10th Conference on Health Care of the Chinese in North America

Herbal Therapy for Women

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Lecture Objectives

- To understand the current political climate surrounding herbal therapies
- To understand the epidemiology of botanical use in this country
- To know the basic concerns about herbal therapies you should share with your patients
- To get a general overview of several of the most commonly used female herbal therapies today

Specifics of Women and Herbal Therapies

- Women often are more interested in using herbal medicines for preventative health than men
- Women are seeking out more alternative and complementary therapies than men
- Women will spend 1/3 of life in menopause, with more recent data on the concerns of using hormonal therapy, women are interested in alternative approaches to menopause
- Women are fearful of having surgeries such as breast surgery, hysterectomy, and oophorectomy. They are interested in having more control over their health choices

Epidemiology of Botanical Use

- Americans spent >$4billion on herbal medicines in 1998
- 15 million US adults took prescription medicines concurrently with herbals
- 4 billion people worldwide use herbal medicine
- 70% of German physicians in general practice prescribe herbal remedies
- phytomedicines comprise 30% of all drugs sold in German pharmacies (St. John's Wort outsells Prozac 7:1!)
- 1/4 of all drugs presently in use are derived from plants
- only 30-40 of the 1200 or so herbs in international commerce have substantial scientific evidence supporting their therapeutic value

Can Consumers Trust What They Buy? Not Always!

Dietary Supplement Health and Education Act of 1994 (DSHEA)

In response to rumors that FDA Chairman David Kessler planned to tighten regulation of the herbal industry, the public waged an active ad campaign in 1993 that resulted in the passage of DSHEA. DSHEA classifies vitamins, minerals, herbs, and amino acids as nutritional or dietary supplements. It allows supplements to be marketed without testing for efficacy, proof of safety, or proof of marketing claims, as long as they make no claim to diagnose, treat, cure or prevent disease.

Manufacturers can make "structure" and "function" claims: products can enhance a normal body function such as thinking, mood, immune function. For example, a product can be labeled "maintains healthy cholesterol" but not claim that it "lowers cholesterol or reduces the risk of heart attacks." "Promoting urinary tract health" is allowed but not "treats urinary tract infections or prostate enlargement."

In addition, the FDA must prove an herbal preparation unsafe for it to be taken off the market (as opposed to OTC and prescription drugs that need to be proven safe and effective by manufacturers before they are approved).

A Recent Kaiser Family Survey of Americans and Dietary Supplements showed that 35% of people surveyed believed the government does regulate dietary supplements and 37% of respondents felt they are adequately tested for safety and purity!

Economics of US Pharmaceuticals: large firms now entering the market

It takes an average of 15 years and $300-500 million for pharmaceutical firms to bring a new drug to market. Until recently, drug companies were not interested in producing herbal products because plants couldn't be patented. Within the last 2 years, however, larger companies are entering the herbal market with brand name products (often made from standardized extracts which they import form German pharmaceutical firms):

Warner-Lambert: Quanterra brands (Gingko, Saw Palmetto and St. John's Wort).

Bayer Corporation: One a Day products: Cold Season (Echinacea, Zinc, and Vitamin C), and Cholesterol Health (Garlic, Soy extract, Vitamin E and Lecithin)

Whitehall-Robins Healthcare: six Centrum Herbal Formulas

Pharmaton (Boehringer Ingelheim): Venastat (Horse Chestnut Seed extract to promote better circulation in the legs), Movana (St. John's Wort), and Ginkgoba.

Many experts feel that these large pharmaceutical companies will bring improved quality control, safety, and credibility to the herbal industry (but with a higher price tag!).

Risks Associated with Taking Herbal Medicines

A review of the risks associated with taking herbal medicines (Ernst 1998) chronicles many examples of why the herbal buyer needs to beware:

Unanticipated/Unwanted effects of the herb itself:

Acute hepatitis has been associated with the Chinese herbal product Jin Bu Huan, the herbs Germander (Laiberte and Villeneuve 1996) and ma-huang (Nadir et al, 1996).

A combination of 8 herbs (PC-SPEC) marketed to balance the immune system in patients with prostate cancer was found to contain potent estrogenic activity in vitro, in animals and in 8 men with prostate cancer who developed breast tenderness, decreased libido, and even DVT (DiPaola et al, 1998).

Contamination of herbs with harmful substances:

Two cases of accidental digitalis toxicity were reported in patients who ingested an intestinal cleansing mixture of 14 herbs. A large patch of plantain (one of the 14 herbs in this mixture) was unintentionally contaminated with Digitalis lanata and then distributed to over 150 manufacturers over a two-year period (Slifman 1998).

Ayurvedic herbs imported from India and Tibetan herbal medicines are often boiled in clay or metal pots, leading to unintentional contamination of the herb with traces of lead, mercury and arsenic.

Safety of Herbal Medicine: Buyer Beware

Consumers of herbal medicines have no guarantee that:

- the plant was accurately identified in the field
- another less effective plant part or species wasn't substituted
- the plant's active ingredients end up in the herbal preparation you buy
- the herb is pure (i.e. no microbial, pesticide or heavy metal contamination)
- the herb is safe
- the herb is effective
- the next bottle of those same pills has the same ingredients at the same dose
- a Good Housekeeping article showed a 17-fold difference in concentration of St. John's Wort in the 6 leading brands!

Advice for Patients Taking Herbs

Purchase only products labeled with the following information:

botanical name of the herb with the part of the plant used, batch or lot number, expiration date, name and address of manufacturer

- Exercise caution taking herbs during pregnancy and lactation
- Use standardized extracts whenever possible (ensures a standardized dose)
- Avoid regular use of a large variety of herbs – most botanicals have not been checked
- for safety themselves, let alone when mixed with OTC and prescription drugs
- Talk with your physician about your use of herbal medicines. Reevaluate their efficacy and safety on a regular basis
- Consider stopping herbal therapies at least 2 weeks before elective surgery

- Report adverse side effects to your doctor and notify the FDA Medwatch Program (1-800-332-1088)
- Exercise caution if immunocompromised due to risk of microbial contamination
- Learn as much as you can!

Premenstrual Syndrome

Evening Primrose Oil (Oenothera biennis)

*** natural source of essential fatty acids**

*** may be useful in medical disorders that have deficiencies**

in essential fatty acid metabolism or deficiency (including cyclical mastalgia and atopic dermatitis)

Current Uses

Premenstrual syndrome (especially mastalgia), menopausal symptoms, atopic dermatitis, diabetic neuropathy, and rheumatoid arthritis.

