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# The Use of Botanicals for the Treatment of Menopausal Symptoms: Weeds or Wonders?

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*Editor's note: This article reflects the opinions of the authors and is not NAMS-endorsed.*

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## Introduction

Menopause can severely impact a woman's quality of life by negatively affecting mood and sleep, disrupting interpersonal relationships and impairing sexual functioning. Furthermore, the reduction in estrogen that accompanies menopause increases a woman's risk of developing vasomotor symptoms, osteoporosis, genitourinary atrophy and, possibly, cardiovascular disorders. Given this situation, finding safe and effective ways to modulate levels of estrogen to offset menopausal symptoms, while at the same time preventing the development of chronic diseases, is crucial.

Until fairly recently, hormone therapy (HT) has been the standard treatment for menopausal symptoms. Since the premature discontinuation of the estrogen-progestogen therapy (EPT) arm of the Women's Health Initiative (WHI), more recent findings from the estrogen-only arm of the study showed no difference in the incidence of heart attacks or breast cancer among women taking estrogen therapy versus placebo after nearly 7 years of treatment.

Despite the more encouraging results of the estrogen-only arm of the WHI, the ramifications of the previously released findings about the potential negative health effects of the combination of conjugated equine estrogens and medroxyprogesterone acetate (MPA) have been significant. Most noticeably, women are reluctant to take HT

because of possible negative health outcomes and, consequently, have searched for safer and more "natural" alternatives. As a result of some patients' refusal to take HT, as well as some physicians' own concerns about possible negative health outcomes, the number of prescriptions written for HT since July 2002 has been drastically reduced.

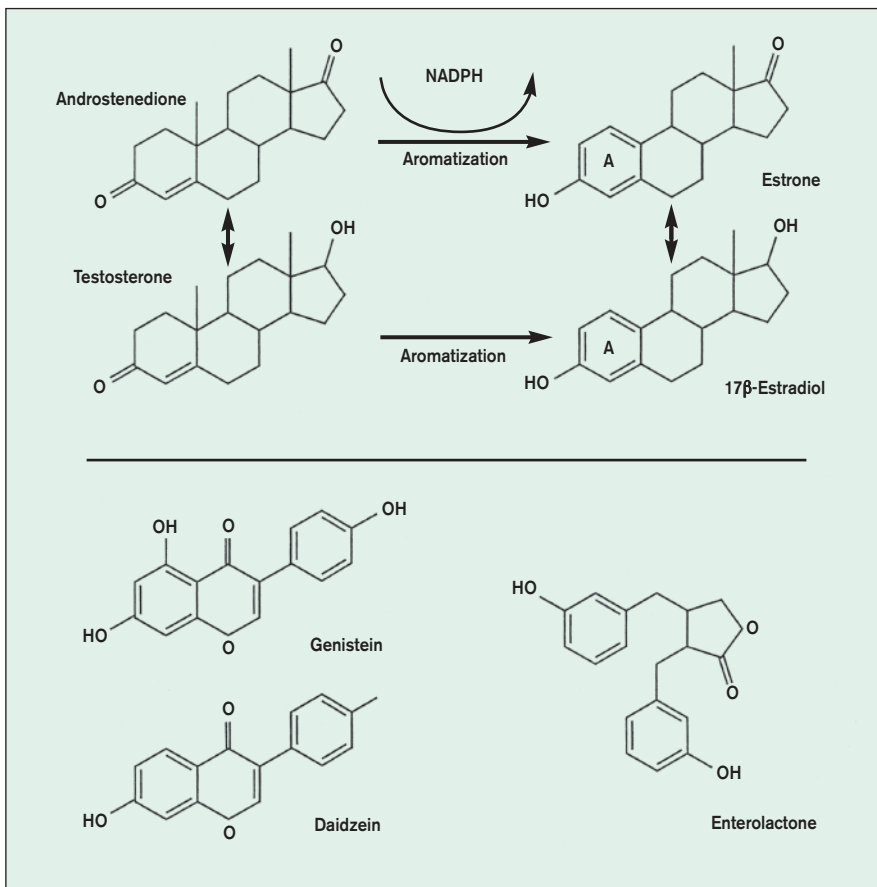
Botanicals are becoming more popular for the treatment of perimenopausal symptoms in women who cannot or will not take HT. A high percentage (79%) of perimenopausal and postmenopausal women use botanical supplements and a majority of these women do not inform their physicians, even when using the supplements in combination with prescription medication.<sup>1</sup> Among women using HT, concomitant use of botanicals is also high (46%).<sup>2</sup> Botanicals may be particularly attractive to women for whom HT is potentially contraindicated because of a history of breast cancer; a family history of breast, uterine or ovarian cancer; or a hormone-sensitive condition such as endometriosis. In fact, women who have a history of breast cancer report a six-fold increase in the use of dietary soy to treat menopausal symptoms when compared to women without such a history.<sup>3</sup>

