

# Review of Black Cohosh, Adaptogens, and Genistein for the Treatment of Symptoms in Menopausal Patients

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## Abstract

The increase in complementary and alternative (CAM) therapies to manage menopausal symptoms in the wake of publicity about hormone replacement therapy risks has caused several ingredients, notably black cohosh, genistein (a non-soy isoflavone), and adaptogens, to be considered in the medical literature as possible remedies. Despite the growing body of CAM-oriented clinical trials in the literature, evaluating CAM studies can be challenging owing to the heterogeneity of the studies. Nevertheless, there is growing evidence that black cohosh, genistein, and adaptogens are safe and may be effective at managing vasomotor symptoms (including hot flashes), psychological stress associated with menopause, insomnia and fatigue, and bone health without conferring cardiovascular risks. Given the excellent safety profiles of these agents and the lack of effective conventional alternatives, clinicians should consider them to address menopausal symptoms.

Key Words: Black cohosh, adaptogen, genistein, menopause, hot flash

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## Introduction

Although hormone replacement therapy (HRT) is approved by the US Food and Drug Administration (FDA) for treating symptoms in postmenopausal women, its use dropped from 91 million American users in 2001<sup>1</sup> (the year before the landmark Women's Health Initiative, or WHI, found HRT carried with it increased risk of breast cancer, stroke, and cardiovascular disease<sup>2</sup>) to 57 million users in 2003. Similar decreases were reported in Canada,<sup>3</sup> Europe,<sup>4</sup> and New Zealand.<sup>5</sup> In a survey of women on HRT (n = 185) pre- and post-release of the WHI report in 2002, about a third reported being "confused, scared, worried, or nervous" about the WHI findings.<sup>6</sup> Despite the decline in the use of HRT, in 2005, there was no appreciable increase in alternative medicine, that is, the use of black cohosh or soy (both 2.0% in 2004) to manage postmenopausal symptoms among those who discontinued HRT.<sup>7</sup> This suggests that many

women with menopausal symptoms today are receiving inadequate relief.

About 75% of menopausal women experience vasomotor symptoms,<sup>8</sup> the most common of which in North America is the hot flash.<sup>9</sup> About 60% of perimenopausal and menopausal women seek medical help to manage their vasomotor symptoms.<sup>10</sup> Other symptoms of menopause include night sweats, headaches, palpitations, arthralgia, myalgia, fatigue, paresthesia, vertigo, agitation, mood swings, irritability, depression, anxiety, insomnia, decreased libido, vaginal dryness, dyspareunia, urinary frequency, urinary incontinence, and joint pain.<sup>11</sup> It is not always clear if such symptoms are specifically related to menopause or are a sign of advancing age or other conditions.

While symptomatic menopausal women actively seek out medical care (women outspend men on healthcare



**Figure 1.** Black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*) has been a mainstay of North American herbal medicine since the times of Native American healers.

by the greatest differential during the age span from 45 to 64 years<sup>12</sup>), there are currently few real options. HRT is risky; lifestyle modifications are not always effective. Complementary and alternative medicine (CAM) holds promise for offering symptomatic relief with low risk. Currently, about 22% of women between the ages of 45 and 65 years are using some form of CAM to manage menopausal symptoms.<sup>13</sup> Although there is no evidence that CAM has bridged the gap in managing under-treated menopausal symptoms to date, American women generally are favorably disposed to CAM in that they (48.9%) are more likely than men (37.8%) to use CAM.<sup>14</sup>

Some of the main substances currently used in CAM products to address menopausal symptoms include black cohosh, adaptogens, and genistein (a non-soy isoflavone). These substances are available as supplements and in different multi-ingredient formulations,

such as a beverage product (GEM Keep it cool, Beveragette Ventures, LLC, Sammamish, Washington). These key ingredients are reviewed herein with respect to their ability to help women manage menopausal symptoms.

## **Black Cohosh**

Black cohosh is a North American perennial plant (known as both *Actaea racemosa* and *Cimicifuga racemosa*) with strong associations to Native American medicine<sup>15</sup> (Figure 1). Related to the buttercup, the plants are unattractive to insects, which accounts for some of its early American names: bugbane, snakeroot, bugwort, rattleroot, and macrotys. Historically, black cohosh was used in the treatment of malaise, gynecological ailments, kidney disorders, malaria, rheumatism, sore throats, colds, constipation, hives, and to induce lactation. In 19th century America, black cohosh was widely used as a home remedy for treating fever and menstrual discomfort. The herb grows wild but is increasingly cultivated.

The active ingredients in black cohosh are thought to be terpenes and glycosides.<sup>16</sup> Black cohosh was thought to activate estrogen receptors, but this belief has been largely discounted<sup>17</sup> since it appears to have no effect on serum levels of luteinizing hormone, follicle-stimulating hormone, prolactin, sex hormone-binding globulin, and estradiol.<sup>18</sup> It may have activity at serotonin receptors.<sup>19</sup> It is believed to act on the CYP3A4 substrate, which means that it has the potential to interact with other drugs.<sup>20</sup> It is marketed in many formulations, the most frequently studied of which is the 20 mg tablet (Remifemin®, Schaper & Bruemmer GmbH & Co, Salzgitter, Germany).