Active Ingredients/Plant Information

A biennial herb that grows to about one to three meters high. Large delicate wildflower, native to North America. The blooms last only one evening. The flowers are yellow in color and the fruit is a dry pod that contains small seeds. The oil extracted from the seed is 60-80% linoleic acid plus 8-14% gamma-linolenic acid/ GLA (an omega six fatty acid that is formed in the human body from the desaturation of linoleic acid). These essential fatty acids are important as cellular structural elements and as precursors to prostaglandins and must be provided by the diet as the body cannot manufacture them.

Mechanism of Action

Linoleic acid is a precursor of prostaglandin E and several other active substances. Patients with dermatitis are often deficient in the enzyme that converts linoleic acid to omega6 fatty acid. People with PMS and cyclic mastalgia may have a defect in the conversion of linoleic acid to its metabolites, gamma linolenic acid, dihomogammalinolenic acid and arachidonic acid.

Preparations/Dosage

Optimal dose and duration of treatment is not known. Several trials for mastalgia have used 500 mg. capsules, 6 per day.

Cost

About 25 cents per pill

Side Effects

EPO appears to be safe and well tolerated. Side effects noted include nausea, softening of stools, headache.

Research

Budeiri et al., Controlled Clinical Trials, 1996

A systematic literature search looking at Evening Primrose Oil for the treatment of Premenstrual Syndrome. Two well-controlled trials failed to show beneficial effects (Khoo et al., used 38 patients in a well done RCT, crossover. Collins et al, also used 38 patients and this study was a RCT).

Pye et al., Lancet, 1985

291 patients in a breast pain clinic were randomized to be given either evening primrose oil, progestins, danazol, or bromocriptine for 6 months. Patients with cyclical and noncyclical mastalgia were studied. For cyclical mastalgia, evening primrose oil seemed the most promising.

Chenoy et al., Br Med J, 1994

A RCT looking at EPO vs. placebo in the treatment of postmenopausal flushing. Negative study.

St. John's Wort (Hypericum perforatum)

*** well-tolerated mild anti-depressant with fewer side effects than standard tricyclic antidepressants**

*** trials are ongoing to see how it compares with SSRIs**

*** may be effective for mood disorders associated with PMS**

Clinical Vignette: 23 year old female with depressed mood during the 2 weeks before her period. She has no significant PMH. She has no history of anxiety or depression during any other time than before her period.

Questions: Would SJW be effective in treating her cyclical depression?

Is there any data to support this? Could she take her SJW 2 weeks during the month or on a daily basis?

Crampbark (Vibernum Opulus)

Traditionally used for menstrual cramps, no data.

Black Haw (Viburnum prunifolium)

Traditionally used for cramps, no data.

Don Quai (Agnelica senensis)

Popular herb used for a variety of menstrual problems, no data. See next section on Menopause.

Chasteberry (Vitex agnus castus)

See section on menopause. No data in English to supports its use for PMS. It acts on dopamingic pathways and inhibits prolactin release. May stabilize the luteal phase and regularize menses.

Pregnancy

Blue Cohosh (Caulophyllum thalictroides)

*** a uterotonic herb to prepare a woman for birth**

Folk History and Traditional Use

Native Americans used it for rheumatism, colic, sore throat, cramps, labor pains, and inflammation of the uterus. Nicknamed "a woman's best friend" because in helps in cases of prolonged labor when fatigue sets in.

Plant Information

A perennial plant that grows well in North America. The mature plant has a peculiar bluish-green color and bears dark blue fruits. It is a member of the family Berberidacae.

Current Use

Aid in childbirth-used to quicken a delayed delivery.

Active Ingredients

The plant root contains a number of alkaloids and glycosides. The main ingredients seem to be the alkaloid methylcytisine and the glycoside caulosaponin.

Mechanism of Action

Animal studies show that methylcytisine resembles nicotine. The compound elevates blood pressure and stimulates uterine motility and intestinal motility. Can also cause coronary vasoconstriction.

Toxicity

Not recommended for patients with high blood pressure or cardiac disease.

Research

No human or animal data during pregnancy.

Ginger (Zingiber officinale)

*** a safe effective herb for the treatment of post-operative nausea and possibly for the treatment of hyperemesis gravidarum**

Folk History/Traditional Use

Ginger has been used in China for thousands of years. Used as a cooking spice as well as medically for a variety of problems including: nausea and vomiting, motion sickness, cough and colds, menstrual cramps, antidote to shellfish poisoning, digestive aide for diarrhea and indigestion, fever, toothaches and more.

Plant Information

A perennial plant that grows in the warm climates of India, Jamaica, and China. The plant has green-purple flowers that resemble an orchid, and aromatic roots and rhizomes. The underground parts of the plant are used in botanical medicine.

Current Use

Post-operative nausea, motion-sickness, hyperemesis gravidarum, chemotherapy-induced nausea and vomiting.

Active Ingredients

The pungent ingredients seem to have the most pharmacologically active components. The main components are gingerol, shagaol, and sesquiterpines (including bisabolene, zingiberene, and zingiberol). The gingerol is the pungent material that is likely to have the most pharmacological activity.

Method of Action

Suspected pharmacologic activities include: antioxidant(increases shelf life of meat), inhibitor of prostaglandin synthesis (including inhibiting thromboxane production which affects platelet aggregation). Other effects seen in animal studies or in vitro include lipid-lowering effects, chronotropic activity, and bactericidal activity. Animal data suggests that ginger's effect on nausea and vomiting is due to a direct effect on the stomach and not the central nervous system.

Side effects/Toxicity

GI discomfort in studies with large doses (>9gm/day). No safety problems seen in pregnant women. However the German Commission E does not recommend ginger during pregnancy. Lactation studies not performed. Concern exists regarding increased risk of bleeding, so caution in patients with bleeding disorders or on blood thinners.

Dosage

Standardized preparations are not necessarily recommended because the clinical trials to date have not used them. There is currently no consensus regarding to which constituents to standardize. The usual dose used for preventing nausea is 1 gram of dried powdered gingerroot.

Research

Fischer-Rasmussen et al., 1991

A RDBPC crossover trial of 30 women suffering from hyperemesis gravidarum, ginger (250 mg QID) significantly decreased the severity of nausea (p=.04).

Phillips et al., 1993 and Bone et al., 1990

2 studies that were RDBPCT report a significant decrease in perioperative nausea and vomiting in gynecological surgery patients who were given 1 gm of ginger before surgery. In one, ginger was as effective as reglan in reducing the number of episodes of nausea or emesis. In neither study was there any mention of any bleeding problems.

Black Haw (Vibernum Prunifolium)

Used for preventing repeated miscarriage in Native American history. Scant data.

Back Cohosh

See section on Menopause – no data

Vitex

See section on Menopause – no data

Raspberry Leaf

Traditionally used for nausea during pregnancy.

