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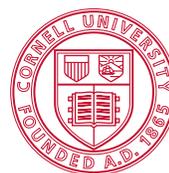
Treatment of
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Herbal Medicines and Breast Cancer Risk

People have used herbal medicines throughout history and they are currently the most commonly used medicines world-wide. In spite of this, the effectiveness and safety of herbal medicines is less well demonstrated and understood than that of conventional medicines. Numerous problems have been found in the quality of commercial herbal medicine products. These problems include a lack of consistency of active ingredients, contamination with other herbs and toxins, inaccurate content, and adulteration with conventional medicines. In contrast to other industrialized countries, there is little regulation of herbal medicines in the U.S. This leaves consumers who wish to use herbal medicines with few guarantees about which ones are safe and effective. This review provides a general discussion of herbal medicines, especially those that may act on the breast or affect breast cancer risk.

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How common is the use of herbal medicines and why are women using them?

A recent national survey found that 14% of all people in the U.S. are using some type of herbal medicine. Middle aged women were the largest users of herbal medicines; 23% of the surveyed women in this age group had used an herbal supplement in the last week. Similar results were found in two other surveys. Common reasons women give for using herbal medicines include treatment of: menopausal symptoms, premenstrual syndrome, and menstrual irregularities, as well as to aid breastfeeding, decrease breast cancer risk, prevent recurrence of breast cancer, and change breast size. This fact sheet will focus on uses of herbal medicines that could potentially affect breast cancer risk.

How are herbal medicines prepared and taken?

There are several ways that herbal medicines are prepared and taken. The method of preparation is important because different preparations of the same herb can contain different ingredients and have different uses and safety. Herbs can be used fresh, dried or as alcohol or water extracts; for example tea is a water extract of an herb. Most herbal medicines are given by mouth but some are used on the skin, as enemas, or as suppositories. Aromatherapy is also used and involves the inhalation of essential oils (volatile distilled oils from plants) or the use of essential oils to scent massage oils.

What types of evidence exists for the safety and effectiveness of herbs and how strong is that evidence?

Only a few herbs have been studied in randomized, double-blind, clinical trials, the type of study that provides the strongest evidence for the effectiveness of a medical treatment. Without the kind of evidence that comes from a clinical trial it is very difficult, if not impossible, to judge the safety and efficacy of herbal medicines. In the absence of evidence from a clinical trial, the potential effectiveness of an herbal medicine can only be judged based on traditional use or research that can only assess one narrow aspect of an herbal medicine. For example, there are cellular and animal studies that can give an estimate of the biological activity of herbal medicines and their potential for various treatments, but these studies poorly reflect their safety and efficacy in the human body. Nonetheless, a single clinical trial can give misleading results. Consistent results from several

well designed and conducted clinical trials are needed to be sure a medicine is safe and effective.

In herbal medicine, the understanding of the effectiveness of treatments is most often based on experience from traditional use. But reports of this type are not very dependable and may not reflect the medicines current use and possibly its abuse. A recent example is ephedra or ma huang. This herbal medicine was marketed to promote weight loss and to increase athletic performance. Ephedra has been described as one of the oldest herbal medicines and has been used without adverse effects in traditional Chinese medicine for more than 5000 years for the treatment of respiratory problems and asthma. However, in April 2004 the U.S. Food and Drug Administration (FDA) banned its sale. After receiving reports of at least 100 deaths and almost 17,000 adverse effects linked to the use of this herbal medicine, the FDA ordered a review of its safety. This review evaluated the safety of ephedra from the clinical trials examining this medicine (50 trials). It found that ephedra use was linked to a two to three fold increase in the risk of high blood pressure, heart palpitations and psychiatric disorders. These risk levels lead the FDA to determine that "ephedra posed an unreasonable risk to those who used it."

Conventional medicine has come to have more of an appreciation of the potential of herbal medicine and a number of the more commonly used herbal medicines have been evaluated in clinical trials. The information which follows is based on the results of the small number of clinical trials that have been conducted to date on herbal medicines of importance to breast cancer and breast health.