## **Adaptogens**

Herbalists apply the term adaptogen to any of several natural plants that raise non-specific resistance toward multiple and diverse stressors (including chemical, biological, and physical) in such a way that helps the patient withstand and adapt to the stress and normalizes overall physiologic function. Known since ancient times, early Chinese medicine referred to these plants as “kingly herbs.” By the late 1950s, Soviet scientists defined adaptogen as any substance that exerts effects on both the sick and well by “correcting” dysfunction(s) without producing side effects.<sup>21</sup> Many plants, including holy basil, ginseng, licorice, reishi, Chaga mushrooms, and others, are thought to have adaptogenic actions.<sup>22</sup>

Adaptogens have been shown to make the body’s natural response to stress less damaging to the body by reducing most signs of the “alarm stage” of the stress

response and delaying or avoiding the exhaustion stage. Adaptogens also may help the body burn fuel more efficiently, promoting energy and well-being.<sup>23</sup>

### Genistein

The relatively low rate of hot flashes among menopausal women in Japan<sup>24</sup> and their good bone metabolism<sup>25,26</sup> have led to several studies that the region's greater soy consumption may play a role in modulating these specific symptoms. Soy foods contain isoflavones, naturally occurring polyphenols with antioxidant properties, many of which act as phytoestrogens, among other actions.<sup>27</sup> The main isoflavones in the soybean include genistein and daidzein and their glycosides (genistin and daidzin).<sup>28</sup> Genistein composes 50% or more of the isoflavones in soybeans and soy foods<sup>29</sup> and has been extensively studied. The literature reports that genistein has anticarcinogenic<sup>30-32</sup> and estrogenic<sup>33</sup> properties. Indeed, its structural similarity to estrogen (estradiol)<sup>34</sup> has been thought to allow it to act as an agonist at estrogen receptor sites<sup>35,36</sup> (Figure 2). These estrogenic properties have raised concern about the safety of genistein in menopausal women. Genistein was found to be safe in animal tests<sup>37</sup> but at high doses could be called a developmental toxicant in a multigenerational study of rats.<sup>38</sup> However, the experimental animal data refers to pure genistein in doses of about 200 mg/d. Despite limited human studies on exposure to pure genistein, a toxicology review of genistein found that adults would be unlikely to consume sufficient amounts of genistein to run the risk of harm.<sup>39</sup>

### Studies of Menopausal Symptom Relief Involving Black Cohosh, Adaptogens, and Genistein

Medically, menopause is a complex time. The cessation of menses provokes specific symptoms, including vasomotor symptoms (including the frequently reported hot flash), anxiety, irritability, and sleep disturbances, among others.<sup>40</sup> With menopause come other physiological changes including bone loss and cardiovascular deficits. Of particular concern to women who find relief with estrogen-based therapy is the potentially elevated risk for breast cancer. The authors reviewed the literature to look specifically at 3 compounds (black cohosh, adaptogens, and genistein) with regard to these specific areas of concern: vasomotor symptoms, psychological symptoms, insomnia, bone loss, cardiovascular health, and risks involving breast cancer.

**Vasomotor symptoms, including hot flashes.** The hot flash, also known as the hot flush, describes a spontaneous sensation of warmth that may be accompanied by perspiration, tachycardia, and anxiety. Skin on the face, neck, and upper body may visibly redden, owing to