Chamomile

Traditionally used for nausea during pregnancy.

Urinary Tract Infections

Cranberry (Vaccinium macrocarpon)

*** decreases bacteriuria and pyuria in asymptomatic women**

*** no studies comparing it to antibiotics in women with UTIs**

Folk History and Traditional Use

The American cranberry is cultivated extensively in the United States and has been used in American cooking since the Thanksgiving time. The American Indians taught the Pilgrims the many uses of the berry.

Current Uses

Treatment and prevention of Urinary Tract Infections.

Active Ingredients/Plant Information

Not known, the ripe fruit is used.

Mechanism of Action

In 1923, American scientists noted that the urine of test subjects taking cranberries was more acidic. They surmised that cranberries might prevent and treat urinary tract infections. In 1967 a study showed that consumption of the commercial cranberry juice cocktail did not acidify the urine sufficiently to produce the antibacterial effect. Subsequent studies have showed that the effectiveness of cranberries in UTI sufferers does not have to do with its ability to acidify the urine. It appears to inhibit the ability of microorganisms, especially E. coli to adhere to the epithelial cells of the bladder. This renders the environment less suitable for the growth of bacteria. An in-vitro study in 1989 showed that cranberry juice had at least 2 inhibitors of lectin-mediated adherence to bladder cells.

Dosage

300-400 mg. of concentrated extract BID, or cranberry cocktail 8-16 ounces per day.

Side Effects/ Drug interactions

None known.

Research

Avorn et al., JAMA, March 1994

A randomized controlled trial with 153 elderly women. They were given 300cc/day of a cranberry juice cocktail or a placebo drink for 6 months. Bacteriuria with pyuria was found in 28.1% of urine samples in the placebo group and only 15% in the group randomized to the cranberry juice. The differences were seen primarily after the first month of study. Subjects in the cranberry group showed less bacteriuria irrespective of pyuria, but this was not statistically significant. The use of antibiotics was significantly decreased in the study group. Future studies using women with UTIs would be helpful to clarify the role of cranberry juice in the treatment of UTIs.

Migraines

Feverfew (Tanacetum parthenium)

*** used for prophylaxis of migraines**

*** no good data comparing it with standard medications**

*** caution in patients on blood thinners**

Folk Use

Traditionally used to treat fevers, headaches, menstrual irregularities, psoriasis, arthritis, and stomach ailments. Feverfew is a member of the daisy family of plants. The 17th century herbalist Culpepper recommended its use in aiding the ejection of afterbirth and stillbirths. The origin of the term parthenium may come from an incident where feverfew was used to save the life of someone who had fallen from the Parthenon during its construction in the 5th century BC. The Greek word parthenios also means "virgin", relating to the herbs' reputation as a treatment for female ailments. Feverfew comes from the Latin febrifuge that means "fever reducer."

Current Use

Used for migraine prophylaxis.

Active Ingredients

The primary active components are the sesquiterpene lactones, particularly parthenolide which makes up 85% of the total sesquiterpene content. Aerial parts of the plant contain the highest concentration of active ingredients, especially leaves.

Plant Information

A perennial plant with a strong-smelling greenish-yellow feather-like leaf grows best in fields and meadows.

Mechanism of Action

The precise mechanism of action is not clear.

In-vitro: inhibits degranulation of both platelets (inhibits the secretion of serotonin) and leukocytes (inhibits lipoxygenase and cyclo-oxygenase).

In-vivo: in animal studies, inhibits prostaglandin, thromboxane and luekotriene synthesis (inhibiting bronchoconstriction and vasoconstriction in guinea pigs after IV administration).

Preparation

Dried aerial parts of the plant which contain at least 0.2% of parthenolide are used.

Dosage

Adult daily dose is 50 mg dried leaf (2-3 fresh leaves/day). Its also available as a dried leaf powder in capsules with the adult daily dose being equivalent to 0.2-0.6 mg of parthenolide. Parthenolide content may be unstable or quite variable, so some recommend keeping feverfew refrigerated. It is recommended that it be taken daily for 3-8 months for prophylaxis (abrupt discontinuation after several years of use has been associated with rebound migraines). No head-to-head trials with prescription migraine medications are available.

Side Effects

Extremely well tolerated. No long-term clinical studies of toxicity have been conducted. Chewing the leaves can cause ulcerations in the mouth and swelling of the lips and tongue. Hypersensitivity reactions have also been reported. Due to its inhibitory effects on platelets, caution should be exercised in patients with bleeding disorders or patients on blood thinners. No safety data in pregnant or breast-feeding are available. No reported interactions with medications, except perhaps NSAIDs which might decrease it's effectiveness by inhibiting prostaglandin synthesis.

Research

Murphy JJ et al. Randomized double blind placebo-controlled trail of feverfew in migraine prevention (1989) Lancet 189-192.

This 4 month trial compared feverfew vs. placebo for the prevention of migraine headaches. Of the 20 men and 56 women with both common and classical migraines, 47% had previously tried prophylaxis, 51% had tried

ergotamine preparations and 22% had not taken either, 23% had previously tried feverfew. On entry to the study, only 12 patients were on a daily prophylactic regimen. After a one-month single-blind placebo run-in period, patients were randomized to feverfew or placebo daily for 4 months then crossed- over to the other treatment arm for

another 4 months. Each feverfew capsule contained 70-114 mg of dried feverfew leaf, equivalent to 0.545 mg of parthenolide. Analysis was restricted to the 79% of patients who finished the study.

Results: 24% reduction (95% CI 14-34%) in the number of attacks during feverfew treatment with no significant alteration in the duration of individual attacks. Significant reduction ($p < 0.02$) in nausea and vomiting with each attack. Global assessment scores on efficacy showed that feverfew was better than placebo. There was no difference in side effects with feverfew vs. placebo. There was a non-statistically significant trend toward decreased severity of migraine symptoms in the feverfew-treated patients.

Vaginitis

Vaginal infections are one of the most common reason why women come to visit their doctor. Despite the common prevalence of yeast vaginitis, bacterial vaginosis, and trichomonas vaginalis, there is little to data to support the use of herbal therapies. Nonetheless, I will include a few that herbalists and naturopathic physicians use for their patients with the above infections who want to have other options besides diflucan, fungal creams, and flagyl.

Botanical Remedies:

Garlic (Allium sativum)-inhibits the growth of candida albicans and has anti-bacterial properties as well. Garlic inserted into the vagina has been used over the years for both candida (yeast vaginitis) and bacterial vaginosis. Carefully peel a clove of garlic and do not nick it and leave in for 6-8 hours. Garlic can be threaded like a necklace as if it were a tampon. You can take garlic supplements orally as well. Dosing is not uniform.

