBG), and estradiol.[22] Three animal studies conducted using black cohosh extracts found no estrogenic increases in uterine weight, stimulation of vaginal cornification, or proliferation of the mammary gland or increases in prolactin, FSH, or LH.[23–25] Recent data from the University of Illinois at Chicago/National Institute of Health Center for Botanicals Dietary Supplements Research in Women's Health demonstrates that black cohosh does not have an estrogenic mechanism of action but rather acts on serotonin receptors and may relieve hot flashes and improve mood through a serotonergic effect.[26, 27]

Much of what is known about black cohosh is due to its use in Germany since the 1940's. There have been at least 12 clinical trials conducted related to menopause, and all but one showed positive results for relief of vasomotor symptoms. However, the methodology in some of these studies was weak and many were sponsored by the manufacturer. The majority of the studies have used a German brand of black cohosh known as Remifemin and consequently we have the most information in terms of safety and efficacy about this particular product.[28–31] Table 1 summarizes several of the clinical trials that have been performed on black cohosh. Overall, these studies show very promising results for relief of menopausal symptoms, primarily hot flashes and mood swings. The German health authorities (Commission E) have approved the use of 40 mg/day of black cohosh (the brand Remifemin) for 6 months for relief of menopausal symptoms, as well as for Premenstrual Syndrome (PMS) and dysmenorrhea.

Black cohosh has also been reported to have a positive safety profile when used for up to 6 months; however, in Germany, many women use this herbal remedy for longer periods of time with physician oversight. The most commonly reported side effects are mild gastric complaints, which tend to dissipate over time. High doses may cause headaches, vomiting, and dizziness. Black cohosh is contraindicated in pregnancy and lactating women.[36]

There have been no documented cases of drug interactions.[40] However, recently there have been three case reports of liver failure in women using black cohosh.[41–43] It is not clear what the contribution of black cohosh was, if any, in these cases; many questions remain about the

composition and purity of the products used, the multiple co-morbidities and other possible causes, the concomitant medications of the women using black cohosh, and an implausible mechanism of hepatotoxicity. Based on the evidence available from published liver-case reports it cannot be concluded that black cohosh was a cause.[22, 44, 45]

An abstract presented in July 2003 at the American Association for Cancer Research meeting raised concerns of increased metastases, but not incidence, of breast cancer in infected mice using black cohosh, however, no paper has been published or plausible mechanism of action presented.[46] This research was conducted on the "transgenic mouse model" which clearly is unsuitable to reflect the human physiological situation given tumor development in the mouse and human are different.[47] To the contrary, both in vitro investigations with breast cancer cells and in vivo data show no stimulation of estrogen-dependent mammary gland tumors with black cohosh.[22, 24, 29–31]

In fact, since black cohosh is not estrogenic, it has been suggested for relief of vasomotor symptoms for women with breast cancer who are prescribed tamoxifen. Three recent trials have provided somewhat mixed findings of efficacy. One 6-month study found a significant reduction in number and severity of hot flashes as compared to placebo (24% vs. 74%).[37] A pilot study of twenty-one postmenopausal women (13 patients had a history of breast cancer and 6 were using tamoxifen or raloxifene) reported a significant reduction in hot flashes as well as improvement in sleeping, fatigue levels and abnormal sweating.[39] However, a short term two-month clinical trial found that although black cohosh cohort had a significant decrease in sweating, there was no difference for other climacteric symptoms between the treatment and placebo groups.[38] This trial may have been too short to see the well known placebo effect diminish.

Black cohosh has not been studied for the long term health conditions associated with aging such as heart disease and osteoporosis, although one recent study compared the effects of black cohosh, conjugated estrogens, and placebo on menopausal symptoms as well as bone markers. The investigators found that black cohosh had an equivalent effect of conjugated estrogens on significantly improving both menopausal symptoms and bone markers compared to placebo.[32]

In summary, black cohosh shows great promise for relief of menopausal symptoms, primarily for treatment of vasomotor symptoms and depression with an overall positive safety profile for up to six months.