The National Institutes of Health has recently established the National Center for Complementary and Alternative Medicine to provide funding, support and encouragement of rigorous research on complementary medicine, including herbs. Their website is located at: <http://nccam.nih.gov/>.

What are the similarities and differences between herbal and conventional medicines?

Herbal and conventional medicines share common historical and biological roots and have similarities. Their basic actions occur by the same mechanisms and the active ingredients in herbal medicines, like those in conventional medicines, can be considered drugs.

There are also differences between herbal and conventional medicines. Most conventional drugs contain a

Table 1: FDA's regulatory requirements for conventional and herbal medicines*

	Over The Counter Conventional Drugs	New Conventional Drugs	Herbal Medicines & Dietary Supplements
Registration Of Product With FDA	✓	✓	
Registration Of Product Manufacturer With FDA	✓	✓	
FDA Approval Before Product Sales Begin		✓	
FDA Defined Good Manufacturing Practices For The Product	✓	✓	UNDER DEVELOPMENT
Voluntary Reporting of Adverse Effects Reporting To FDA After Product Sales Begin	✓	✓	✓
Required Reporting of Adverse Effects To FDA After Product Sales Begin		✓	
FDA Defined Safety-Related Labeling Of Product	✓	✓	

*Modified from: Office of Inspector General, Department of Health and Human Services, 2001, available at: <http://oig.hhs.gov/oei/reports/oei-01-00-00180.pdf>.

single active chemical. In contrast, the individual herbs and multi-herb preparations used in herbal medicine typically contain many active ingredients. Sometimes the presence of more than one active ingredient makes the herbal medicine more effective. But having more than one active ingredient may also cause problems and make it more difficult to use safely and effectively. This is because multiple active ingredients in herbs may have different strengths or degrees of effectiveness, and they may also work on different biological systems in the body, which can be related or unrelated to the health problem being treated.

Herbal and conventional medicines also typically contain different amounts of active ingredients. In most, but not all, cases the active ingredients in herbal medicines are more dilute than those found in conventional medicines. This presence of lower amounts of active ingredients decreases the potential for problems with their use, but it can also limit effectiveness. Nonetheless, both herbal and conventional medicines should be used with care because all drugs carry the possibility of harmful or 'adverse' effects on health.

Herbal and conventional medicines also differ in consistency. The amount and purity of the single active ingredient found in most conventional medicines

are monitored and controlled. In contrast, herbal medicines can vary in both active ingredient levels and purity. The various active ingredients in herbal medicines can vary widely since they can be affected by the conditions in which the source plants are grown and how they are processed. Large differences in the amounts of active ingredients have been reported for a number of herbs both from the same producer and among different producers. Standardized extracts, which contain a minimum level of a specific chemical in the herb, are available for some herbs. But there are only a few herbs for which the active ingredients are known.

How are herbal and conventional medicines regulated in the U.S.?

Although herbal medicines have been used for a much longer time than conventional medicines, the safety and effectiveness of conventional medicines has been studied more and is much better understood. This is mainly the result of government regulations that require that the manufacturers of conventional medicines must present proof of the safety and effectiveness of the medicine, as well as, guidelines for its use to the U.S. Food and Drug Administration (FDA) before the

product is marketed. Table 1 lists additional regulatory requirements that the FDA requires for conventional drugs. These regulations add considerably to the cost of releasing a new drug but produce a substantial level of understanding of the medicine. This greatly increases the amount of confidence consumers can have in a drug's safety and effectiveness.