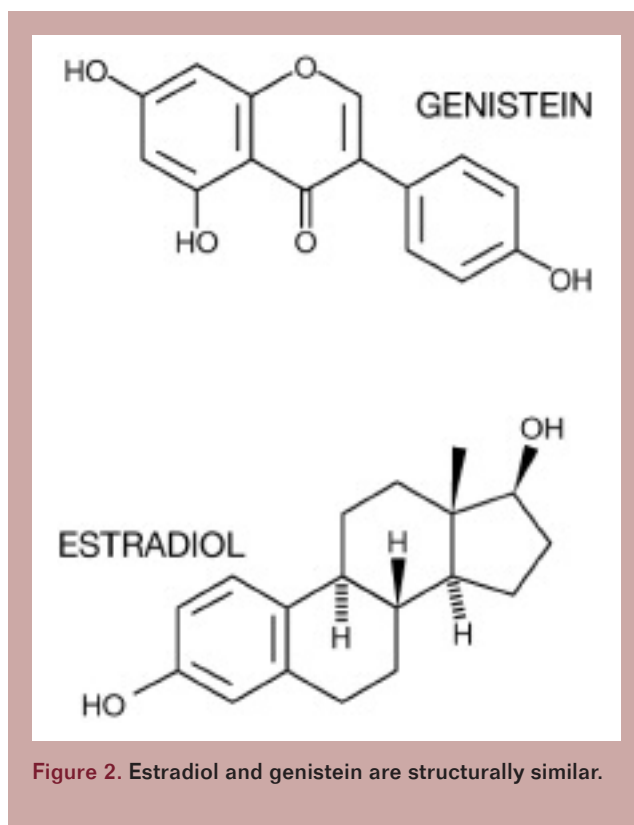
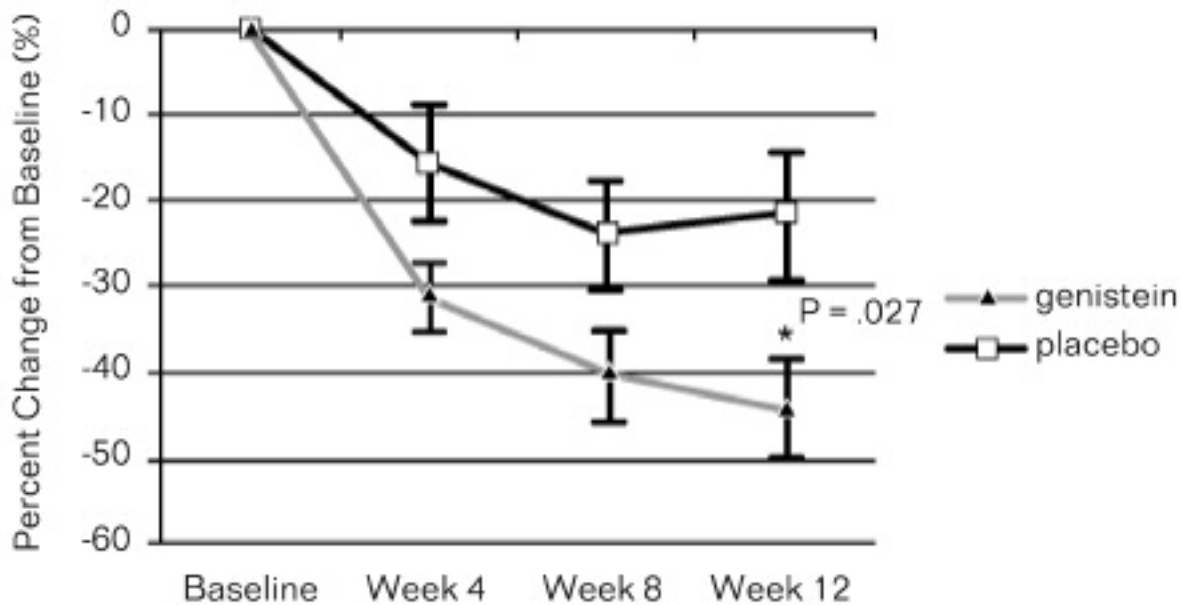


Figure 2. Estradiol and genistein are structurally similar.

increased peripheral vasodilation, blood flow, and skin temperature. Hot flashes are a vasomotor response to the declining levels of estrogen in the body, although the exact process is unclear. It is thought that dwindling estrogen enhances the release of norepinephrine and serotonin, which, in turn, could reduce the body's set point for thermoregulation.<sup>41</sup> Interestingly, the prevalence of hot flashes during menopause varies by geography. Western women report the hot flash as the most common menopausal symptom,<sup>42</sup> and 60% state that hot flashes negatively impact their quality of life.<sup>43</sup>

**Black cohosh.** Black cohosh does not appear to have an estrogenic mechanism of action but seems to work on serotonin receptors. Most studies of black cohosh in the literature are based on a commercial product introduced in Germany in the 1940s and available globally today (Remifemin).<sup>44</sup> In Germany, 40 mg/d black cohosh is approved for up to 6 months for relief of menopausal symptoms<sup>45</sup> but has been used under physician supervision for considerably longer periods of time.<sup>46</sup> The North American Menopause Society (NAMS) states that menopausal women whose vasomotor symptoms are not controlled by lifestyle modifications may consider an herbal remedy, including black cohosh.<sup>47</sup>

In reviews of the literature, black cohosh generally appears to be cited as one of the most effective herbal



**Figure 3.** Patients on a synthetic formulation of genistein showed a significant 44% reduction in average number of hot flashes at 12 weeks ( $P = .027$ ).

treatments for vasomotor symptoms of menopause,<sup>16,48,49</sup> although not all studies yield significant results favoring black cohosh over placebo.<sup>20,50-52</sup> In 3 studies that used a known comparator (hormonal therapy), no significant differences between black cohosh and the hormonal product were observed.<sup>53-55</sup>