Soy/Isoflavones

Soy foods and supplements have been the subject of much interest for the reduction of menopausal symptoms because of their high concentrations of phytoestrogens (formononetin, biochanin A, daidzein, and genistein). The three main classes of phytoestrogens are isoflavones, lignans, and coumestans. The phytoestrogens found in soy/isoflavones are thought to possess estrogenic properties, although the mechanism of action is not fully understood. In a study by Teede et al, 50 women were randomized to consume either soy protein isolates (40 g soy protein and 118 mg isoflavone) or placebo, and then measures of hepatic proteins and gonaditropin concentrations were assessed. At the end of three months, there were no differences between the treatment and control group suggesting that soy/isoflavones do not affect in vivo biological indicators of estrogenicity and most likely act more like Selective Estrogen Receptor Modulators (SERMs) and as such may be safe for breast and endometrial tissue.[48]

Asian diets are high in soy based foods (40–80 mg per day of isoflavones in Asian diets as compared to <3 mg per day in American diets), and many women in these countries express

few menopausal complaints.[49] It is unknown if the lower prevalence of hot flashes and other menopausal symptoms are due to dietary make-up, cultural factors, or a combination of both.[50]

Although soy is the most heavily studied plant/food for alleviation of menopausal symptoms, to date, data from clinical trials have not provided a clear answer to the role of soy in reducing menopausal symptoms. It is also difficult to compare these trials since product, dose, formulation (dietary or capsule), and length of use vary across studies. A recent review of the evidence for the treatment of menopausal symptoms suggests that phytoestrogens available as soy foods and soy extracts do not improve hot flashes or other menopausal symptoms.[51] A review of the data from the more rigorous trials shows, at best, only minimal effects on hot flashes.

The most promising news for soy may be its positive effect on lipid profiles. A meta-analysis of 38 controlled human studies of soy consumption provides compelling evidence for its positive effect on improved lipid profiles including reduction in low density lipid (LDL) and triglycerides and an increase in high density lipid (HDL) levels.[61, 62] The FDA has approved a health claim for isoflavone rich soy protein to reduce cholesterol with 25 g of soy protein consumption daily.[63] However, it is important to note that it appears to require that soy isoflavones are consumed intact in soy protein.[64]

The bone data, although not nearly as strong as lipid data, holds some promise. Animal studies show consistent bone conserving effects or improvement in bone mineral density (BMD). The human studies are mixed showing some modest yet significant gains in BMD and bone mineral content.[65–70] However, a recent study in which 25g of soy protein was substituted for meat in the diet showed no improvement of calcium retention, cardiovascular, or bone health indicators in postmenopausal women.[71] Studies of soy in targeted populations, such as postmenopausal Chinese women with lower bone mass, have shown a greater effect on increasing bone mineral content for women consuming a high dose of soy extract compared to placebo.[70]

Studies of improved cognitive function have shown inconsistent results. The SOPHIA study, found significant improvement on category fluency (verbal memory) compared to placebo with a pattern of improvement (although not significant) on other tests of verbal memory, tracking and attention.[72] These results are similar to the effects seen of estrogen on cognition. However, a recently published long term study of the effect of soy protein containing isoflavones on cognitive function, BMD, and plasma lipids showed no difference from placebo after 1-year.[73]

The research on soy and breast and endometrial cancer is interesting. Animal studies show compelling evidence of 25–50% fewer tumors than controls.[74] Human studies are mixed but suggest a protective effect of soy on breast tissue, and case-control studies in Asian countries show decreased rates of breast cancer.[75–77] It is interesting to note, however, that when Japanese women move to the US, the cancer risk increases. The presumed protective effect of isoflavones may be a combination of several factors including the consumption of soy early in life, a low fat and high fiber diet, as well as a less sedentary lifestyle.

One paper which presents research on soy and red clover using breast cancer cells demonstrates different action patterns with soy/red clover exhibiting estrogen-agonistic activities in the absence of estradiol and antagonistic effects in estradiol which induced cell proliferation. This may suggest a different treatment strategy for perimenopausal women (with higher levels of estradiol) and postmenopausal women (with lower levels of estradiol).[78]

Similarly, the studies examining the effect of soy on the endometrium have shown no negative effects without any increased risk of endometrial cancer.[79] In fact, one case-control study showed higher consumption of isoflavones in the diet was linked to reduced risk for endometrial cancer.[80]

Although data on the effects of soy/isoflavones for menopausal symptoms is minimal at best, considering the cardiovascular benefits as well as the potential beneficial effects on bone and possibly cognition, it would seems that soy in the diet of peri and postmenopausal women, not withstanding a soy allergy, is beneficial.[63]

Red clover (*Trifolium pretense*)

Red clover was traditionally valued as an antispasmodic[81–83] and an anticancer treatment, not an estrogenic agent. Red clover and soy share similar but distinct chemical profiles--both contain genistein, daidzein, formononetin, and biochanin A, but red clover has significantly higher levels of the *O*-methylated isoflavones, formononetin and biochanin A.[84–85] It is these isoflavonoid and coumestan components believed responsible for estrogen-like effects. One of the most commonly used red clover products is Promensil, a red clover derivative with concentrated levels of isoflavones (each 500mg tablet contains 40mg isoflavones).