## Mechanism of Action

Some of the most popular botanicals, including soy, black cohosh, and red

clover, supposedly act as phytoestrogens that mimic the effects of estradiol, although to a lesser extent. These non-steroidal plant compounds are converted by gut bacteria into weak estrogenic substances. They are structurally similar to estradiol (Figure),<sup>4</sup> have an affinity for beta estrogen receptors and act like selective estrogen-receptor modulators with both estrogenic and anti-estrogenic properties. The three major types of phytoestrogens are isoflavones, lignans and coumestans. Isoflavones are found in legumes, soybeans and red clover, lignans are found in oily seeds such as flax, and coumestans in red clover, sunflower seeds and bean sprouts.

Phytoestrogens have an age-related effect that may, in part, be related to current levels of estradiol and the ongoing competition for receptor sites. The estrogen-stimulating effects of phytoestrogens are weak in comparison to natural estrogen itself. In fact, the relative potency of phytoestrogens is only 2% that of estradiol. Premenopausal women with adequate levels of estrogen may play host to an intense competition for receptor sites. For these women, phytoestrogens could exert an anti-estrogenic effect.<sup>5</sup> In postmenopausal women, however, in whom there is a decrease in estrogen and, subsequently, less competition for available receptor sites, phytoestrogens may act in an estrogen-stimulating



**Figure.** Structure and production of endogenous estrogens and structure of phytoestrogens. Androstenedione and testosterone are the obligatory precursors of estrogens (top panel). The P450 aromatase monooxygenase enzyme complex catalyzes their conversion into estrogens. In this three-step process, three molecules of oxygen and three reducing equivalents from NADPH\* are used. In the liver, estradiol can be converted into estriol (not shown). Genistein and daidzein are isoflavonoids, and enterolactone is a lignan (bottom panel). In isoflavonoids, the number and positions of the hydroxyl substituents determine the degree of steric homology with 17β-estradiol, and therefore the binding affinity for the estrogen receptor. The phenyl groups in isoflavonoids and lignans mediate the antioxidant capacity of these compounds.

\*nicotinamide adenine dinucleotide phosphate

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manner, and ultimately help mitigate perimenopausal symptoms.

### Factors in Assessing Efficacy

In the United States, botanicals are considered dietary supplements, and are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. Under the DSHEA, there are less stringent criteria for assessing efficacy of botanicals than those applied by the FDA in regulating prescription medications. For example, under the DSHEA botanicals do not have to be shown to be safe or effective before they are marketed. Furthermore, the only way for a botanical to be removed from the mar-

ketplace is for it to be proven unsafe.

Design limitations in the studies of botanicals further complicate assessments of their efficacy. For example, studies are frequently too short, often lasting only 6 to 12 weeks. This duration is insufficient, given that menopause can last 3 to 4 years, with symptoms varying in severity across time. Further, as with all experiments, having too few study participants does not allow for statistically significant results, and diminishes the likelihood of finding meaningful differences between groups. Another complicating factor is the lack of conformity in the production and purity of the substances that are manu-

factured, which makes comparisons of findings across studies difficult.

Finally, the kind of experimental designs that have been used to assess efficacy have often been methodologically weak. For example, case series designs are common, in which participants' reactions to an intervention are simply described without either a comparison to a control group or the inclusion of double-blind procedures. In contrast, randomized controlled trials, although the most methodologically rigorous, are less common. In this brief review, we focus primarily on the results of randomized controlled trials.