Goldenseal (Hydrastis canadensis) and Oregon Grape Root (Berberis vulgaris)-these herbal remedies contain contents called berberine that has an anti-bacterial property as well as an immune stimulating effect. The berberine chemical has antimicrobial activity against yeast and bacterial vaginosis. These herbs can be taken by orally or intravaginally in suppositories. To treat an acute infection take 2 capsules 1-2 times per day orally, or one capsule intravaginally q day.

Tea Tree (Melaleuca alternifolia)-has been used against trichomonas, candidia and bacterial vaginosis. Studies do support its effect in curing trichomonas and yeast vaginitis. The most common way of using it is in the form of suppositories or pessaries.

Other herbal combinations include the use of myrrh, geranium, yarrow, marshmallow, and calendula.

Other agents:

Lactobacillus acidophilus - given as a supplement orally or intravaginally is effective for treating yeast and bacterial vaginosis. There has been some data to support eating a cup of yogurt a day in the prevention of candidal infections. When buying a lactobacillus product

in yogurt, make sure the label says lactobacillus. When purchasing lactobacillus capsules, request product analysis information to assure quality.

Boric Acid - can be supplied in suppository form in the treatment of candidal vaginitis. 600 mg suppositoris twice/day for 2-4 weeks can treat chronic resistant yeast infections of the vagina (BID for 7 days for an acute infection). For prevention of yeast infections, can use a 600 mg suppository 4 days per month during menses for 4 consecutive days.

Genital and Oral Herpes

Nutritional supplements to consider: L-Lysine 1 gram TID or an acute infection, 1 gram daily for prevention, Vitamin C supplementation about 2 grams/day during the prodromal phase, Vitamin E-topical application may provide pain relief, Zinc supplementation of 25 mg BID during an acute eruption.

Botanicals: Lemon balm topically can reduce the healing time of an cold sore or genital lesion, licorice ointment can decrease healing time. Topical myrrh and goldenseal have been used as well.

Menopause

Don Quai (Angelica sinensis)

*** age-old Chinese herb used for a variety of female problems**

*** no data to support its use in the treatment of menopausal hot flushes**

*** concern of increased bleeding in women on coumadin**

Folk History and Traditional Use/Plant Information

An herb grown and use widely in the orient for thousands of years to treat female gynecological problems. The root of the plant has been used for a variety of ailments including uterine cramps, headaches, PMS, menstrual irregularity, and arthritis. Care in harvesting angelica is urged, as it looks similar to the deadly poison hemlock. Angelica seed and roots are used as flavorings in several alcoholic beverages included gin.

Most Common Current Uses

PMS, irregular menses, infertility, and menopause

Active Ingredients

There are approximately 6 coumarin derivatives that have been isolated as the main active ingredients, they include: oxypeucedanin, osthol, psoralen, and bergapten. These appear to be the most active ingredients.

Mechanism of Action

Coumarins have been shown to exert vasodilatory and antispasmodic effects on the uterus. Has also been shown to lower blood pressure.

Preparations/Dosage

Standard dosage is 2-6 grams/day of the dried root in divided doses. Capsules are available.

Side Effects

The stems of the angelica plant contain psoralen which can induce photosensitization and dermatitis. Potential interacton with the coumarin-like derivatives creates a theoretical concern for patients taking anticoagulants, or who are experiencing heavy bleeding.

Research

* use in post-menopausal hot flashes- Hirata et al., 1997

71 postmenopausal women randomized to receive don quai vs. placebo for 6 months in a DB trial. No statistically significant differences were found in the number of vasomotor flushes. Traditional Chinese medicine practitioners criticize this study because they rarely prescribe don quai alone.

Black Cohosh (Cimicifuga racemosa)

*** used for treating menopausal symptoms**

*** does not appear to have significant estrogenic effects**

Folk history and Traditional Use

A native American favorite for menopausal symptoms, PMS, and childbirth (used in conjunction with blue cohosh in the last week of pregnancy to prepare the uterus for childbirth). It was called "Squaw Root" because it predominantly helps with gynecological problems.

Plant Information

This is a native North American plant. The root is odorless and has a bitter taste. The root supplies estrogenic sterols.

Current Use

Treatment of postmenopausal hot flushes in women who cannot or do not want to take estrogen replacement therapy, facilitate labor

Active Ingredients

The active ingredients include triterpene glycosides, including actein and cimicifugoside. Another active ingredient is the isoflavanoid formononetin. The standardized extract of Remifemin contains 2 mg of 27-deoxyactein. The standard dose in most studies is 2 tablets BID.

Mechanism of Action

Animal and human studies have been conducted. Similar to the weak estrogen, estriol, black cohosh weakly binds to estrogen receptors for a short duration. Estrogen-binding studies in-vitro show evidence of antiproliferative effects on the growth of breast carcinoma cells. Animal and human studies show the herb lowers LH levels. There is no data on black cohosh's estrogen-like effects on the endometrium or the vagina. Animal data supports its oxytoxic properties which enhance uterine contractions.

Dosing

Most studies use 40 mg/day of the crude drug. The most widely used brand is Remifemin. The standard dose of this tablet is 2 tablets BID. See Table 1.

Table 1. Selected formulations of black cohosh used in European controlled clinical trials (adapted from Rotblott's article, WJM, September 1999)

US product (importer)	European product (manufacturer)
Remifemin (Enzymatic Therapy)	Remifemin (Schaper & Brummer)

Cost

$12-30/month

Side Effects/Toxicity

Mild side effects include GI complaints, HA, dizziness, and weight gain. Despite its traditional use during the third trimester of pregnancy, there is no safety data during pregnancy and lactation.

Research

Duker et al. Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats (1991)Planta Med 57(5):420-424.

110 menopausal women on no HRT for 6 months were randomized to take 2 tablets BID of the brand Remifemin (2 mg tablets of C.r. in each tablet) vs. placebo for a 2 month period. Blood levels of LH and FSH were taken. Results show that LH levels were significantly reduced in the women treated with black cohosh. Mean FSH levels were similar in both groups.

Liberman. A review of the effectiveness of Cimifuga racemosa for the symptoms of menopause (1998) Journal of Women's Health 7(5):525-529.

There are at least 5 controlled studies comparing black cohosh extract with placebo or estrogen therapy in women with menopausal symptoms. Significant changes in a series of standard psychometric scales and the Kupperman index have been reported compared with placebo but none of these studies were double-blinded. Most were of short duration and some did not show and improvement in symptoms in the estrogen-treated arms.