Red clover's use for menopausal symptoms is fairly recent, and similar to soy products, most studies show at best a minimal effect for relief of hot flashes with three of four clinical trials showing no significant difference from placebo. Given its similarity to soy this is not surprising. The Isoflavone Clover Extract (ICE) Study[86] compared two doses of red clover (Promensil 82 mg or Rimostol 57 mg) against placebo and found decreased frequency in hot flashes across all three groups, although the Promensil group received significant relief faster than the other two groups. One possible limitation of this study, as with many of the other botanical studies, is that it lasted for only three months, just about the time one would expect to see the placebo effect begin to wane. The previously mentioned Krebs review of evidence for the treatment of menopausal symptoms also suggests that phytoestrogens available as red clover extracts do not improve hot flashes or other menopausal symptoms.[51] Table 3 summarizes several studies on red clover.

Similar to soy, red clover has been suggested as a preventative treatment for osteoporosis, lipid profiles, and possibly cognition, although once again the evidence is limited. Two clinical trials showed modest effects for improvement in BMD compared to placebo. In one study while all women lost BMD, those taking red clover lost significantly less than the placebo group and the authors also noted there were no differences in mammographic breast density between the two groups. In another RCT, women in the red clover group had increased bone mineral density in proximal radius and ulna only.[89–90]

Three of the four trials that have been published examining the effects of red clover on blood lipid levels showed no improvement in lipid profiles,[91–93] and the fourth study showed a significant increase in HDL only compared to placebo.[90]

There is disappointing evidence for the use of red clover to relieve menopausal symptoms, however similar to soy/isoflavones, it remains to be seen if it will have uses for age related health concerns such as osteoporosis, heart disease, and cognition. Red clover has a positive safety profile, appears not to negatively affect the endometrium with few adverse events reported in published literature.[94] The side effects reported are mild and include headache, myalgia, and nausea.[86]

Other commonly used botanicals

Many other botanicals are commonly used for menopause including chastetree (*Vitex Agnus Castus*), hops (*Humulus lupulus*), dong quai (*Angelica sinensis*), evening primrose (*Oenothera biennis*), Ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), kava (*Piper methysticum*), valerian (*Valeriana officinalis*), licorice root (*Glycyrrhiza glabra*), motherwort (*Leonurus cardiaca*), St. John's Wort (*Hypericum perforatum*), lemon balm (*Melissa officinalis*) and wild yam (*Dioscorea villosa*). There is very little data available on the efficacy and safety of many of these compounds. Table 4 summarizes the available data on some of the randomized trials that have been conducted on these botanicals for menopausal women in particular. However, much of the research that does exist has been conducted on non-menopausal populations and the findings related to sleep, anxiety, and mood have been extrapolated to the menopausal experience, which may not be valid.

Many of the aforementioned botanicals are not used alone but rather in combination with other supplements in the form of a multibotanical, of which there is even less science to support efficacy and safety. For example, licorice is often used as part of a multibotanical formulation and is thought to be useful for PMS, but is largely unstudied in menopause. It is worth mentioning because large doses have been associated with congestive heart failure using as little as 500mg/day for 7 days. Most menopausal remedies contain 75 mg of licorice and if taken 2–3 times per day, this amounts to 150–225 mg of licorice a day.[103]

Overall, dong quai is one of the most commonly prescribed Chinese herbs for problems unique to women and has been traditionally known as "a female tonic." Traditional systems of medicine and folk medicine have used dong quai for a variety of complaints including abnormal menstruation and menopausal symptoms.[104] Merck introduced the herb to the Western world in 1899 under the trade name Eumenol®, as a product that was said to positively affect menstrual disorders. There is debate as to whether there is any estrogenic activity in dong quai as human studies do not support any estrogenic mechanism of action. Little research has been conducted on dong quai for menopausal symptoms. The one RCT of 71 women with hot flashes showed no difference from placebo in menopausal symptoms (hot flashes, vaginal dryness) and there was no sign of estrogen-like stimulation of uterine lining in either group.[95] Taken alone, dong quai does not appear to be beneficial for menopausal hot flashes; however, it is mostly used in multibotanical formulations and is still considered to be a valuable female tonic by herbalists around the world.