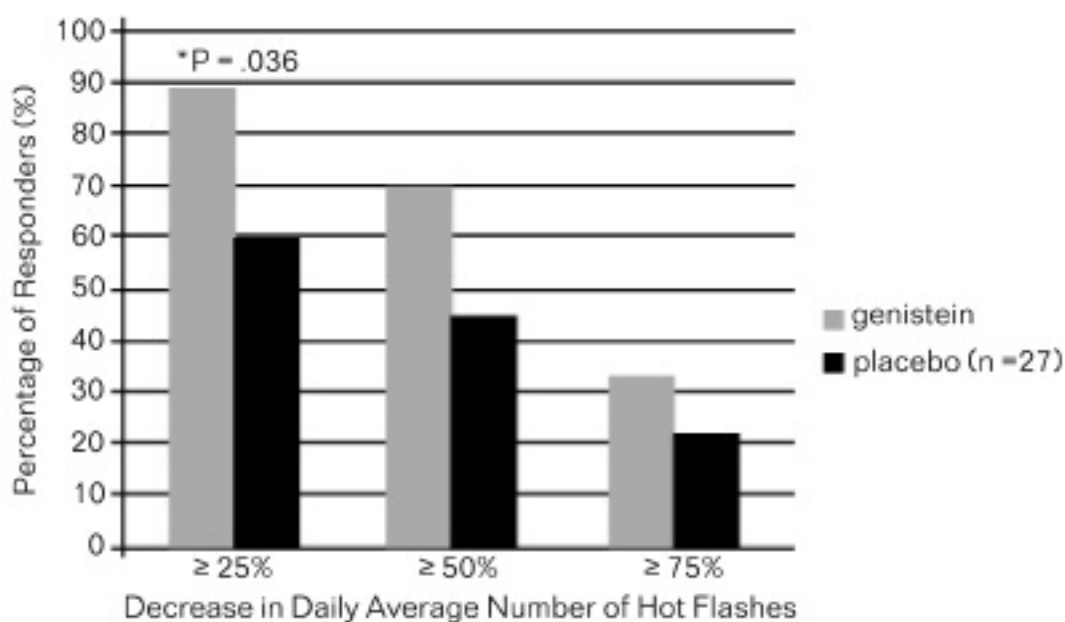
A pilot study randomized women ( $n = 21$ ) with frequent hot flashes ( $\geq 14$  per week) into 2 groups: black cohosh (Remifemin) or placebo for a 4-week trial.<sup>56</sup> Thirteen of the participants had breast cancer. Patients in the black cohosh group had a 50% reduction in hot flash frequency (95% CI, 34%-65%), which investigators deemed larger than the anticipated 20% to 30% placebo effect. This pilot study was used to support a larger phase III trial, which failed to show any significant benefit of black cohosh over placebo.<sup>57</sup>

A randomized, double-blind, placebo-controlled study of black cohosh extract (40 mg drug or placebo) over 12 weeks enrolled 304 patients.<sup>58</sup> The black cohosh group had a significantly reduced incidence of hot flashes ( $P = .007$ ) with greater benefit conferred on women in the early stages of climacteric symptoms versus those in the late phase.

An Australian randomized, double-blind, placebo-controlled trial evaluated an herbal compound that included black cohosh along with 7 unnamed "traditional Chinese

herbs."<sup>59</sup> A total of 93 healthy women (ages 45-65 years) took 3,150 mg of dry herbal preparation daily (or placebo) over 20 weeks and were evaluated on number and severity of vasomotor symptoms, including keeping a hot flash diary. Both groups showed a decrease in hot flash score, but there was no significant difference favoring the herbal group at any point in the study.

*Genistein.* The literature contains conflicting reports about genistein and the reduction of hot flashes in menopausal patients.<sup>13</sup> Since the placebo effect in such studies can be as high as 59%, these studies can show strong results and yet be considered inconclusive.<sup>60</sup> One difficulty in assessing genistein results is that meta-analyses or reviews often conglomerate a large number of studies using different formulations in studies of varying design with a variety of endpoints. Some of these reviews concluded that phytoestrogens (including but not limited to genistein) are not effective at reducing climacteric symptoms in menopausal women when, in fact, some of the studies reviewed showed a significant beneficial effect.<sup>13,46,61-64</sup> Some other reviews reported modest benefits for isoflavones.<sup>13,20,65-67</sup> Thus, the paradoxical problem confronting a physician seeking guidance in the use of genistein to manage climacteric symptoms in menopausal patients is too much heterogeneous evidence. More meaningful results can be found by identifying specific substances, such as genistein, and spe-



**Figure 4.** 88.5% of patients on a synthetic formulation of genistein had a significant 25% or greater reduction in hot flash burden (total duration of time spent in hot flash per day).

cific dose ranges (such as > 15 mg/d), aimed at specific outcomes, such as reducing hot flashes.<sup>68</sup>

A randomized, double-blind, placebo-controlled multicenter trial (n = 84) used a synthetic pure genistein formulation (geniVida™, DSM Nutritional Products, Switzerland) at a dose of 30 mg and found a significant reduction in the number of daily hot flashes in a patient at 8 and 12 weeks ( $P = .045$  and  $P = .015$ , respectively).<sup>69</sup> Genistein patients had 44% reduction in the average number of hot flashes ( $P = .027$ ) at 12 weeks (Figure 3). Genistein patients also had a reduced hot flash burden (total duration of hot flashes per day) at 12 weeks ( $P = .02$ ). The decrease in hot flash burden was 25% or more in 88.5% of genistein patients at 12 weeks (Figure 4).