In contrast, almost all herbal medicines used in the U.S. are classified as dietary supplements and as such, they are regulated like foods. Because of this there are few regulatory requirements for these products (see Table 1). Manufacturers are not required to demonstrate either the effectiveness or the safety of herbal medicines (supplements) before they are sold. Further, if an herbal medicine is unsafe, this condition must be demonstrated by the FDA, instead of the manufacturer needing to demonstrate safety. Proof of a lack of safety is also complicated by the absence of a requirement that manufacturers record and report adverse effects of herbal medicines. Some monitoring of adverse effects is required but by the much less strict system designed to oversee adverse effects of foods. In addition, the manufacturers do not have to test the quality of the final product as they do for conventional drugs. This has unfortunately set up a system where herbal medicines are considered safe until enough adverse events occur to prompt the FDA to prove otherwise. Such an open market for these medicines has been highly criticized and has been described by some as "a disaster waiting to happen." This absence of regulation offers producers and consumers of herbal medicines a great deal of freedom about what kinds of herbal medicines are available, but it also gives consumers very little confidence that the herbal supplements available to them are either effective or safe. The National Research Council has recently proposed a new revised framework for the evaluation of the safety of dietary supplements including herbs.

How are herbal medicines regulated in other countries?

In other industrialized countries, there is more strict regulation of herbal medicines than in the U.S. For example, the European Union has recently updated its legislation regulating herbal medicines. Under this legislation all herbal medicines undergo regulation. Traditional herbal medicines are less regulated, in that they do not have to demonstrate effectiveness. But there are regulations regarding the demonstration of

safety, the specificity of labeling, the manufacturing procedures and the product quality. In addition, manufacturers must be licensed.

Are herbal medicines safer than conventional medicines?

Just because herbal medicines are "natural" products does not mean they are safer than conventional medicines. The ingredients in herbal medicines, that can lead to health problems or adverse effects, are generally found in lower amounts in plants, making it more difficult to get a large dose. But many herbal medicines are concentrated to increase effectiveness and this process may also eliminate this potential 'margin of safety.'

Detection of adverse effects is also more difficult for herbal medicines as they are currently marketed in the U.S. There is no focused safety testing of herbal medicines or required reporting of adverse effects. Detection by individual doctors is very limited in scope. In most cases, an individual doctor would have to treat an exceedingly large number of patients with the same medicine before an adverse effect could be detected.

Have problems been reported with the use of commercial herbal medicines?

Many problems, some of them serious, have been reported when herbal medicines are used. Some of these problems come from the herbal medicines themselves. Others come from interactions of herbal medicines with other medications; many of these interactions have been reported. Some examples are shown in Tables 2 and 3 below.

Several studies have also reported various types of contamination of herbal medicines. Contaminants in herbal medicines that have been reported include other herbs, microorganisms, toxins produced by microorganisms, pesticides and toxic heavy metals. In addition there are many reports of herbal products being adulterated with conventional drugs. Several of these problems have resulted in deaths.

Are there herbal medicines that might increase or decrease breast cancer risk or prevent recurrence in breast cancer survivors?

There is no direct evidence that the use of any herbal medicines can increase or decrease breast cancer risk. However, herbs that have estrogen-like actions raise concern. Several years ago, estrogen-like compounds from

Table 2: Results of clinical trials of the effectiveness and safety of herbal medicines used for treatment of menopausal symptoms

Herbal Medicine	Number of Clinical Trials	Effectiveness	Safety
Black Cohosh	7	May have some effectiveness in reducing menopausal symptoms but most of the trials are flawed.	No long term studies of safety have been conducted. Presence of estrogen-like activity is uncertain.
Red Clover	4	Three of these studies did not report a benefit for red clover extracts for menopausal symptoms. The fourth positive study was small and lasted for a short period of time.	Red clover extracts contain phytoestrogens. It is unclear if use will have estrogen-like effects on the breast and uterus which could change cancer risk in both these organs. No long term studies of safety have been conducted.
Soy & Soy Extracts	16	Results are mixed but twice as many studies reported no effect on menopausal symptoms as noted improvement. There were many different types of studies; some examined diet changes other examined supplement use.	Safety of soy supplements is uncertain as estrogen-like effects on the breast have been reported. See BCERF fact sheet No 1, <i>Phytoestrogens and Breast Cancer Risk</i> .
Dong Quai	1	Improvements in menopausal symptoms were not reported in this single study. Estrogen-like activity was not seen.	May interact with anticoagulants and lead to bleeding problems. No long term studies of safety have been conducted.
Evening Primrose Oil	1	No benefit in menopausal symptoms was reported.	No adverse effects have been reported but long term effects have not been examined.
Ginseng Extract	1	No benefit in menopausal symptoms was reported.	Induction of vaginal bleeding after menopause has been reported. This adverse effect could possibly arise from estrogen-like chemicals produced by <i>Fusarium</i> fungi; these chemicals have been found in ginseng preparations. No long term studies of safety have been conducted.
Kava kava	4	Kava kava (used alone in two studies, with calcium in one study and with postmenopausal hormone treatment in another study) has been reported to be beneficial for menopausal symptoms. See the section on important safety concerns below.	Kava kava use has been reported to be linked to hepatitis and liver failure. This effect can occur after a short period of use (varied between 2 weeks and 2 years). Sale of Kava kava has been banned in several countries. See the section below.