Botanicals commonly used for PMS and early menopausal symptoms

Some of the more commonly used botanicals for PMS and early menopausal symptoms are chastetree/Vitex, wild yam and evening primrose. Chastetree/Vitex is often recommended for women in early menopause experiencing irregular menstrual cycles and has been approved by German health authorities for PMS, breast tenderness, and irregularities in the menstrual cycle.[105] The progesterone like effect of Vitex has been verified by endometrial biopsy, analysis of blood hormone levels, and examination of vaginal secretions.[106] Chastree/Vitex is often found in combination with black cohosh and other herbs. The majority of research has been limited to PMS and breast tenderness (mastalgia) and very little is known about the efficacy related to menopausal symptoms. In a study performed in peri and postmenopausal women, participants applied 2.5 ml of lotion (a 1.5% solution of essential oil) on the skin, one time per day 5–7 days per week for 7 months and reported improvement in emotional problems and hot flashes, although the study had no placebo or comparison group.[102]

Wild yam was formerly referred to as "colic root" and has been promoted as effective for gastrointestinal irritation and spasm. Historically, it was also used for menstrual cramps and postpartum pain. Despite promotional claims, wild yam does not convert to a progesterone

when taken internally or applied topically. One RCT of topical wild yam extract cream versus placebo showed no difference in alleviation of menopausal symptoms or serum/salivary hormone levels.[96] Though popular for menopause, there is no contemporary or historical evidence of benefit.

Evening primrose contains gamolenic acid which is believed to reduce vasomotor symptoms of menopause.[107] There has only been one RCT of evening primrose for menopausal symptoms which randomized 56 women to either 500mg of evening primrose oil or placebo for six months. The investigators found no differences in the reduction of hot flashes between the two groups.[97]

Botanicals commonly used for sleep, anxiety, memory and mood disorders

A number of botanicals products have been recommended for many of the problems associated with menopause and aging such as sleep disturbances, nervousness, depression, mood swings, and memory loss (e.g., ginkgo, hops, motherwort, ginseng, valerian, kava, and St. John's wort), although, most of these products have not been tested specifically on menopausal women.

Ginkgo biloba has been promoted as having an effect on the vascular system by improving blood flow and has been used for Raynauds Syndrome (cold hands and feet).[108–110] It has been approved by the German Commission E for cerebral insufficiency, vertigo and tinnitus, and peripheral vascular disease.[111] Ginkgo works primarily by increasing blood flow to the brain, increasing uptake of glucose by brain cells and improving transmission of nerve signals.[109] Studies related to improved memory are promising.[112–114] There have been 40 clinical trials conducted examining the effect of ginkgo on cognition, particular difficulty concentrating and memory. Eight were of good quality and seven showed a positive effect. Some studies have even shown a positive effect for adults with dementia.[115]

The German Commission E has approved hops for mood disturbances such as anxiety and restlessness and sleep disturbance.[116] Hops extracts bind to the estrogen receptor in molecular assays and animal models have shown hops to have an estrogenic effect on the uterus, however the data is inconsistent.[28, 117] Its estrogenic effects have been shown to be due to prenylflavonoids, a class of nonsteroidal phytoestrogens. Because of its estrogenic actions it may be effective for menopausal symptoms such as hot flashes; however, it does not appear to exert SERM-like selectivity so it may have uterotrophic effects in postmenopausal women.[118] More research on the effect of hops on menopause is needed to determine if it safe and effective.