A critical review of 11 studies of isoflavones, including genistein, found 6 of these studies reported a significant decrease in hot flashes.<sup>68</sup> Closer analysis revealed the important role of genistein dose. In those studies, 5 used a dose of 15 mg or more of genistein per treatment; they all found genistein significantly decreased the incidence of hot flashes. Of the 6 studies that used less than 15 mg of genistein per dose, only one was able to demonstrate a statistically significant decrease in hot flashes. Thus, the dose of genistein appears to be a relevant factor in decreasing the incidence of vasomotor symptoms.

A recent randomized, double-blind, placebo-controlled study (n = 389) of menopausal patients found that genistein significantly decreased the mean number of hot flashes at all evaluation points (1, 3, 6, and 12 months) resulting in a significant 56.4% reduction for genistein patients versus placebo.<sup>70</sup> Patients received 2 daily tablets containing 500 mg calcium carbonate and 400 IU vitamin D; the genistein group's tablets also contained 27 mg total isoflavone (genistein purity 98%).

A randomized, placebo-controlled, double-blind study of early postmenopausal women (n = 90) compared estrogen-progestogen therapy (EPT) to genistein (54 mg/d) to placebo over the course of 12 months to evaluate the effectiveness of the treatment of hot flashes.<sup>71</sup> Genistein patients showed a significant mean 22% reduction in the number of daily flashes at 3 months ( $P < .01$ ), a mean 29% reduction at 6 months ( $P < .001$ ), and a mean 25% reduction at 12 months ( $P < .01$ ) compared to placebo. EPT patients showed a significant mean 53% decrease at 3 months ( $P < .001$ ), a mean 56% at 6 months ( $P < .001$ ), and a mean 54% at 12 months ( $P < .001$ ) compared to placebo.

In a randomized, double-blind, placebo-controlled trial (n = 80) of menopausal women taking isoflavone (23.3 mg genistein plus 6.2 mg daidzein and 3.8 mg glycitein and soy protein) versus placebo, the isoflavone patients

had significantly fewer hot flashes ( $P < .01$ ) at 4 months.<sup>72</sup> Another recent study ( $n = 80$ ) randomized menopausal women who reported a minimum of 5 hot flashes daily at baseline into 2 arms: 1 group received 100 mg per day of isoflavone in a soy extract (2 capsules per day, each containing 125 mg of soy extract plus 50 mg of isoflavones, 25 mg of which was genistein); the other group received the placebo.<sup>73</sup> Climacteric symptoms were evaluated at 10 months. At the end of the study, both study arms showed a significant reduction in the frequency of hot flashes, but the isoflavone group was significantly superior to the placebo group ( $P < .001$ ) and had significantly reduced hot flash severity ( $P < .001$ ).

A randomized, double-blind, placebo-controlled study of menopausal outpatients ( $n = 75$ ) reporting a minimum of 7 hot flashes daily at baseline were randomized to receive a soy isoflavone extract capsule (325 mg capsule containing 17.5 mg each of genistein, daidzein, biochanin, and formononetin) or placebo capsule for 4 months.<sup>74</sup> Women taking the genistein extract had a 38% reduction in the mean number of hot flashes at week 4, a 51% reduction at week 8, and a 61% reduction at week 16. However, a large number of withdrawals in this study confounded the results. Investigators identified certain subjects in this study as “responders,” defined as those who had their mean number of daily flashes reduced by at least 50% at week 16. Of the responders, 65.8% were in the genistein group, while 34.2% of responders were in the placebo group ( $P < .005$ ).

A community-based study in Japan ( $n = 1,106$ ) evaluated women aged 35 to 54 years over a 6-year period with questionnaires and found that hot flashes were significantly and inversely associated with the consumption of soy products.<sup>75</sup> These women took no isoflavone supplements but rather consumed soy foods as part of their normal diet; investigators estimated isoflavone content. Women with the lowest incidence of hot flashes were those who consumed the most soy foods ( $P = .005$ ) and those with the highest isoflavone intake ( $P = .002$ ).

**Psychological symptoms (anxiety and irritability).** Most randomized clinical trials of CAM products for relief of menopausal symptoms focus on vasomotor symptoms rather than somatic symptoms, but menopausal women reported in the Study of Women Across the Nation (SWAN) that psychological and psychosomatic symptoms rank just behind the classic hot flash in terms of causing distress and discomfort.<sup>76,77</sup> Anxiety often occurs concurrently with hot flash, as a study of African-American women found that those with the highest anxiety scores were 5 times as likely to have vasomotor

symptoms of menopause than those with lower anxiety scores.<sup>78</sup> Thus, there is not always a clear dividing line between vasomotor and somatic symptoms. Ethnicity also may play a role. For example, depression is more common among black and Hispanic menopausal women than similar women who are white or Asian.<sup>77</sup>

Furthermore, although psychological symptoms are common during menopause, possibly even exceeding vasomotor symptoms,<sup>79</sup> medical care for their management is not.<sup>80</sup> This suggests what many have observed in clinical practice, namely that many women are looking to CAM remedies in particular to manage such complaints as mental stress, cognitive deficits, anxiety, irritability, and depression.

