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Bust-Enhancing Products

By Adriane Fugh-Berman, MD

EXPENSIVE "BUST-ENHANCING" DIETARY SUPPLEMENTS, SOMETIMES in conjunction with topical creams, are being widely marketed. Whether or not bra cups are filled, wallets are emptied; a typical product costs $229 for an eight-week supply.

These products contain variable combinations of herbs, the most popular being hops (*Humulus lupulus*), saw palmetto (*Serenoa repens*), damiana (*Turnera diffusa*), dong quai (*Angelica sinensis*), chaste-tree (*Vitex agnus-castus*), blessed thistle (*Cnicus benedictus*), dandelion (*Taraxacum officinale*), wild yam (*Dioscorea villosa*), kava (*Piper methysticum*), fennel (*Foeniculum vulgare*), black cohosh (*Actaea racemosa*, syn. *Cimicifuga racemosa*), and fenugreek (*Trigonella foenum-graecum*).

Is there any reason to think that these products work? Web sites for these products are full of testimonials, but not one clinical efficacy trial has been published. Nevertheless, it is plausible that some of these combinations may have an effect; some of these herbs are hormonally active and it is conceivable that a combination could exert a sufficient pharmacological effect to cause mammoplasia (breast enlargement in women).

Estrogenic Herbs

Estrogens are known to increase breast size; some women notice this effect with birth control pills. Phytoestrogens are much weaker than endogenous estrogens, but there is a broad range of activity among phytoestrogens. Although genistein and daidzein present in beans may be considered safe, the long-term safety of other phytoestrogens has not been established. Herbs that may have estrogenic effects include hops, fennel, and black cohosh.

Hops: Several herbal products promoted for bust enhancement are based on or contain hops, which contain 8-prenylnaringenin, an unusual and potent phytoestrogen that may be topically absorbed *(see accompanying hops article)*.

Fennel: Fennel is estrogenic in animal studies. In female rats, oral administration of fennel seed acetone extract for 10 days caused vaginal cornification and estrus. Moderate doses increased the weight of mammary glands; higher doses increased the weight of oviduct, endometrium, myometrium, cervix, and vagina.[1]

Black cohosh: Several studies have found that black cohosh decreases hot flashes. Reduction of hot flashes is usually, although not always, an estrogenic effect; in vitro and in vivo studies of estrogenicity are mixed *(see* Alternative Therapies in Women's Health *November 2001).* Black cohosh does not appear to contain the phytoestrogen formononetin,[2] but it does contain a more recently identified phytoestrogen, fukinolic acid (2E-caffeoylfukiic acid),[3] which has shown estrogenic activity in a breast cancer cell line and increased uterine weight in rats.

Other Hormonally Active Herbs

Saw palmetto: Used to treat benign prostatic hypertrophy (BPH), saw palmetto inhibits binding of dihydrotestosterone to androgen receptors in prostate cells (specifically the cytosol) and inhibits binding of [3H] DHT to its receptor in human foreskin fibroblasts.[4] Saw palmetto also inhibits prolactin[5] and has potent α1-adrenoceptor effects in vitro.[6] Studies are mixed on whether saw palmetto inhibits 5α-reductase.[7-9]

An anti-estrogenic effect was noted in a placebo-controlled trial of 35 men with BPH who received *S. repens* 160 mg bid.[4] If saw palmetto inhibits the conversion of testosterone to dihydrotestosterone, it is possible that a higher testosterone:dihydrotestosterone ratio increases the susceptibility of the breast to estrogenic action. A higher testosterone:dihydrotestosterone ratio has been linked to spontaneous gynecomastia in adolescent males.[10]

In women, increasing free testosterone levels may be detrimental; elevated free testosterone has been associated with increased breast cancer risk.[11]

Kava: Kava may have dopamine antagonist effects; acute dystonic reactions have been reported in three cases.[12] Dopamine antagonists increase prolactin secretion, which may be associated with mammoplasia. An observational study in 59 women treated with selective serotonin reuptake inhibitors (SSRIs) or venlaxafine for more than two months found that 23 of 59 (39%) reported some mammoplasia.[13] The effect was more common with SSRIs and was associated with weight gain. Serum prolactin increased significantly among those who used paroxetine.

Chaste-tree: Chaste-tree berry decreases follicle-stimulating hormone, increases luteinizing hormone, and inhibits prolactin activity in vitro. None of these effects should be associated with mammoplasia.

Other Herbs

Wild yam and fenugreek: Both wild yam and fenugreek contain diosgenin, which can be converted to progesterone in the laboratory; there is no evidence that such conversion takes place endogenously.