Ginseng is known as a traditional "tonic" herb that is reported to cope with stress, and boost immunity. The German Commission E lists its uses as "a tonic for invigoration and fortification in times of fatigue and debility and for declining capacity for work and concentration".[119] An RCT found that 30 days of therapy with Korean red ginseng reduced fatigue, insomnia, and depression in 12 postmenopausal women experiencing symptoms and also found that the cortisol/DHEA-S ratio decreased significantly over this time period.[98] Several other studies have showed no estrogenic effects, no improvement in vasomotor symptoms, but improvement in somatic complaints (fatigue, insomnia, depression) and a very favorable effect on depression and well-being health subscales compared with placebo.[99, 107] Because of increased breast cell proliferation *in vitro*, its use may not be advisable in the presence of breast cancer, although more research on ginseng's effects on breast cells *in vivo* is needed to know its true safety.[120]

Kava is a South Pacific herb used medicinally and socially and data suggest efficacy for treatment of anxiety.[121] Two trials evaluating kava's effect on menopausal symptoms showed significant improvement in irritability and insomnia compared with placebo.[100] However, there are a number of safety issues related to kava. The sale of kava has been banned in Canada,

Australia, and several European countries because of potential hepatotoxicity, although the exact mechanism of harm is not well understood. The stem peelings may contain a toxic alkaloid. In response to reports of hepatotoxicity that may be associated with kava, the FDA, American Botanical Council, and various industry trade organizations have advised consumers of rare but potential risks of severe liver injury associated with the use of kava containing preparations.[122] Extreme caution should be exercised if kava is used, limiting duration of use to 6–8 weeks and it is best to avoid this botanical completely. It is certainly not advised for those taking hepatotoxic medications, consuming excess alcohol, or with liver problems.

Motherwort is another botanical historically revered as a calmative agent for the heart, especially palpitations.[123] The German Commission E has approved its use for nervous cardiac disorders and as an adjuvant for thyroid hyperfunction.[124] It is also found in many menopausal formula for women experiencing this symptom and was typically combined with black cohosh as a “superior antispasmodic and nervine,” however, contemporary research is lacking on efficacy and safety.

Valerian has been used for centuries by Greeks, Romans, Chinese, Europeans, and American Indians. In the 20th century, it has been approved by the German Commission E for “states of unrest and nervous sleep disturbances.”[125] Three RCTs have been conducted that have shown improved subjective sleep quality, although none of the studies were conducted with menopausal women.[126–128] There have been no reported drug interactions; side effects, such as nausea, headache, dizziness, and upset stomach, have been reported in less than ten percent of subjects in RCTs.[129]

St. John’s wort is one of the most heavily studied botanicals for treatment of depression. The vast majority of studies have been conducted on non-menopausal populations. In thirty-seven out of thirty-nine clinical trials the herb has been shown to be superior to placebo or equivalent to antidepressant medications (61–75% improvement in mild-moderate depression) with minimal side effects as compared to some of the antidepressants.[130] A recent meta-analysis of St. John’s wort for depression found that trials restricted to subjects with major depression found only minor improvements compared to placebo; however, other trials of patients with mild to moderate depression have shown beneficial effects similar to standard antidepressants.[131] One non-placebo controlled clinical trial conducted in women experiencing climacteric symptoms found that 900 mg of St. Johns wort taken for 12 weeks, significantly improved psychological and psychosomatic symptoms and sexual well-being.[101]

St. John’s wort is often combined with black cohosh for treatment of menopausal symptoms (hot flashes, irritability, minor depression, mood swings, and insomnia). A multi-center non-placebo-controlled clinical trial of 911 pre, peri and postmenopausal women with psychovegatative disorders demonstrated a synergistic effect of this combination of botanicals.[132] The adverse herb-drug interactions are well documented. St. John’s wort can interact with anticoagulants, cyclosporine, digoxin, and protease inhibitors used for HIV, specifically decreasing blood concentrations of these drugs. In addition, women using oral contraceptives have reported breakthrough bleeding and in some cases, unplanned pregnancies.[133]

Discussion and Future Directions

Although there have been a number of observational and epidemiologic studies conducted for relief of menopausal symptoms, there is a continued need for further research on the effectiveness and long term safety of botanicals and dietary supplements. A growing body of scientific literature suggests that incorporation of some form of alternative therapy could result in improved clinical outcomes.[134, 135]

Of the botanicals reviewed in this paper, based on the evidence, black cohosh appears to be the most effective herb for relief of menopausal symptoms, primarily hot flashes and possibly mood disorders. Phytoestrogen extracts, including soy foods and red clover appear to have at best only minimal effect on menopausal symptoms but have positive health effects on plasma lipid concentrations and may reduce heart disease. St. John's wort has been shown to improve mild to moderate depressive symptoms, but not major depression, in the general population.[130–131] It appears to show efficacy for mood disorders related to the menopausal transition, although more research should be done in the menopausal population, especially for the combination of St. John's wort and black cohosh. The other commonly used botanicals discussed in this paper have limited evidence to demonstrate safety and efficacy for relief of symptoms related to menopause.