plants (phytoestrogens) were thought to have the potentially positive effect of acting like weak estrogens in the body. It was proposed that these weaker estrogens could block effect of estrogen in the body and possibly decrease breast cancer risk, as well as disease recurrence in breast cancer survivors. This idea changed when clinical studies showed proliferation (increased cell multiplication) in the breasts of women on diet high in soy phytoestrogens. To the surprise of the researchers conducting these studies, women on the high soy phytoestrogen diets had increased breast proliferation, an estrogen-like effect, which may be a preliminary step in cancer formation or could lead to the growth of latent cancer cells. (See BCERF fact sheet No 1, *Phytoestrogens and Breast Cancer Risk*.) Herbal medicines with estrogen-like actions should not be used for long periods of time, especially by women with a past history or high risk of breast cancer.

Some of the interactions of herbal medicines and drugs arise through stimulation or inhibition of the body's metabolism of these drugs. Such an effect by a herbal medicine could potentially either increase or decrease the formation of cancer causing chemicals and, in theory, could lead to an increase or decrease in cancer risk in general. Interactions of herbal medicines with drugs used in cancer treatment have also been reported.

What herbal medicines have been studied for the relief of the symptoms of menopause? Are they effective?

Use of herbal medicines for the relief of menopausal symptoms is an active area of research. The results of this research summarized in Table 2.

Problems with the use of Kava kava (listed in Table 2) illustrate how complicated herbal medicine use and regulation can be. Clinical trials of Kava kava have demonstrated a benefit for the treatment of both menopausal symptoms and anxiety. These trials detected few side effects and this herbal medicine has been used by natives of South Pacific islands for centuries. However, there have been reports of hepatitis and liver failure for people in Western countries using Kava kava. This is a serious effect and resulted in the need for liver transplants in about one fifth of the people affected; some individuals died. In Germany, herbal medicines are closely regulated and monitored and the majority of adverse cases linked to Kava kava use have been detected there (39 cases between 1990 and 2002). This effect is rare and could have been missed without the program

in Germany that monitors adverse effects. In the U.S. two cases were reported over this period. Why this toxic effect has not been reported with the traditional/native use is unclear. Differences in the preparation of the Kava kava are one possibility. Traditional use of Kava kava involves mashing underground parts of the plant with coconut milk whereas Western use involves alcohol or acetone extracts which have a different composition. In addition, Western preparations may contain other plant parts that can contain possible toxins. Other theories involve genetic differences in liver metabolism and possibly interactions with other medicines. The FDA has issued an advisory for Kava kava warning consumers of this potential effect. Sale of Kava kava has been banned in several countries including Germany.

What herbal medicines have been studied for menstrual problems? Are they effective and safe?

Herbal medicines have been studied in clinical trials for two types of menstrual problems, premenstrual syndrome and menstrual pain (dysmenorrhea). The results of these studies are presented in Table 3.

What herbal medicines have been studied to help with breastfeeding? Are they effective?

Very little study has been conducted examining herbal medicines used for the treatment of breastfeeding disorders. Four trials have examined cabbage leaves and an extract made from them to relieve engorgement for breastfeeding women. None of these studies found this treatment to be effective.