Chasteberry (Vitex agnes-castus)

*** long folk-history of its use**

*** no data to support its use for PMS or menopause**

Folk History and Traditional Use/Plant Information

This berry has been used for over 2000 years. The Latin name agnus castus means chaste lamb. This refers to the property of the seeds which were known to decrease sexual desire. The medieval monks used it to keep their vow of chastity (also called Monk's Pepper). The herb consists of dried ripe fruits of the Chaste tree. The plant is native to the Mediterranean region. The hard, black berries have an aromatic odor and a slight peppery taste.

Current Use

Menstrual Problems, Menopause, Prevention of Miscarriage

Active Ingredients

The chaste berry contains a volatile oil which has agnoside and aucubin. The active ingredients have not been identified.

Mechanism of Action

Animal studies suggest the berries have a prolactin-inhibiting action. More specifically, it acts on the D2-type dopamine receptors. The herb can stimulate the secretion of LH and can help maintain the corpus luteum.(animal data only).

Dosing/Pharmacokinetic

No studies

Side Effects

Nausea, diarrhea, mild skin rash.

Research

No data on menopausal symptoms

No English data on menstrual irregularity and the use of chasteberry

Soy (Glycine max)

*** an example of a phytoestrogen compound**

*** no prospective human data on reducing risk of CHD or osteoporosis or breast cancer**

*** decreases hot flashes**

Folk history and Traditional Use/ Plant Information

An essential part of the Asian diet. Typical Asian diet has 40-80 g/day as compared to the American diet of <5 g/day. The soybean plant belongs to the "pea" family, Leguminosea. The soybean is an annual plant.

Active Ingredients

Important compounds include fatty acids as well as phytoestrogens. In fact, soybeans are probably the richest source of phytoestrogens. Phytoestrogens can be classified as lignans (including enterolactone and equol) mainly found in seeds and grains, and isoflavones (including genistein and daidzein), found in legumes.

Mechanism of Action

Soy has shown to have anticancer effects in-vitro (breast cancer, endometrial cancer, and prostate cancer models). Soy contains phytoestrogens which are weaker than the body's own estrogen. In premenopausal women, phytoestrogens compete with the more potent estrogen in the body, thus reducing the total effects of estrogen. In menopausal women, phytoestrogens supplement the body's waning estrogen levels. Phytoestrogens bind weakly to the alpha estrogen receptor (alpha= receptors in reproductive tissue). Genisten may have similar affinity for the beta receptor as estradiol (beta-receptors in bone tissue). No data on risk of fractures and phytoestrogen use. No good data regarding phytoestrogens and coronary artery disease.

Toxicity/Side Effects

Tolerance to soy in human studies has been excellent. There is no safety data for the role of soy in infant formulas. Inhalation of soy dust caused an asthma epidemic in 26 patients. Animal data shows that soybean isoflavones may inhibit thyroid synthesis.
Dosing

Typical dosing is 40-80 mg/day.

Research Hot Flashes:

Albertazzi et al., Obstetrics and Gynecology, 1998

A DB RCT of 104 post-menopausal women looking at the effect of daily dietary supplementation of soy protein isolate powder on hot flushes in post-menopausal women. 51 patients took 60 g of isolated soy protein daily and 53 took placebo. The study lasted 12 weeks. Soy was significantly superior to placebo in reducing the mean number of hot flushes per 24 hours after 4, 8, and 12 weeks. By the end of the 12th week, patients taking soy had a 45% reduction in hot places versus a 30% reduction in the placebo group

Breast Cancer:

Epidemiologic studies show a reduction in breast cancer risk in women who ingest large quantities of soy (mostly in premenopausal women). However, the results are not consistent. There is a lack of double-blind, placebo-controlled studies. There have only been case-controlled studies looking at the dietary patterns of women diagnosed with breast cancer. Wu et al. (Cancer Epidemiol Biomarkers Prev), in 1996, showed in a case-controlled study that in both pre-menopausal and post-menopausal women, the risk of breast cancer decreased with increased frequency of tofu ingestion.

Osteoporosis:

Soy consumption may reduce the risk for osteoporosis. However, long-term randomized controlled trials are lacking. There was a 6 month double-blind trial of 66 post-menopausal women looking at bone mineral density and intake of milk protein vs. a medium or high soy protein drink (Potter 1998, Am J Clin Nut 68:1375S-1379S). The high soy protein group had a 2% increase in BMD of the vertebral spine ($p<0.005$).

Cholesterol:

Eating a diet rich in soy (at least 25 grams/day may decrease cholesterol levels. Overall in one study, there was a decrease in cholesterol:

T-Chol of 9.3%, LDL of 12.9%, and Triglycerides of 10.5% (Anderson 1995, NEJM 333:276-82) The FDA approved labeling to include that soy may reduce cholesterol when used in conjunction with a diet low in fat/cholesterol.

Wild Yam (Dioscorea) and Natural Progesterone Products

Folk History and Traditional Use

Used for abdominal colic, cough, vomiting, gastritis, irritable bowel syndrome, dysmenorrhea, and much more.
Current Popular Use

PMS, menopausal symptoms, osteoporosis.

Plant Information

There are over 600 species in the Dioscorea family. They are found mostly in the tropics and subtropics throughout the world. The wild yam eaten in the United States, isn't even a yam, it is a type of sweet potato, Ipomoea batatas. Yams contain the ingredient diosgenin which is in higher concentrations in the Mexican yam. The human body cannot convert disogenin into progesterone; this requires laboratory conversion.

Mechanism of Action

Has estrogenic activity in animal models.

The take home point/research

Dr. John Lee supports the theory that the wild yam is an excellent source of natural progesterone. He has written two popular books on natural progesterone: Natural Progesterone, 1993, and What Your Doctor May Not Tell You

About Menopause, 1996. According to Dr. Lee, the chemical diosgenin in the wild yam can be converted in the human body into progesterone. Diosgenin is used as a source for the preparation of steroid hormones by the pharmaceutical industry. Diosgenin provides about 50% of the raw material for steroid synthesis and is chemically modified invitro to produce these hormones(for example, it is converted first to pregnenolone and then progesterone). The oral progesterone is the only form of natural progesterone that has been studied in clinical trials to test the effect on blood lipids and on protecting the uterus from estrogen. In the Postmenopausal Estrogen/Progestin Trial (PEPI), estrogen taken with natural progesterone and estrogen taken alone produced the most favorable increases in HDL levels. Estrogen taken with oral micronized progesterone showed no endometrial hyperplasia.