Whatever decision menopausal women chose to make related to use of botanicals for relief of menopausal symptoms as well as to promote long term health, it is critical to discuss these issues with their health care providers so they can assist them in managing these alternative therapies through an evidence-based approach.

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Table 1

Studies of Black Cohosh (*Cimifuga racemosa*)

Menopausal symptoms **Reference**	**Study Design**	**# of Participants**	**Dosage**	**Duration**	**Results**
Wuttke et al, 2003 [32]	RCT with 3 groups: Black Cohosh (BC), conjugated estrogen (CE), and placebo	62 postmenopausal women	BC: 40 mg CE: 0.6 mg	3 months	BC showed a significant reduction in symptoms compared to placebo, equivalent effect of CE.
Liske et al, 2002 [33]	RCT with 2 groups: Standard (S) and High (H) dose of Remifemin	152 peri and postmenopausal women	S: 39 mg H: 127.3 mg	24 weeks	Found decrease of Kupperman-Menopause index (KPI) for both groups, no difference between standard and high dose.
Duker et al, 1991 [34]	Placebo-controlled trial	110 women with menopausal complaints	Remifemin: dosage not reported	8 weeks	Significant reduction in LH levels compared to placebo, no significant change in FSH was observed
Lehmann- Willenbrock & Riedel, 1988 [35]	Randomized comparison group study: Estriol (E), conjugated estrogen (CE), estrogen-gestagen (EG), Remifemin (R)	60 women with hysterectomies and climacteric symptoms	E: 1 mg/day CE: 1.25 mg/day EG: 1 tablet/day Trisequens ® R: 48–140mg/day	6 months	Remifemin produced a decline in KPI no significant differences were observed among treatment groups.
Petho, 1987 [36]	Open trial	70 women changing from hormone injections to black cohosh.	Remifemin 48–140 mg/day	6 months	After 2 months, significant improvement in mean menopausal index, 82% reported black cohosh preparation good or very good for relief of menopausal complaints
Warnecke, 1985 [36]	Open trial with 3 groups groups: Remifemin (R), Conjugated estrogens (CE), or Diazepam (D)	60 women with menopausal complaints	R: 48–140mg/day CE: 0.6 mg/day D: 2 mg/day	12 weeks	Remifemin and CE showed vaginal cytology changes, improvements in hot flashes and psychological symptoms in all three groups.
Geller, ongoing UIC	RCT with 4 groups: black cohosh (BC), red clover (RC), HRT, and placebo	72 planned, 41 randomized	BC: 128 mg/day RC: 120 mg/day HRT: Prempro ®	1 year	No data yet, ongoing clinical trial.
Kronenberg, ongoing Columbia	RCT with 2 groups: black cohosh v. placebo	unknown	BC: 80 mg/day	1 year	No data yet, ongoing clinical trial.
Vasomotor symptoms in breast cancer survivors					
Reference	Study Design	# of Participants	Dosage	Duration	Results
Hernandez Munoz & Pluchino, 2003 [37]	2 arm randomized trial, open label: Group 1—Tamoxifen only, Group 2—Tamoxifen + black cohosh	136 breast cancer survivors, perimenopausal	Tamoxifen: 20 mg/day BC: 40 mg/day	6 months	Group taking combination therapy experienced significantly less severe hot flashes vs. group on tamoxifen only (24% vs. 74%)
Jacobson et al, 2001 [38]	RCT: Placebo and black cohosh, stratified on tamoxifen use	85 breast cancer survivors experiencing daily hot flashes	BC: 40 mg/day	2 months	Black cohosh and placebo both reduced number and intensity of hot flashes during the study. There was no significant difference between BC and P.
Pockaj et al, 2004 [39]	Open trial	21 postmenopausal women, 13 w/ history of breast cancer	Remifemin: dosage not reported	4 weeks	Significant reduction from baseline in hot flashes and improvement in sleeping, fatigue levels, and abnormal sweating.