### Black Cohosh

Black cohosh (*Actaea racemosa*) may have estrogenic-stimulating properties,<sup>6</sup> although this claim has been disputed.<sup>7</sup> Commission E, part of the German agency that is similar to the United States' FDA, has approved black cohosh as a nonprescription drug to treat premenstrual discomfort, dysmenorrhea and menopausal symptoms. If black cohosh is taken for less than 6 months, then the risk of side effects is minimal.

Improvement in menopausal vasomotor symptoms (ie, hot flashes) has been the most consistent finding in women using black cohosh. One randomized controlled trial compared the effects of black cohosh to those of conjugated estrogens and placebo, and found that women taking black cohosh reported a decrease in the number of hot flashes compared to women in either the conjugated estrogen or placebo groups.<sup>8</sup>

Studies have also examined the effects of black cohosh in breast cancer survivors. In one recent study,<sup>9</sup> female survivors of breast cancer took either black cohosh with tamoxifen or tamoxifen alone. Women taking black cohosh and tamoxifen reported a reduction in occurrence of hot flashes compared to those taking tamoxifen alone. In another randomized controlled trial, women with a history of breast cancer who were assigned to either a black cohosh

treatment group or a tamoxifen group reported a greater decrease in excessive sweating when compared to the placebo group.<sup>10</sup>

### Soy

Soy (*Glycine max* [L]. Merr.) is a natural dietary source of isoflavones, with genistein and daidzein being its two main isoflavones. With regard to soy's efficacy in alleviating perimenopausal symptoms, the research evidence is mixed. While some studies suggest that soy-derived isoflavones may provide an advantage over placebo in reducing hot flashes,<sup>11-12</sup> more recent studies find no difference.<sup>13-15</sup> In addition to investigating the effects of soy on vasomotor symptoms, studies have also examined its effects on other perimenopause-related changes. For example, in a randomized controlled trial by Kreijkamp et al,<sup>16</sup> no difference in cognition, bone mineral density or lipid levels was found in postmenopausal women taking soy protein isoflavones versus placebo.

### Red Clover

Red clover (*Trifolium pratense*), like soy, contains phytoestrogens. Biochanin A and formononetin, which are metabolized in vivo to genistein and daidzein, are the principal isoflavones in red clover. Like soy, the research evidence on the effectiveness of red clover in alleviating perimenopausal symptoms is mixed. The results of two recent randomized controlled trials suggest positive effects of red clover. In one study,<sup>17</sup> after 12 weeks of treatment, a 44% decrease in the frequency of hot flashes was observed in women taking red clover compared to women in a placebo group. In another study,<sup>18</sup> postmenopausal women taking red clover for 4 months reported both a reduced frequency of hot flashes, as well as a reduction in perceived severity of hot flashes, as compared to women taking a placebo.

Negative trials have also been reported. For example, in a recent ran-

domized controlled trial, the effectiveness of the red clover supplements Rimostil and Promensil was compared with that of a placebo in alleviating hot flashes.<sup>19</sup> After 12 weeks of treatment, no difference in the overall reduction of hot flashes was observed between the three groups. In regard to possible adverse effects, because red clover contains coumarin and coumarin-like compounds, it may alter platelet aggregation and, subsequently, increase the risk of bleeding. Therefore, its use must be closely monitored or avoided in patients taking anticoagulants or antiplatelets.

### Dong Quai

Traditionally, dong quai (*Angelica sinensis*) has been used by herbalists in Asian countries for relief of amenorrhea, dysmenorrhea and menopausal symptoms. Its mechanism of action is unclear, although it is believed to have estrogen-like effects, despite the fact that no scientific evidence in either animal or human studies has shown this to be the case. In one of the few methodologically sound studies on dong quai,<sup>20</sup> no difference in frequency of hot flashes was reported between women who took dong quai versus women in a placebo group.