Progesterone content of body creams

Aeron LifeCycles Laboratory of San Leandro, California screened a number of commercial cream products for progesterone content. Of the 27 different creams tested:

* 12 contained more than 400 mg of progesterone per ounce

* 5 contained between 2 and 15 mg of progesterone per ounce

* 10 contained less than 2 mg per ounce

For alleviating menopausal symptoms, the cream should contain at least 400 mg per ounce. It is important to note that the creams do produce physiologic levels of progesterone. Women can actually get too much progesterone. It is important that healthcare professionals monitor these patients.

Depression

St. John's Wort (Hypericum perforatum)

*** well-tolerated mild anti-depressant with fewer side effects than standard tricyclic antidepressants**

*** trials are ongoing to see how it compares with SSRIs**

Clinical Vignette: 56 year old school teacher with moderate-severe depression, well-controlled on 40 mg Prozac is unhappy with the sexual side effects and wants to change to St. John's Wort.

Questions: Will SJW be effective for her depression?

Will she have fewer sexual side effects?

Can she safely combine SJW with her SSRI?

Folk History and Traditional Use

This herb has been used since ancient times for wound healing, depression, snakebites, kidney stones and treatment of chronic neuropathic pain. It grows in Europe and the United States, including Northern California. The Greek word "hypericum" means "over an apparition" which alludes to its use in ancient times for protecting against demonic possession. "Perforatum" means holes, as the leaves of the plant have numerous small holes when held up to the light. The name St. John's Wort may come from the fact that the flowers bloom around St.John's day (June 24) or because the red pigment that comes when the buds and flowers are squeezed is likened to the blood of St. John the Baptist.

Current Uses

Used internally as an anti-depressant, topically for wound healing and arthritis pain and as a possible anti-viral (a just published phase I study of hypericin in HIV-infected patients was disappointing, however, as only 2 out of 30 patients were able to complete the 24 week trial because of toxic side effects without any change in CD4 counts or viral loads. (Gulik et al (1999) Ann Intern Med. 130:510-514).

Active Ingredients/Plant Information

Many constituents with biological activity have been identified which include napthodianthrones, flavonoids, and xanthones. The flowering tops have the greatest concentration of these ingredients followed by the upper leaves and stems.

Most preparations are standardized to hypericin (a napthodianthrone) and pseudohypericin. Recent data suggest that there may be up to five other active ingredients, including hyperforan.

Mechanism of Action

In-vitro, SJW has MAO-inhibitory properties, although this has not been clearly demonstrated in-vivo. There is no clear consensus for mechanism of action, although SJW is believed to also interact with serotonin, dopamine, and NE receptors.

Preparations/ Dosage/ Pharmacokinetics

Most commonly sold as a 300mg pill, standardized to contain 0.3% hypericin. Usual dose is 300 mg TID. T 1/2 is approximately 24-26 hours for hypericin and 16-36 hours for pseudohypericin. See Table 2 below for selected formulations in European controlled clinical trials.

Table 2: Selected formulations of SJW used in European controlled clinical trials (adapted from Rotblatt's article, WJM, September 1999)

US Products (importer)	European product (manufacturer)
Kira (Lichtwer Pharma)	Jarsin (Lichtwer Pharma)
Quanterra (Warner-Lambert)	LI-160WS (Lichtwer-Schwabe)
Movana (Pharmaton)	Neuroplant (Schwabe)
Perika (Nature's Way)	Neuroplant (Schwabe)

Cost About $15/month

Side Effects/ Drug Interactions

Side effects include mild photosensitivity, insomnia, irritability, loose stools. Two recent cases of hypomania have been reported, as well as a case of a neuropathy in a sun-exposed distribution. There has been concern that patients taking SJW and SSRI's might develop serotonergic crisis. Overall-very well tolerated. Most experts do not suggest taking this herb with other anti-depressants, particularly MAO inhibitors. No safety data are available during pregnancy and lactation. Some recent concern about SJM may interact with anesthetics, so should consider discontinuing 2 weeks before elective surgery. One recent single-blind, placebo-controlled parallel study looked at the interaction of digoxin and SJW. Results showed a decrease in digoxin levels (Johne et al., Clin Pharmacol Ther 1999). The FDA put out a public health advisory that there is an interaction between SJW and the protease inhibitor Indinavir. A study conducted by the NIH showed that SJW substantially decreased plasma concentrations of indinavir (Piscitelli et al., Lancet, Feb 2000).

Research

Linde K et al., St John's Wort for depression - an overview and meta-analysis of randomized clinical trials (1996) BMJ 313(7052)253-258.

Meta-analysis of 23 randomized trials looking at 1757 outpatients with mild to moderately severe depression. Results showed that the herb was significantly superior to placebo and was as effective as the antidepressants maprotiline, imipramine and amitriptyline. 20 of the 23 trials were double-blind, 1 was single-blind, and 2 were open label. Critics of these

studies point out that in most of these studies, the diagnosis of depression was not well established, the does of standard antidepressants was low, the dose of hypericin varied six-fold and the duration of treatment varied from 2 weeks to 12 weeks. At least 6 more RCTs have been published, including:

Schroder et al., Hypericum treatment of mild-moderate Depression in a Placebo-Controlled Study(1998) Human Psychopharmacology 13:163-169.

56% of the 162 patients randomized to a new Swiss hypericum extract ZE117 vs. placebo reported improved depression vs. 15% of the placebo-treated group.

Phillip et al., Hypericum extract versus imipramine or placebo in patients with moderate depression: randomized multicenter study of treatment for 8 weeks (1999) BMJ 319:1534-1539.

The hypericum extract was more effective than placebo and as effective as imipramine in the treatment of moderate depression.

Gaster et al., St. John's Wort for Depression, A Systematic Review(2000)Archives of Intern Med 160:152-156.

In this review of 8 methodologically acceptable RCTs (4 comparing SJW vs. Placebo, and 4 comparing SJW to TCAs), there is good data to suggest it is more effective than placebo. In comparing SJW to TCAs, many of the studies used low doses of TCAs and showed either equal efficacy or slight superiority of TCAs over SJW.

Ongoing Research

The Office of Alternative Medicine has awarded > 3 million dollars to Duke University to study 336 patients who will be randomized to SSRI vs. placebo vs. St. John's Wort.

Herbs and Cardiac Disease

Garlic (Allium sativum)

*** safe herb with mild cholesterol and blood pressure lowering effects**
*** caution in patients on blood thinners**

Folk History/Traditional Use

Garlic has been cultivated for at least 5000 years as a medicinal agent: it has been used to lower blood pressure in Chinese medicine, to increase strength in ancient Egypt, and to prevent the bubonic plaque in Europe.
Active Ingredients/Plant Information

Garlic is a member of the allium plant family along with onions, shallots, and leeks. These plants contain sulfur-rich derivatives of the amino acid cysteine which are thought to have

medicinal benefits. When garlic is crushed, chewed, or chopped, an odorless cysteine derivative (alliin) is brought into contact with the enzyme allinase and converted to allicin (which is what gives garlic its characteristic odor). The most commonly studied powdered formulation used in clinical trials is a 300 mg tablet which is standardized to an allicin content of 1.3% and is marketed under the name Kwai.