There is no evidence that diosgenin increases breast size. An article provided by one company as evidence that diosgenin increases mammary size actually states no such thing. This experiment, in which 20 or 40 mg/kg diosgenin was given with or without estrogen to ovariectomized mice, found no difference in wet or fat-free dry weight of mammary glands in diosgenin-treated mice.[14] Diosgenin did significantly affect mammary maturation, increasing terminal end bud differentiation (an effect that takes place in late pregnancy or under estrogen treatment). Although the words "growth stimulator" and "mammary development" are used, in this case maturation is what is meant.

Roasted fenugreek seeds reputedly were used by harem women to enhance buxomness.[15]

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Dong quai: A Chinese herb used in many women's formulas, dong quai has been tested for hot flashes in a randomized, double-blind clinical trial; there was no effect on hot flashes, vaginal mucosa, or endometrium.[16] There is a report of dong quai-associated gynecomastia in a man in Singapore;[17] however, the product was not analyzed, and may have been adulterated with drugs.

Damiana: Traditionally used as an aphrodisiac, damiana is thought to be safe; however, little information is available on it.

Dandelion: Dandelion increases bile flow in animals and may have a diuretic effect;[18] there is no evidence of a hormonal effect, nor is it used traditionally for hormonal effects.

Blessed thistle: No relevant information was identified for blessed thistle. High doses (> 5 g/cup of tea) can cause gastric irritation or vomiting.[19]

Discussion

Drugs associated with gynecomastia or mammoplasia include estrogen, protease inhibitors, penicillamine, neuroleptics, tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors.[13] Products marketed for bust enhancement contain hormonally active herbs that may have pharmacological effects. Hops, fennel, and black cohosh contain recently identified phytoestrogens; saw palmetto may increase free testosterone levels; and kava may increase prolactin—all actions that may affect the breast.

There are no long-term safety data on any of these herbs, singly or in combination. Estrogenic stimulation could potentially increase the risk of endometrial or breast cancer. Given that these products are aimed at young women, effects on fertility or fetal effects are also of concern. If a product increases breast size, it is active enough to raise concern about long-term adverse effects. ❖

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Hops and Women's Health

By Stuart Milligan, MA, DPhil

"WHILE YOU ARE WORKING HERE, IT IS VERY LIKELY that your menstrual cycles will be disturbed." These words greeted my wife when she started work in a laboratory involved in hops processing: The subsequent truth of this prediction led me (as a reproductive biologist) into a fascinating new research world of hops, herbs, and beer.

Without some additional flavoring, beer is a sickly bland drink. The female flowers (strobiles, or cones) of hops (*Humulus lupulus* L.) have been used for centuries to add aroma and bittering to beer, although their initial use was to provide a bacteriostatic and fungistatic effect that extended beer's shelf-life. The flavoring and preservative properties reflect the complex chemistry of the lupulin glands within the hop flowers. They contain hundreds of secondary metabolites, ranging from the hop acids, which provide the bittering activity, to volatile hop oils.[1,2]

Although the hop plant belongs to the same family (Cannabaceae) as marijuana, hops do not contain any cannabinoids. However, medicinal properties have been attributed to hops for centuries.[2] Nicholas Culpeper, the famous astrologer-physician of the early 17th century, stated that: "Half a dram of the seed in powder taken in drink kills worms in the body, brings down women's courses, cures the yellow jaundice, eases the headache that comes of heat, and tempers the heat of the liver and stomach."[3] Belief in the medicinal properties of hops has faded with time, although hop pillows are still produced for their reputed soporific effects.

Estrogenic Activity

The suggestion that hops have estrogenic activity has a very long history. In Germany, hop baths were used for the treatment of gynecological disorders.[4] Changes in menstrual cyclicity were reportedly common in women hop pickers,[1] and in Belgium, this legendary effect was attributed to the "hop devil."[5]

More recently, hop extracts have been reported to be effective in reducing hot flashes in menopausal women.[6] Early scientific studies confirmed that hops possess very high estrogenic activity,[4,7,8] but the chemical nature of hops was unresolved until just a few years ago.

Following the reports of menstrual disturbances among women associated with hops, my laboratory undertook to find the cause. Fractionation of the polyphenol components of hops led us to the identification of a minor component, 8-prenylnaringenin, as the agent responsible for the estrogenic activity of hop flowers.[9-11] The same compound also has been isolated from a crude Thai drug that is derived from the heartwood of *Anaxagorea luzonensis* A. Gray (Annonaceae).