### Kava

Kava (*Piper methysticum*) has been used as a treatment for anxiety in Europe and, more recently, in the United States. Kava's efficacy in treating perimenopausal anxiety has been well-documented as a sole agent,<sup>21</sup> in combination with HT,<sup>22</sup> and in combination with other compounds, such as calcium.<sup>23</sup> In a recent study,<sup>23</sup> perimenopausal women received either calcium alone, or calcium and kava in one of two different dosages (100 mg/day versus 200 mg/day). A greater reduction in anxiety was seen in the groups taking both kava and calcium as compared to the group taking calcium alone. While the anxiolytic effects of kava are well-documented, health warnings by the FDA to consumers and physicians

about the possible hepatotoxicity of kava make its use very controversial.

### St. John's Wort

St. John's wort (*Hypericum perforatum* L.) is used as a treatment for depression; in fact, it is the most widely used antidepressant in Europe. One randomized controlled trial<sup>24</sup> investigated the effects of a combination of St. John's wort and black cohosh on perimenopausal symptoms. Women in the combination group reported a greater decrease in menopausal symptoms (as measured by Kupperman index scores; decrease from 31.8 to 18.7 for combination group versus 30.3 to 22.3 for placebo). However, because a combination product was used, it is impossible to separate the effects of St. John's wort from those of black cohosh. Additionally, concerns have arisen recently regarding possible drug interactions with St. John's wort and medications metabolized by the cytochrome P450 system.

### Botanicals Warranting Further Scientific Investigation

*Green tea extracts.* Green tea extracts are purported to have strong antioxidant and anti-carcinogenic activity. They may also have positive effects on lipid levels, especially in persons who already have elevated cholesterol levels. Drinking green tea is also associated with a reduced risk of breast cancer, even after controlling for life style factors (ie, diet).<sup>25</sup> A recent randomized controlled trial found that when a theaflavin-enriched green tea extract was combined with a low-fat diet in men and women with hypercholesterolemia, the treatment group demonstrated a 16.4% reduction in low-density lipoprotein (LDL) and a 2.3% increase in high-density lipoprotein (HDL) cholesterol.<sup>26</sup> In regard to menopausal symptoms, a study by Sun<sup>27</sup> found a reduction in hot flashes and an improvement in sleep when perimenopausal women consumed green tea as part of a combination product. Because a combination product was

used, however, the separate effects of the tea cannot be identified.

**Valerian root.** Sleep disturbances such as insomnia and early awakening are a frequent complaint among menopausal women. Inadequate sleep can severely impact mood, resulting in elevated levels of depression and irritability, as well as impaired cognitive processing of information. Valerian root has been used successfully to treat sleep disturbances. In one randomized controlled trial<sup>28</sup> of perimenopausal-age women (median age, 49 years), administration of valerian root resulted in increased sleep efficiency and reduced slow-wave sleep latency. In the previously mentioned study by Sun,<sup>27</sup> valerian root was also part of the combination product used to treat menopausal symptoms, offering further evidence of valerian roots' possible efficacy in women of menopausal age. Valerian root is safe if used in recommended doses for short or intermediate periods of time (4-6 weeks). However, users may experience a withdrawal syndrome if they use valerian root for prolonged periods.

**Flaxseed.** Flaxseed also shows promise in treating menopausal symptoms. Flaxseed is a rich source of the essential fatty acid, alpha-linolenic acid (biologic precursor to omega-3 fatty acids) and lignans, with presumed health benefits for the prevention of cancer and lowering of lipid levels. Because flax is high in fiber and lignans, it has the potential to decrease carcinogenic estrogen levels by preventing reuptake of estrogen in the intestine.<sup>29</sup> In regard to its potential to modulate estrogen levels, flaxseed has been found to alter estrogen metabolism in postmenopausal women to a greater extent than soy.<sup>30</sup> In fact, one study<sup>31</sup> showed that daily consumption of one tablespoon of ground flaxseed for 7 weeks dramatically altered estrogen metabolism and levels of urinary estrogen metabolites in postmenopausal women. Flaxseed has been shown to be equally effective as HT in alleviating mild menopausal symptoms.<sup>32</sup>

**Evening primrose oil.** The active com-

ponent in evening primrose oil is gamma-linolenic acid, an omega-6 essential fatty acid that can only be obtained from the diet. Evening primrose oil has been approved in England for the treatment of non-cyclical breast pain (mastalgia). This botanical may also hold promise for treatment of menopausal symptoms, although more randomized controlled trials are needed to provide definitive evidence.