**Black cohosh.** Reviews of studies of black cohosh on psychological symptoms have discovered mixed results.<sup>46,81</sup> However, the fact that black cohosh may have activity at the serotonin receptors suggests that it could improve mood.<sup>19</sup>

A randomized, double-blind, placebo-controlled trial ( $n = 15$ ) examined the use of black cohosh in women with menopause-related anxiety disorder over a course of 12 weeks. At 12 weeks, patients were administered the Hamilton Anxiety Rating Scale (HAMA-A), the Beck Anxiety Inventory, and the Psychological General Well-Being Index as well as climacteric measures.<sup>82</sup> While black cohosh significantly decreased vasomotor symptoms in this population, there were no significant anxiolytic effects.

**Genistein.** A review of 8 studies (2000–2007) on the effect of isoflavones on cognition in menopausal women found mixed results (4 positive studies).<sup>61,83</sup> A randomized, double-blind, placebo-controlled study ( $n = 80$ ) of menopausal women treated with isoflavones versus placebo found that isoflavones significantly reduced nervousness and melancholia in menopausal women along with vasomotor symptoms.<sup>72</sup>

**Insomnia and fatigue.** Disturbed sleep, including insomnia, is a commonly reported menopausal symptom.<sup>84</sup> In some cases, vasomotor symptoms produce “night sweats,” which are actually vasomotor symptoms that intrude on proper sleep. Menopausal women report lack of sleep and the resulting excessive daytime sleepiness and fatigue as bothersome symptoms.

**Adaptogens.** Although adaptogens are better known for immunological effects, they have been studied for promoting endurance<sup>85,86</sup> and remain a traditional remedy for fatigue.<sup>87</sup> In a randomized, placebo-controlled study ( $n =$

96) of chronic fatigue patients, there was no significant difference in fatigue between groups at the end of the 2-month study course, but fatigue severity and fatigue duration were significantly decreased in the adaptogen group versus placebo ( $P < .05$ ).<sup>88</sup> In this study, patients with moderate levels of fatigue responded better to adaptogens than those with more severe fatigue.

**Bone loss.** Osteoporosis is characterized by low bone mass, deterioration of the bone architecture, weakened bone strength, and a higher likelihood of fracture.<sup>89</sup> Bone metabolism is governed by a process called remodeling, in which osteoblasts control bone formation and osteoclasts control bone resorption. In premenopausal women, bone metabolism is roughly in equilibrium (formation/resorption), but with advancing age, menopause, and certain diseases, bone resorption outpaces bone formation resulting in decreased bone mineral density (BMD), deteriorated bone structure, and increased bone porosity.<sup>90</sup> The link between menopause and osteoporosis was established as far back as 1941,<sup>91</sup> and the literature states that HRT prevents bone loss.<sup>2</sup>

Epidemiological studies show that ethnicity plays a role in bone metabolism. Black women have higher peak bone mass and geometry,<sup>92,93</sup> resulting in a lower rate of osteoporosis than white and even Asian women, in whom bone mineral content is similar.<sup>94</sup> Asian women have a lower rate of osteoporosis than white women, but it is higher than that of black women.<sup>95,96</sup> Japanese men and women have a lower incidence of hip fracture than whites (about 50%). These distinctions are blunted by increasing age: by around age 70, the risk of osteoporosis rises sharply in men and women of all ethnicities.<sup>97</sup> However, the lower rate of hip fractures and osteoporosis in menopausal Asian women versus white women, despite their similar bone mineral content, gave rise to speculation that the estrogenic effects of dietary soy may play a role in prolonging healthy bone metabolism.

**Black cohosh.** The benefits of black cohosh on bone metabolism were first demonstrated in animal studies,<sup>98,99</sup> but more recently in studies of postmenopausal women. In a randomized, double-blind, placebo-controlled study of 62 postmenopausal women treated with black cohosh (40 mg/d) or placebo, markers of bone turnover (bone-specific alkaline phosphatase, CrossLaps) indicated that black cohosh conferred a benefit on patients versus placebo by stimulating osteoblastic activity.<sup>100</sup>

**Genistein.** Many studies have reported on the beneficial effects of genistein on bone metabolism in menopausal women<sup>25,101-109</sup> with a couple of studies showing no con-

clusive benefits.<sup>110,111</sup> Authors of a recent review of clinical and epidemiological data recommended the use of soy foods (including genistein) for postmenopausal women concerned about bone health.<sup>112</sup>

In a recent randomized, placebo-controlled study of early postmenopausal women ( $n = 90$ ) receiving twice-daily isoflavone tablets (containing 29.8 mg genistein per tablet) over 6 months, genistein significantly increased BMD of L2-4 T score ( $P = .00$ ) and Ward triangle T-score ( $P = .00$ ); femur neck T-score was increased but not to the point of statistical significance.<sup>113</sup>

Genistein (54 mg/d) was compared to HRT and placebo in 90 postmenopausal women for 1 year.<sup>114</sup> At the end of the study, genistein and HRT patients experienced significantly increased BMD of the femur (femoral neck: genistein =  $3.5 \pm 2\%$ , HRT =  $2.4 \pm 2\%$ , placebo =  $0.65 \pm 0.1\%$ ,  $P < .001$ ) and lumbar spine (genistein =  $3 \pm 2\%$ , HRT =  $3.8 \pm 2.7\%$ , placebo =  $-1.6 \pm 0.3\%$ ,  $P < .001$ ).