In vitro, the estrogenic activity of 8-prenylnaringenin has been demonstrated in a yeast screen bearing the human estrogen receptor alpha (ERα), in a human endometrial cell line (Ishikawa Var 1), and in competitive binding assays using rat uterine cytosol and pure human estrogen receptors (both ERα and ERβ).[9-11] The compound also showed typical estrogenic activity on the reproductive tract of mice, after subcutaneous injection and when given in the drinking water.[12] The compound also suppressed bone loss in ovariectomized rats when given by daily injection.[13]

In both in vitro and in vivo tests, 8-prenylnaringenin appears to be one of the most potent phytoestrogens, with an estrogenic activity considerably greater than that of established phytoestrogens such as genistein and daidzein.[9-11] Even so, it should be emphasized that the estrogenic activity of 8-prenylnaringenin is considerably weaker than that of 17β-estradiol (< 1/100 in vitro). The weak estrogenic activity of phytoestrogens is one of the confounding factors in any interpretation of the biological significance of these compounds in humans. Other confounding factors include limited data on other bioactivity, bioavailability, and metabolism after oral intake.[14]

Other Biological Properties of 8-Prenylnaringenin and Related Compounds

Prenylflavonoids are quite rare compounds in nature, but 8-prenylnaringenin is just one of a number of related prenylflavonoids in hops; others include xanthohumol, desmethylxanthohumol, isoxanthohumol, 6-prenylnaringen, 6,8-diprenylnaringenin, 3'-geranylchalconaringenin, 6-geranylnaringenin, 8-geranylnaringenin, and 4'-O-methyl-3'-prenylchalconaringenin.[15,16] Although the estrogenic activity of 8-prenylnaringen has received the most attention (reflecting the current general interest in phytoestrogens), other biological activities of hop prenylflavonoids have been described.

In vitro studies have revealed that the compounds show variable antiproliferative effects on breast and colon cancer cell lines, inhibit cytochrome P450-mediated activation of procarcinogens, and inhibit diacylglycerol acyltransferase activity.[17-19] 8-prenylnaringenin, like 17β-estradiol, also has been shown to stimulate E-cadherin-dependent aggregation and growth of breast cancer cells in vitro.[20] Oral intake of freeze-dried beer extracts was anticarcinogenic in mice.[21] Both hop alpha-

acids and xanthohumol inhibit the synthesis of cyclooxygenase 2 and inhibit osteoporosis in rats.[22,23]

Hops provide a rich source of polyphenolic compounds with a wide variety of bioactivities. Is exposure to any of these, singly or in combination, of potential use or threat to humans?

Hop Compounds in Beer

Over the last few years, scientific and public interest in the potential role of estrogenic compounds in the environment and diet has intensified. Exposure to industrial chemicals with estrogenic activity has been suggested as a possible cause of reported reductions in sperm counts and reproductive tract abnormalities in men,[24,25] while phytoestrogens have been implicated as having a variety of beneficial health effects.[26,27] In both cases, although exposure to large amounts of these compounds may produce significant effects in humans, the effects of normal, low-level exposures are debatable.[14,28]

The identification of 8-prenylnaringenin as a potent phytoestrogen could provide an obvious explanation for the menstrual disturbances in female hop workers in the past, presumably due to exposure via transdermal absorption or dust inhalation. However, hop picking is now done mechanically and the only widespread human exposure to 8-prenylnaringenin is likely to be via beer consumption.

The amount of 8-prenylnaringenin in beer is dependent on the brewing process and the nature of the raw materials used.[16,29] In beers that include extracts from processed hops, very little 8-prenylnaringenin may be present. Although most beers contain less than 30 ug/L of 8-prenylnaringenin, the compound can occur at levels of up to 240 mcg/L in beers made using whole hops.[16] This is consistent with the amount of 8-prenylnaringenin in dry hops (100 mg/kg) and the small amount (only a few grams) of hops used per liter of beer in brewing.

The concentration of 8-prenylnaringenin in beer is considerably greater than that of the widely known isoflavonoid phytoestrogens (formononetin, daidzein, genistein: 0.1-15 Nm).[30] However, despite the relatively high estrogenic activity of 8-prenylnaringenin, the total estrogenic activity of beer made using whole hops still is very low,[31] and no detrimental health effects due to estrogens in beer have been reported or are to be expected. A study examining the effect of 8-prenylnaringenin in mice showed that levels of 100 mcg/mL were required to produce any sign of estrogenic activity, i.e., at least 400-fold greater than that found in any beer![11]

Moderate intakes of isoflavonoid phytoestrogens (e.g., in soy) have been associated in some reports with a reduction in incidence of breast and prostate cancer, cardiovascular disease, and menopausal symptoms;[26,27] however, the evidence for beneficial effects is debatable.[14,28] It also has been suggested that resveratrol, an extremely weak phytoestrogen found in grapes and wine, may contribute to the beneficial effects of wine consumption (e.g., the French paradox),[32] but again, critical experimental evidence is lacking. Whether the intake of 8-prenylnaringenin or any related compound contributes to the reported beneficial health effects of moderate beer consumption[33] is an open question. Beers with a high polyphenol content also have high antioxidant activity and it may be this contribution to the total antioxidant environment of the body that is important.[34]

The sparse knowledge of the bioavailability of the hop compounds, their metabolic fates, and their in vivo bioactivity will allow speculation to continue until experimental evidence is available to clarify the situation.