Current Uses

Lipid Lowering Effects

A number of studies suggest that garlic may have a mild lipid-lowering effect at a dose of about one raw clove/day, especially in subjects with elevated cholesterol. Many well-designed studies, however, have failed to show a significant benefit from taking garlic supplements (the varying quality of garlic preparations may contribute to these varying results). A 1994 meta-analysis revealed that a dose of 600-900 mg/day of powdered garlic reduced total cholesterol by 9% in 410 subjects. In a 1996 study, however, there was no effect in 115 subjects taking 900 mg/day of powdered garlic for a 6 month duration. At least 8 trials published since then have also shown inconsistent results: 4 showed no significant decrease in cholesterol and 4 showed a 6-13% reduction in total cholesterol. A recent randomized double-blind, placebo-controlled trial of 25 patients with elevate cholesterol revealed no influence of a garlic oil preparation on cholesterol after 12 weeks. No well-designed long-term studies using raw or cooked garlic have been conducted.

Hypertension

11 of 12 studies published between 1988 and 1992 showed statistically significant reductions in SBP and DBP: (2-17%) in patients taking 600-900 mg/day of powdered garlic. A 1994 meta-analysis of 8 studies including 415 patients had a reduction of 7.7 mm Hg systolic and 5 mm Hg diastolic BP.

Anti-platelet and Thrombolytic Effects

Some studies have shown an antiplatelet effect while other studies have shown none.

Anti-atherosclerotic effects

Animal models suggest that garlic might also reduce oxidant injury, smooth muscle proliferation and/or oxidized LDL vascular injury.

Anti-cancer effects

Epidemiologic studies in China and Italy reported a decreased incidence of stomach cancer in patients who consumed a high amount of garlic. A Dutch study of over 120,000 patients aged 50-59 followed over 3 years, revealed no association between use of a garlic supplement and a decrease in incidence of lung, breast, or colon cancer.

Other effects

Garlic has been reported in vitro to have antibacterial, antifungal, antiprotozoal, and antiviral activity. Conflicting results have been published regarding its hypoglycemic effect.

Mechanism of Action

In vitro studies suggest an HMG-CoA reducatase inhibition as well as stimulation of nitric oxide production.

Dosing

A daily dose of 600-900 mg/day is recommended. The pills are taken in divided doses with meals. This dose is equivalent to 1/2 to one fresh clove of garlic/day.

Side Effects/Drug Interactions

Raw garlic can cause stomach upset, GERD, and gas. In a study of 2000 patients, 6% reported nausea, 1.3% reported hypotension, and 1.1% allergic reaction. Perceived odor and garlic taste were reported in 20-50% of patients. There is a case report of a spontaneous spinal epidural hematoma in a patient eating 4 cloves/day. There are no case reports of drug interactions, but caution is advised in patients taking blood thinners and BP medications. Historically, no toxicity has been noted during pregnancy or lactation.

Research

Neil HA et el. Garlic Powder and Plasma Lipids and Lipoproteins. A Multicenter, Randomized, Placebo-Controlled Trial (1998) Arch Intern Med 158:1189-1194

Bertold HK et al. Effects of a Garlic Oil Preparation on Serum Lipoproteins and Cholesterol Metabolism. A RCT(1998) JAMA 279:1900-1902.

Issacsohn JL et al. Garlic Powder and Plasma Lipids and Lipoproteins: A Multi-Center Randomized Placebo Controlled Trial (1998) Arch Intern Med 158(11):1189-94.

Other Popular Herbal Therapies:

Echinacea (Echinacea purpurea)

*** popular "immune booster" used for treatment and prevention of colds**

*** recent Cochrane Collaboration found insufficient data to support this**

Clinical Vignette: 26 year old college student with classic symptoms and signs of an upper respiratory tract infection.

Is there any utility for using echinacea?

What is the data?

Folk History and Traditional Use

Echinacea is a native American wildflower used initially by the Indians and then introduced into Western medicine in 1871 by Dr. Meyer of Nebraska. He used it to prepare a "blood purifier" which he claimed to be useful in treating many conditions including rheumatism, migraine, dyspepsia, pain, wounds, skin conditions, rattlesnake bites, and infections such as malaria, and diphtheria. In the 1930s and 40's when antibiotics were first introduced, Echinacea use fell out of favor.

Current Uses

Treatment and prevention of cold and flu, supportive treatment of recurrent infections of the ears, respiratory tract, and urinary tract.

Active Ingredients/Plant Information

Echinacea, a member of the daisy family (Asteracea), is native to the eastern US but grows easily in other parts of the country. The genus Echinacea has nine species. Three of the most common are E.purpurae, E.angustifolia, and E.pallida. The best-researched form of Echinacea is fresh-pressed juice made from the above-ground portion of E.purpurae (including leaves and flowers). Herbal preparations from the roots of E.purpurae and E.angustifolia are also sold. Intravenous formulations are available in Europe, but not in this country. Several active ingredients have been identified..

Mechanism of Action

In vitro studies have shown that when human granulocytes are incubated with Echinacea, their phagocytic activity is stimulated. Other studies showed that cells exposed to Echinacea release IL-1, TNF, and interferon. The polysaccharides in this herb bind to the T lymphocyte receptor, stimulating the production of interferon and other immune stimulants. Caffeic acid derivatives and echinacosides have been shown to have antibacterial activity.

Preparations/Dosage/Pharmacokinetics

The dose of the fresh-pressed juice of E.purpurae which contains a minimum of 2.4% beta-1,2-fructo-furanosides, in a 22% ethanol solution is 2-3 mls.every 2-3 hours. Numerous formulations and dosing suggestions are available.

Side Effects/Drug Interactions

No reported serious toxicity, although many of the liquid preparations have a strong taste. Side effects may include hypersensitivity reactions, rashes, pruritis and dizziness. Due to its ability to cause immune stimulation, it is not recommended presently to people with autoimmune or HIV disease. It is not clear if it is safe to take on a chronic basis or not. The German Commission E monograph recommends not taking Echinacea for more than 8 weeks at a time. It is likely that the immune stimulant properties of Echinacea wane with continued use. No data on safety in pregnancy are available. There was a case report of echinacea-induced anaphylaxis (chest tightness, burning of mouth and throat, and urticaria) in a woman with a history of multiple food and plant allergies (Mullins, Med J Aust 1998)

Research

Melchart D et al., Immunomodulation with Echinacea - a systematic review of controlled clinical trails (1994) Phytomedicine 1:245-254.