RCT=Randomized-controlled trial (double-blind, placebo controlled)

Prempro=0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone acetate

Table 2

Studies of soy/isoflavones

Menopausal symptoms Reference	Study Design	# of Participants	Dosage/form	Duration	Results
Albertazzi et al, 1998 [52]	Multicenter RCT: placebo vs. soy protein	104 postmenopausal women	Soy protein isolate: 60 g daily	12 weeks	Significant 15% reduction in hot flashes for soy group compared to placebo
Washburn et al, 1999 [53]	RCT, crossover trial: placebo vs. soy protein	51 women with vasomotor symptoms	Soy protein: 20 g with 34 mg phytoestrogens	6 weeks	Significant reduction in severity of vasomotor symptoms compared to carbohydrate placebo.
Upmalis et al, 2000 [54]	Multicenter RCT: placebo vs. isoflavone extract	177 postmenopausal women with hot flashes	Soy isoflavone extract: 50 mg	12 weeks	Marginally significant (p=.08) reduction in hot flashes.
Faure et al, 2000 [55]	Multicenter RCT: placebo vs. isoflavone extract	75 postmenopausal patients with hot flashes	Soy isoflavone extract: 70 mg genistein and diadzein	16 weeks	Significantly reduced hot flashes 40% more than placebo over the course of the trial.
Crisafulli et al, 2004 [56]	RCT with 3 groups: (1) isoflavone, (2) estrogen/ progestin therapy (3) placebo	90 postmenopausal women	Genistein: 54 mg/day	1 year	Genistein significantly reduced hot flashes by 24% after 1 year compared to placebo. Estrogen/progestin therapy significantly reduced hot flashes compared to placebo and genistein.
Van Patten et al, 2002 [57]	RCT: stratified by tamoxifen use Soy vs. placebo beverages	123 postmenopausal women with hot flashes previously treated for breast cancer	Soy beverage with 90 mg isoflavones, Placebo: rice beverage	12 weeks	No significant difference in number or severity of hot flashes between rice beverage and soy beverage groups.
Secreto et al, 2004 [58]	RCT with 4 groups: (1) soy isoflavones (2) melatonin (3) soy+melatonin (4) placebo	232 postmenopausal women	Isoflavone supplement: 80mg	3 months	No significant difference in reduction of hot flashes between placebo, isoflavone only, melatonin only, and isoflavone+melatonin.
Murkies, 1995 [59]	Randomized trial of soy vs. wheat flour supplement to usual diet	58 postmenopausal women with hot flushes	Soy flour	12 weeks	Both groups had significantly decreased hot flushes compared to baseline, soy did not decrease hot flushes significantly more than wheat.
Burke, 2003[60]	Randomized, double-blind trial. 3 preparations of soy: (1) without isoflavones (2) 42 mg isoflavones/day—LO (3) 58 mg isoflavones/day—HI	241 women with vasomotor symptoms	Soy Protein: 25g daily-3 preparations with varying levels of isoflavones	2 years	All groups had significantly reduced hot flashes compared to baseline. No significant differences in hot flashes were observed between the groups.

RCT=Randomized-controlled trial (double-blind, placebo controlled)

Table 3

Studies of Red Clover (*Trifolium pratense*)