Hops and Hot Flashes

A methodologically flawed French study in 25 women found a benefit after 30 days of treatment with large doses of hop extract (1,600-2,600 mg/d, titrating down to 1,200-1,600 mg).[6] The study was not randomized, and the control group was apparently composed of five women who had been accidentally treated with a low dose of hops (300 mg), which, since it had no benefit, was considered a placebo. In 17 of the 20 treated subjects, reduction of hot flash score (intensity $\times$ frequency) was significantly better than control (neither statistical test nor significance level was stated). Some subjects apparently received another herb, hawthorn, as well as hops.

Reduction in hot flashes would be consistent with the estrogenic activity of 8-prenylnaringenin, but such an effect needs confirmation in a properly controlled clinical trial, with attention to possible side effects and identification of side effects of the active agent(s).

Hops as a Breast Enhancement Supplement

Although hops are used to impart flavor, bitterness, and other properties to beer, the amount of hops used in brewing is relatively small and 8-prenylnaringenin therefore is not a significant dietary component. However, hops are now incorporated into a number of herbal preparations for women, including some that claim the ability to enlarge breasts.

Claims for the effectiveness of at least some breast enlargement preparations are based partly on their phytoestrogen content. The concentration of 8-prenylnaringenin in one breast-enhancing preparation containing hops was 10.9 mcg/g, which would result in a daily

intake of approximately 130 mcg/d.[35] This value is less than that found in a liter of some beers; there is no evidence as yet that such an amount would have a significant estrogenic effect in humans. When tested in mice, the hops-containing supplement showed no evidence of estrogenic activity following administration either in the feed or by subcutaneous injection of the extract.

If breast enhancement products do contain 8-prenylnaringenin, the question must then be asked: Are such products either effective or safe? In terms of efficacy, a peer-reviewed clinical trial has yet to be published. However, even if an effect did occur, real fears over safety issues exist. The breast is an important site of hormone-dependent cancer and is very sensitive to estrogens. Inappropriate estrogenic stimulation of this tissue would be of considerable concern. In addition, estrogenic effects would not be expected to be limited to breast tissue alone and this is consistent with reports of menstrual disturbances associated with some of these supplements. Any disturbance of menstrual cyclicity is of obvious concern in relation to normal fertility and adverse interactions with contraceptives.

An additional concern is that women may be taking such breast enhancement products in the early stages of pregnancy and the fetus may be inadvertently exposed to relatively large amounts of bioactive compounds with unknown fetal effects. Hop phytoestrogens would not be expected to be problematic; they are far weaker than pharmaceutical estrogens, which (with the exception of DES) have not been linked to birth defects. However, hops, and other ingredients in these preparations, contain many compounds for which reproductive toxicology information is lacking.

The Need for Caution

There are many target sites for estrogenic activity in the body, ranging from the reproductive tract and breast, through bone, fat, and blood vessels, to the bladder and brain.[36] The significance of estrogenic effects at many of these sites is still unclear. In 1996, researchers discovered that there are two, rather than one, estrogen receptors (ERα and ERβ).[37] These two estrogen receptors have differing affinities for various estrogens and differing tissue and cellular distributions, and may interact with the vast array of nuclear receptor coactivators and corepressors in varying ways.[36] These observations have opened a surprising new dimension in our ignorance of how 17β-estradiol works. Understanding the molecular mechanisms and activity of the much weaker phytoestrogens is a long way off.