**Ginkgo biloba and ginseng.** Ginkgo biloba has been used to treat Alzheimer's disease, age-related dementias, poor cerebral and ocular blood flow, and premenstrual syndrome. Because difficulties in memory and concentration are frequent complaints of perimenopausal women, ginkgo biloba's cognition-enhancing properties may be particularly useful for this population. In a recent randomized, controlled trial,<sup>33</sup> postmenopausal women given ginkgo biloba for 1 week showed better nonverbal recognition memory and an improvement in frontal lobe-mediated functions than women in a placebo group.

Ginkgo biloba is sometimes used in combination with Panax ginseng which, in its own right, has been shown to improve mental performance. Ginseng may also have implications for elevating perceived quality of life in postmenopausal women. In one randomized controlled trial, postmenopausal women reported an improvement in levels of depression, well-being, and health when compared to women in a placebo group.<sup>34</sup>

**Diindolymethane (DIM).** Diets high in vegetables are correlated with a lower incidence of estrogen-related cancers. DIM, an indole found in cruciferous vegetables, may be particularly effective in modulating estrogen metabolism, and acting as a potent anticarcinogenic agent. Specifically, DIM may reduce activity of the estrogen-receptor system, and may shift estrogen metabolism in a way that increases the levels of 2-hydroxy and 2-methoxyestrogen metabolites. These metabolites are the

“good estrogens” that function as antioxidants and participate in the elimination of damaged or cancerous cells.<sup>35</sup> Therefore, for perimenopausal women who are at increased risk for cancer, the consumption of DIM may be of particular benefit in optimizing the estrogen environment.

**Dehydroepiandrosterone (DHEA).** DHEA is an endogenous hormone that is a precursor to androgens and estrogens. Its production decreases with age in both men and women. DHEA can be synthesized in the laboratory from wild yam extract. While supplementation with DHEA can elevate estrogen to normal levels, there is no evidence of endometrial stimulation. To minimize side effects, such as acne and hirsutism, the lowest effective dosage should be used (25-50 mg/day). In addition to being available as an oral supplement, DHEA can be applied topically as a vaginal cream to relieve vaginal dryness and increase libido.

Recent studies documented the positive physical and psychological effects of DHEA on menopausal symptoms. One recent study of postmenopausal women<sup>36</sup> examined the physiological and psychological effects of 25 mg per day of DHEA supplements over a 1-year period. Levels of steroids associated with DHEA metabolism (eg, allopregnanolone,  $\beta$ -endorphin, progesterone, and estrogen) increased, and an improvement in psychological symptoms (as measured by the Kuperman index) was observed. In an earlier randomized controlled trial,<sup>37</sup> postmenopausal women receiving 50 mg of DHEA per day over 6 months reported improvements in perceived physical and psychological well-being, including increased energy, and improved mood and quality of sleep.

## Conclusions

In a recent position statement, The North American Menopause Society recommended that the treatment of choice for perimenopausal women with mild vasomotor symptoms should be lifestyle changes, either alone or in

combination with a nonprescription remedy (ie, black cohosh, dietary isoflavones, vitamin E).<sup>38</sup> In regard to lifestyle changes, we believe that finding safe ways to modulate internal levels of estrogen, such as maintaining an ideal body weight by exercising and consuming a diet high in cruciferous vegetables and fiber, is prudent. Limiting intake of fat and restricting consumption of excessive amounts of alcohol may also be beneficial. With regard to nonprescription botanical remedies, our review suggests that black cohosh shows the best results based on scientific evidence.

In conclusion, use of botanicals may be an effective way for some women to alleviate bothersome menopausal symptoms. Given the popularity of botanicals to treat menopausal symptoms, and considering the fact that most women do not voluntarily offer information about usage, we recommend that physicians routinely ask their patients about botanical use, and continue to educate themselves about their safety and effectiveness. We refer readers to these Web sites for useful, updated scientific information on botanicals:

1. www.menopause.org
2. www.naturalstandard.com
3. www.mskcc.org/aboutherbs ■

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