In a randomized, double-blind, placebo-controlled study, 389 osteopenic postmenopausal women received genistein (54 mg/d) or placebo for 24 months.<sup>115</sup> At the conclusion of the study, BMD increased in the genistein group and decreased in the placebo group at the anteroposterior lumbar spine ( $P < .0001$ ) and femoral neck ( $P < .001$ ). The BMD of the femoral neck increased by a mean 2.4% in the first year and by a mean 5.2% by the end of the second year with genistein; this compares with a loss of 2.2% at year 1 and a loss of 5.3% of BMD at 2 years with placebo.

**Cardiovascular health.** Every year since 1984, more American women than men died of cardiovascular disease (CVD), to the extent that more women died of heart disease than all other causes of death.<sup>116</sup> The risk of CVD increases with advancing age, and the old notion that HRT conferred a heart health benefit has been disproved.<sup>117</sup> Since the WHI, it is well known that estrogens can increase the risk of CVD in women,<sup>2</sup> because, in part, estrogens increase coagulation and can lead to increased incidence of venous thromboembolic diseases.<sup>118</sup>

**Adaptogens.** Although potentially toxic to neonatal and fetal cardiomyocytes, adaptogens have been demonstrated in an animal study to have mild cardiotoxic effect on adult cardiomyocytes *in vitro*.<sup>119</sup> Traditionally, herbs classified as adaptogens are often used as a heart tonic.

**Genistein.** Postmenopausal women who consume high amounts of phytoestrogens, particularly isoflavones

including genistein, have lower rates of CVD than similar subjects who eat the typical American diet.<sup>120</sup> Soy isoflavones do not appear to activate the hemostatic system in postmenopausal women and show no significant estrogenic effect on coagulation, fibrinolysis, or endothelial function.<sup>121,122</sup>

A number of studies have demonstrated the beneficial effect of soy isoflavones on serum cholesterol levels, and a prominent meta-analysis showed significant improvements in reducing both low-density lipoprotein (LDL) levels and triglycerides, without impacting the high-density lipoprotein (HDL) levels.<sup>123</sup> The FDA has stated that the addition of soy protein to the American diet could reduce coronary heart disease risk in men and women by lowering cholesterol levels.<sup>124</sup>

In a randomized, double-blind, placebo-controlled study of healthy postmenopausal women (n = 60) on a low-fat diet and 6-month therapy with genistein (54 mg/d) versus placebo, investigators found that genistein conferred benefits to patients in terms of specific markers for CVD. Namely, genistein lowered fasting glucose ( $P < .001$ ), lowered fasting insulin ( $P < .001$ ), reduced insulin resistance (HOMA-IR) ( $P < .001$ ), decreased fibrinogen ( $P < .001$ ), lowered serum osteoprotegerin ( $P < .001$ ), and increased serum levels of sex hormone-binding globulin (SHBG) ( $P < .05$ ).<sup>125</sup>

**Breast cancer risk.** HRT significantly increases a woman's risk for breast cancer.<sup>2</sup> Even relatively short-term use of HRT (estrogen plus progestin) increases the incidence of breast cancer compared with placebo and substantially increases the number of women presenting with abnormal mammograms.<sup>126</sup>

**Black cohosh.** Percent mammographic density (PMD) is held to be a strong independent risk factor for breast cancer<sup>127</sup> and one that may be influenced by such factors as exogenous hormones.<sup>128</sup> In a 6-month, prospective, open-label, uncontrolled study of 65 women treated with black cohosh (40 mg/d), mammograms and breast cells collected by percutaneous fine-needle aspiration showed no increase in mammographic breast density and no increase in breast cell proliferation in any subject.<sup>129</sup> This study suggests that black cohosh exerts no adverse effects on breast tissue.

**Genistein.** Epidemiological studies have suggested that high dietary soy consumption is linked with reduced incidence of endometrial cancer,<sup>130</sup> breast cancer,<sup>131,132</sup> and prostate cancer.<sup>133,134</sup> In terms of breast density as a potential predictor of breast cancer, an Italian randomized study comparing 54 mg/d genistein to placebo (n = 67)

over 3 years found that there was no significant change in mammographic breast density of endometrial thickness in the genistein group versus the placebo group.<sup>135</sup>

In fact, isoflavones have been shown *in vitro* to possess cancer-fighting properties,<sup>136</sup> although the exact mechanisms of this action are not understood.<sup>137</sup> In fact, since lifetime estrogen exposure is thought to increase the risk of breast cancer, the protective role of phytoestrogens, with their estrogenic properties, seems counterintuitive on the surface<sup>138</sup> but may relate to angiogenesis, which is required for tumor growth. Angiogenesis in tumor growth depends on endothelial cell attachment, migration, and proliferation,<sup>139</sup> which certain phytoestrogens may inhibit. Genistein is known *in vitro* to reduce basic fibroblast growth factor-induced endothelial cell migration<sup>140</sup> and has antiproliferative effects in breast cancer cells,<sup>30</sup> although the exact mechanisms have yet to be described.