It also is inappropriate to assume that phytoestrogens only have estrogenic activity. Each phytoestrogen may have multiple biological activities completely independent of its estrogenic activity. This is illustrated by the activities of genistein, which include inhibiting the activities of enzymes such as 5α-reductase, aromatase, 17β-hydroxysteroid dehydrogenase, tyrosine kinase, and topoisomerase II.[14] The fact that genistein is a potent inhibitor of proliferation even in estrogen receptor-negative breast cancer cells illustrates that the estrogenic activity of the compound probably is not responsible for all of its biological effects.[14]

It would seem dangerously naïve to assume that human exposure to a complex combination of compounds with a wide spectrum of bioactivities (as exists in hops) would have a single target (e.g., the breast) and that the actions at this target would be solely beneficial. The reproductive tract and breast are important sites of hormone-dependent cancer and are very sensitive to estrogens.[38] Estrogens have many effects on other tissues. Uncontrolled exposure to large amounts of unstudied hops compounds is inadvisable, to put it mildly! ❖

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CME Questions

22. Wild yam and fenugreek contain:

a. 8-prenylnaringenin.
b. progesterone.
c. diosgenin.

23. 8-prenylnaringenin, a phytoestrogen found in hops:

a. is less potent than other phytoestrogens.
b. is more potent than other phytoestrogens.
c. is equivalent in potency to 17β-estradiol.

24. Levels of 8-prenylnaringenin found in beer have estrogenic effects.

a. True
b. False

Clinical Abstracts

With Comments by Adriane Fugh-Berman, MD

Vitamin E and Dysmenorrhea

Source: Ziaei S, et al. A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhea. *BJOG* 2001;108:1181-1183.

Design/Setting/Subjects: A randomized, double-blind, placebo-controlled trial in 100 young women ages 16-18 years with primary dysmenorrhea in Tehran. Stratified randomization was done based on severity of the pain (mild, moderate, or severe on visual analog scale).

Intervention: Vitamin E 500 IU/d beginning two days before the expected onset of menses and continued for the first three days of the menses.

Outcome Measures: Severity of pain by visual analog scale. Wilcoxon matched pairs rank sum test was used to compare the severity of the pain before and after treatment; the Mann-Whitney U test was used to analyze the differences between vitamin E and placebo.

Results: At two months, both groups experienced a significant decrease in median pain scores; vitamin E was significantly better than placebo (P = 0.02).

Funding: Not stated.

Comments: Vitamin E appears to decrease prostaglandin levels by preventing phospholipid peroxidation, the release of arachidonic acid, and its conversion to prostaglandin. Fish oil has previously been shown to be helpful for the treatment of dysmenorrhea. A placebo-controlled, randomized, crossover trial in 42 adolescents (37 completed), found that two months of fish oil (daily dose contained 1,080 mg eicosapentanoic acid, 720 mg docosahexaenoic acid, and 1.5 mg vitamin E) was superior to placebo.[1] The vitamin E in these capsules was not meant to be therapeutic; it was included as a preservative. Fish oil and vitamin E certainly are benign and may be useful as treatments or adjuncts for dysmenorrhea. ❖

Reference

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Calcium and Lipid Concentrations

Source: Reid IR, et al. Effects of calcium supplementation on serum lipid concentrations in normal older women: A randomized controlled trial. *Am J Med* 2002;112: 343-347.

Design/Setting/Subjects: In a substudy of a larger trial assessing the effects of calcium on fracture incidence, 223 postmenopausal women (not receiving therapy for osteoporosis or hyperlipidemia) were randomized to calcium citrate (1 g/d) or placebo for one year.

Outcome Measures: Fasting serum lipid concentrations, obtained at baseline, 2, 6, and 12 months.

Results: Compared to the placebo group, high-density lipoprotein (HDL) cholesterol levels in the calcium group were significantly higher, about 7% above baseline (0.09 mmol/L, 95% confidence interval [CI] 0.02-0.17, P = 0.01). The ratio of HDL to low-density lipoprotein (LDL) also increased more in the treated group (0.05 mmol/L, 95% CI 0.02-0.08). There was no significant difference in triglyceride levels, LDL cholesterol levels, or body weight. Baseline calcium intake, fat intake, or lipid levels did not affect response to supplementation.

Funding: Health Research Council of New Zealand.

Comments: Calcium may benefit lipids as well as bone. A previous crossover study in 56 hypercholesterolemic patients treated with placebo or calcium carbonate (1.2 g/d × six weeks) found that in the treated group, LDL decreased by 4% and HDL cholesterol increased by 4%.[1] Another study, however, found no benefit of calcium carbonate (1 g/d or 2 g/d × four months) over placebo on lipid parameters in 193 men and women.[2]

Calcium binds to fatty acids and bile acids in the gut, thus interfering with lipid absorption. As previously reported in *Alternative Therapies in Women's Health* (April, 2001), the addition of calcium to chocolate bars decreases fat absorption. The idea that calcium may decrease fat absorption may be a potent incentive for patients to take calcium supplements (and, perhaps, to take them with chocolate). ❖

References

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In Future Issues:

Acupoint Stimulation for Morning Sickness

Topical Progesterone and Wild Yam Creams