Menopausal symptoms Reference	Study Design	# of Participants	Dosage	Duration	Results
Knight et al, 1999 [61]	RCT, 3 groups: placebo, low dose & high dose red clover	37 postmenopausal women	Low: 40 mg/day High: 160 mg/day	12 weeks	No significant differences in incidence of hot flushes between the three groups.
Tice et al, 2003 [86]	RCT, 3 groups: placebo, Promensil, Rimostil	252 postmenopausal women with >35 hot flashes a week	Promensil: 82 mg/day Rimostil: 57 mg/day	12 weeks	All 3 groups decreased frequency of hot flashes, no significant differences between groups.
Van de Weijer, 2001 [87]	RCT: Placebo and Red Clover (Promensil)	30 postmenopausal women	Promensil: 30 mg/day	16 weeks	Decreased hot flashes and other menopausal symptoms
Baber et al, 1999 [88]	Cross-over design trial: 12 weeks placebo or red clover, 1 month washout, 14 weeks alternate treatment.	51 postmenopausal women	40 mg/day red clover	12 or 14 weeks of treatment	No difference between treatment and placebo group in reduction of hot flashes.
Geller, ongoing	RCT with 4 groups: black cohosh (BC), red clover (RC), HRT, and placebo	72 planned, 41 randomized	BC: 128 mg/day RC: 120 mg/day HRT: Prempro ®	1 year	No data yet, ongoing clinical trial.
Bone Density Reference	Study Design	# of Participants	Dosage	Duration	Results
Atkinson et al, 2004 [89]	RCT: Placebo and Red clover isoflavone supplement	205 women aged 49– 65	Red clover: 56 mg/day	1 year	All women lost bone mineral density, but red clover group lost significantly less. No differences between 2 groups in mammographic density.
Clifton-Bligh et al, 2001 [90]	RCT, 3 groups: placebo & low, medium, and high dose of Rimostil (red clover extract)	46 postmenopausal women	L: 28.5 mg/day M: 57 mg/day H: 85.5 mg/day	6 months	Response to low dose not significant. Significant increase in BMD of proximal radius and ulna for medium and high dose groups.
Lipids Reference	Study Design	# of Participants	Dosage	Duration	Results
Blakesmith et al, 2003 [91]	RCT: Placebo and Red clover isoflavone supplement	25 premenopausal women	Red clover: 86 mg/day	12 weeks	No significant changes in blood lipid levels
Clifton-Bligh et al, 2001 [90]	RCT, 3 groups: placebo & low, medium, and high dose of Rimostil (red clover extract)	46 postmenopausal women	L: 28.5 mg/day M: 57 mg/day H: 85.5 mg/day	6 months	HDL increased significantly for all three treatment groups. There was no dose response effect.
Howes et al, 2000 [92]	RCT: placebo or isoflavone in increasing doses, low isoflavone diet	75 postmenopausal women with elevated cholesterol	4 weeks: 43 mg/day 4 weeks: 86 mg/day	12 weeks	No changes in lipid levels

Menopausal symptoms Reference	Study Design	# of Participants	Dosage	Duration	Results
Nestel et al, 1999 93	RCT: placebo or isoflavone in increasing doses	17 postmenopausal women	5 weeks: 40 mg/day 5 weeks: 80 mg/day	14 weeks (treat + run-in)	No changes in lipids, improved arterial compliance.

RCT=Randomized-controlled trial (double-blind, placebo controlled)

Table 4

Studies of Other Botanicals

Menopausal symptoms Reference	Drug/ Dosage	Study Design	# of Participants	Duration	Results
Hirata et al, 1997 [95]	**Dong quai root**: 4.5 g. daily	RCT: dong quai vs. placebo	71 postmenopausal women	24 weeks	Hot flash incidence decreased in dong quai group, compared to placebo, effect not significant.
Komesaroff et al, 2001 [96]	**Wild yam cream**	Double-blind, placebo-controlled, cross-over study	23 postmenopausal women	3 months	No changes in FSH, estradiol, progesterone, or hot flashes.
Chenoy et al, 1994 [97]	**Evening primrose oil**: 500 mg daily	RCT: evening primrose oil vs. liquid paraffin	56 women with 3 or more hot flashes a day	6 months	No differences in hot flash frequency between the two groups.
Tode et al, 1999 [98]	**Korean red ginseng**: 6 g daily	Non-placebo controlled trial	12 women with climacteric symptoms	30 days	Red ginseng improved fatigue, insomnia and depression. Cortisol/DHEA-S ratio was significantly decreased.
Wiklund et al, 1999 [99]	**Ginseng**: 100 mg daily	Multicenter RCT: ginseng extract vs. placebo	384 postmenopausal women	14 weeks	No benefit of ginseng over placebo in reduction of hot flashes.
Warnecke 1991 [100]	**Kava extract**: 100 mg, 3 X daily	RCT: kava vs. placebo	40 women with climacteric symptoms	8 weeks	Significant improvement in Kupperman index and HAMA anxiety score.
Grube et al, 1999 [101]	**St. John's wort**: 900 mg daily	Non-placebo controlled trial	111 women with climacteric symptoms	12 weeks	Significant improvement in psychological and psychosomatic symptoms of menopause. Improvement in sexual well-being
Lucks, 2003 [102]	**Vitex agnus castus oil**: 2.5 ml dermally	Survey of volunteers, no comparison group	52 peri- and postmenopausal women	3 months	33% reported major improvement in troublesome symptoms, most often emotional problems and hot flashes.

RCT=Randomized-controlled trial (double-blind, placebo controlled)