Breastfeeding women are advised to use caution when considering the use of any drug, conventional or herbal. This is because some drugs can enter into breast milk and, in some cases, there is also concentration of the drugs in breast milk. Because of the lack of studies in this area, as well as the problems with the quality of many herbal medicines, women should be very cautious about using herbal (and other) medicines while they are breastfeeding.

What herbal medicines have been studied for increasing breast size? Are they effective and safe?

Several expensive herbal preparations are currently marketed as effectively increasing ('enhancing') bust size. There is no evidence that they are effective in any

Table 3: Results of clinical trials of the effectiveness and safety of herbal medicines used for treatment of menstrual problems

Herbal Medicine	Number of Clinical Trials	Effectiveness	Safety
PREMENSTRUAL SYNDROME			
Evening Primrose Oil	3	The results were mixed. The two best designed studies were limited in size (38 women) and evaluation time (3 or 4 menstrual cycles for each treatment.) Neither found any benefit for evening primrose oil. Other studies reported some relief for about half of the women examined.	There have been no reports of adverse effects but the safety of long term use of evening primrose oil is unknown.
Chaste Tree Berry Extracts	3	May have a beneficial effect for some women. All three trials reported a beneficial response for about half of the women studied.	Adverse effects are rare but include itching, rash, fatigue, headache, agitation, and nausea. This herb may decrease the effectiveness of oral contraceptives. The safety of long term use of this herbal medicine is unknown.
Ginkgo Biloba Extract	1	No benefit over placebo was reported.	Adverse effects are rare but include rashes, headaches and stomach and intestinal upset. The safety of long term use of ginkgo biloba extract is unknown.
MENSTRUAL PAIN (DYSMENORRHEA)			
Toki-shakuyaku-san (Japanese Herbal Medicine)	1	Beneficial effect reported in this single study.	There are no reports on the short or long term safety of use of this herbal medicine.
Toki-shakuyaku-san with Shakuyaku-kanzo-to (Japanese Herbal Medicines)	1	Beneficial effect reported in this single study.	There are no reports on the short or long term safety of use of this herbal medicine.

way. No clinical trials or animal studies examining the effectiveness of any of these products have been published. Several drugs including estrogen have been linked to increases in breast size. Two of these products have been examined for estrogen-like action in animals. One study found no estrogen-like action and a second poorly-conducted study found minor estrogen-like action. Some of the herbs in these products contain phytoestrogens (estrogen-like chemicals found in

plants) but it is unlikely that their levels are sufficient to make the products effective. Some of these products contain grains or hops and these ingredients might contain a potent phytoestrogen if they had been allowed to become moldy. Reports have documented a breast enlargement disease in a section of China where grain contamination with a certain type of mold, *Fusarium*, is common. *Fusarium* mold has been shown to produce a potent phytoestrogen. One of these breast

'enhancement' products has been tested for the presence of Fusarium mold and found to be free of this contamination. There is no evidence for its consistent presence in any of these products.

There has been no direct study of the safety of these breast enhancement products. Although the effectiveness of these products is unlikely, it should be noted that for such products to work they would have to generate proliferation in the breast. Factors that cause proliferation in the breast, such as estrogen, have been linked to an increase in breast cancer risk. Accordingly, there is the possibility that if these products were effective, they may well be linked to breast cancer risk. Concern about these products also arises because they are aggressively marketed to adolescent women. Adolescence is a period of life when breast cancer risk may be high due to the ongoing development of the breast. Exposures that might alter this development should be avoided.

What can women do now?

If women choose to use herbal medicines they should do so with caution because the quality of these medicines varies and the safety, especially after long term use, is uncertain. Because of this, women should be sure to choose high quality products from reputable sources. Women should also be careful to keep in mind that these are medicines and choose doses carefully. Women should also tell their health care providers about all of the herbal medicines they are taking in case these medicines might interact with other treatments.

Some herbal medicines show promise for the treatment of problems with menstruation and menopause and other conditions that affect women. It is unfortunate that their quality and safety are not better controlled. ■

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