The role of genistein in cancer prevention is far from conclusive, as a recent meta-analysis of epidemiological studies of urinary isoflavones excretion and breast cancer risk found that phytoestrogen intake did not appear to mitigate the risk of breast cancer.<sup>138</sup> Another review of the literature found that phytoestrogens did not increase the risk of breast cancer in postmenopausal women.<sup>141</sup>

**Safety.** In the many meta-analyses and reviews of isoflavones, none found any significant safety issues with the short-term use of phytoestrogens, including but not limited to genistein. In fact, their relative safety makes them a viable treatment option, even to authors who maintain certain reservations about their efficacy.<sup>63</sup> In a study that showed the efficacy of genistein for reducing hot flashes versus placebo, genistein was the only treatment in the 3-arm study (genistein 54 mg, estrogen-progeston therapy or EPT, placebo) that did not result in endometrial thickness greater than 5 mm in patients.<sup>71</sup>

Black cohosh has been widely used in Europe for relief of menopausal symptoms and is found to be safe when used at appropriate doses.<sup>18</sup> A meta-analysis of black cohosh safety trials (n > 2,800) found 97% of all reported adverse events to be minor and described them as "rare, mild, and reversible."<sup>142</sup> However, there are a few isolated case reports in the literature of more serious effects. Among these case reports were patients who took black cohosh together with other botanicals, black cohosh at high doses (including 2 cases where 500 to 1,000 mg/d was taken over several months), or black cohosh taken for more than a year. This underscores the

fact that although black cohosh, like many other herbal remedies, is fundamentally safe within certain dose ranges and dose durations, clinical caution must be exercised to treat these supplements as therapeutic agents with risks as well as benefits. The Herbal Alternatives for Menopause (HALT) trial (n = 351) found that black cohosh, used alone or as part of a combination supplement, had no effects on the vaginal epithelium, endometrium, or reproductive hormones.<sup>51</sup>

### Discussion

Studies of CAM treatments are increasingly published in the literature, paralleling clinical and consumer interest in alternative medical therapies. Menopausal women, in particular, are good candidates for CAM treatments for several reasons. First, many women feel that menopause is a natural condition rather than a disease and should therefore be addressed with natural, holistic care rather than pharmacological interventions, such as HRT. Second, the recently publicized risks associated with HRT have caused a substantial number of women on HRT for effective management of menopausal symptoms to discontinue that therapy, even though conventional medicine has no effective “replacement” for HRT. Third, women more than men purchase CAM treatments and seem favorably disposed toward the concept of alternative care. Finally, there is growing evidence in the literature and among consumers that some alternative remedies are safe and effective.

However, it can be challenging for clinicians to navigate through the burgeoning citations related to CAM. Supplements are not regulated in the same manner as conventional drugs with the result that a wide variety of formulations exist with variable purity and quality. Thus, reviewing substances like genistein, adaptogens, or black cohosh involves assessing studies that used these agents in different formulations, varying strengths, and sometimes combined with other active agents. Reviews and meta-analyses of CAM often rely on heterogeneous studies, which can distort their findings. Furthermore, some CAM studies are small and underpowered; a few are poorly designed or inadequately controlled. Thus, the evidence in the literature for CAM is growing but not nearly as “hard” as evidence in conventional medicine.

The authors believe that more can be gleaned when studies are viewed in specific. Meta-analyses in conventional medicine can be extremely helpful, but such studies in CAM involve too much heterogeneity to weigh meta-analyses too highly. For that reason, major meta-analyses in the literature are mentioned for the sake of completeness, but important individual trials are highlighted and discussed in detail, since they can better

help guide therapeutic decisions. There is evidence in the literature to support black cohosh, genistein, and adaptogens for the management of certain menopausal symptoms. The evidence is perhaps not unanimous and there is much that remains to be understood, but the studies cited here and the excellent safety profiles of these substances taken in appropriate doses over an appropriate course of treatment make them important substances for addressing menopausal symptoms in women who seek CAM alternatives to HRT.

### Conclusion

Although HRT was effective in treating menopausal symptoms, concerns of increased cancer risk and cardiovascular disease have caused women to seek symptomatic relief in CAM. This article evaluated 3 important supplements used to treat menopausal symptoms; these substances, genistein (and the proprietary formulation, *geniVida*, a non-soy isoflavone), adaptogens, and black cohosh, have been shown to be safe and effective at addressing certain menopausal symptoms. While evidence is inconclusive (and there are problems with heterogeneity in meta-analyses of CAM products), specific and well designed studies have shown these agents to relieve menopausal symptoms safely at appropriate doses. Placebo-controlled CAM trials for menopausal symptoms can produce a substantial placebo effect, but many of the studies cited here showed therapeutic benefit that exceeds the large placebo effect. Given the excellent safety profile of these agents, physicians should consider them for treating specific menopausal symptoms. ■

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