Meta-analysis of 26 controlled clinical trials (18 were randomized, and 11 were double-blind) on the immune-stimulant effects of Echinacea. In these studies, both single and multiple-herb combinations were used. Only 8 of the studies meet the criteria for inclusion into the study. The studies primarily looked at the effect of Echinacea on patients with respiratory tract infections. The highest rated study was done by Dorn et al., 1989. 100 patients with viral URI were randomized to Echinacea or placebo. The results showed a decrease in duration of symptoms. Symptom duration was decreased up to 1/3.

Melchart D. and Linde K. The Cochrane Collaboration Database of Systematic Reviews, January, 1999

Only 16 of the 40 identified trials of Echinacea met inclusion criteria for this systematic review. A total of 3396 participants were studied. All but 2 of the trials were conducted in Germany and not a single trial was published in a Medline-listed journal. The majority of the studies reported clearly positive results relative to placebo (the relative risk reduction of developing a cold when taking prophylactic Echinacea was 15-20%), but there was insufficient data to recommend any one specific Echinacea product in the treatment or prevention of common colds. The authors felt limited by the wide variety of herbal preparations that were studied, the inferior quality of many of the trials, and their knowledge of at least 5-10 unpublished trials which had negative results.

Ginkgo biloba

*** may be effective in Alzheimer's disease**

*** caution in patients on blood thinners**

*** may be effective for SSRI-induced sexual dysfunction**

Clinical Vignette: 65 year old professor on aspirin for CAD prevention is concerned about his memory. He is interested in taking gingko as he has a positive family history of dementia.

Question: How do you counsel him?

He also tells you his granddaughter is taking gingko to help her study during finals.

Question: Does gingko work in this setting?

Folk History and Traditional Use

Ginkgo biloba is one of the world's oldest, heartiest tree species. Medicinal use has been traced back to the Chinese Materia Medica from 2800 BC The German physician Engelbert Kaempfer was the first European to discover the tree and its medicinal potential in the late 17th century.

Current Uses

Gingko is used for symptomatic treatment of cognitive deficits due to organic brain disease, treatment of peripheral vascular disease, headache, vertigo, asthma, and tinnitus. An open trial also suggests that it may be effective in treating antidepressant-induced sexual dysfunction (Cohen, J Sex Marital Ther, 1998).

Active Ingredients/Plant Information

Gingko leaves are extracted with an acetone-water mixture. The organic solvent is then removed and the extract processed and dried. Active ingredients include Ginkgo flavone glycosides, heterosides, terpene molecules, and organic acids. Extracts are standardized to contain 24% flavanoid glycosides.

Mechanism of Action

Tissue effects: membrane-stabilization, free radical-scavenging, enhancement of cell utilization of glucose and oxygen. Nerve cells have the highest amount of unsaturated fatty acids in their membranes, so are most susceptible to free radical damage.

Vascular effects: can lead to vasodilatation by stimulated prostacyclin.

Platelet effects: inhibition of platelet aggregation, adhesion, and degranulation due to direct membrane and antioxidant effects, and antagonism of PAF (platelet activating factor).

Preparations/Dosage

Extracts are standardized to contain 24% ginkgo heterosides.

40 mg capsules are usually taken TID. Dose range is 80-240 mg. per day:

120-240 mg/day in divided doses for dementia

120-160 mg/day for PVD

60-240 mg/day for SSRI-induced sexual dysfunction

The dose of 1:1 fluid extracts made with 25% alcohol is 1-2 ml. TID. See Table 2 below for different preparations.

Table 2: Selected formulations used in European controlled clinical trials (adapted from Rotblatt's article, WJM, September 1999)

US Product (importer)	European product (manufacturer)
Ginkgold (Nature's Way)	Tebonin{Egb761} (Schwabe)
Ginkoba (Pharmaton)	Tebonin {Egb 761} (Schwabe)
Quanterra (Warner Lambert)	Tebonin {Egb 761} (Schwabe)
Ginkai (Lichtwer)	Kaveri {LI-1370} (Lichtwer)

Side Effects/Drug Interactions

Four case reports of bleeding in patients taking gingko have been reported including subarachnoid hemorrhage, subdural hematomas and hyphemas. Two of these patients were also taking blood thinners. Caution should therefore be exercised in patients on blood thinners of any kind. Consider stopping gingko prior to surgery.

The most common side effects are GI distress and headache. No data of safety during pregnancy are available. No toxicity reported with the leaf, but skin contact with the fruit can cause a poison-ivy-type syndrome. There has been a report that Gingko can interact with thiazide diuretics to cause hypertension (Shaw, Drug Safety, 1997)

Research

Le Bars DL et al., A Placebo-Controlled, Double-Blind, Randomized Trial of an Extract of Ginkgo Biloba for Dementia (1997) JAMA 278(16)1327-1332.

A 52-week study double-blind RCT of 202 patients with dementia. Using intention to treat analysis there was improvement in cognitive functioning and social functioning (as assessed by caregivers) in those patients taking 120 mg/ day of Egb761. No safety problems were reported. The dropout rate in this study was very high.

Peters et al., Demonstration of the efficacy of gingko biloba special extract Egb 761 on intermittent claudication (1998) VASA 27:106-110.

111 patients with PVD/claudication were randomized to placebo vs. gingko biloba for 6 months. The gingko –treated patients increased their pain-free walking distance by 22, 32, and 45 meters after 8, 16, and 24 months compared to placebo-treated subjects.

Kava kava (Piper methysticum)

popular herb used for anxiety concern with drug and alcohol interactions

Clinical Vignette: 54 year old female with generalized anxiety and a history of panic attacks has been prescribed Xanax PRN. She decides on her own to also take kava kava.

Questions: How do you discuss this combination with her?

She enjoys drinking wine with dinner: is this a problem?

Folk History and Traditional Use

The root was used in the 18th century to create a ceremonial drink in the island communities of the Pacific Ocean-Polynesia, Melanesia, and Micronesia. This drink was taken to induce relaxation, sleep and to calm nerves.

Current Modern Uses

To treat anxiety, insomnia and muscle tension.

Active Ingredients/Plant Information

Kava kava is extracted from the roots of this hearty perennial shrub with heart-shaped leaves. The two main active ingredients are methysticin (a kavalactone) and yangonin.

Mechanism of Action

Although Kava resin and pyrones exert weak effects on benzodiazepine-binding sites in vitro, this has not been correlated to pharmacologic activity in vivo.

Dosage/Pharmacokinetics

One of the best studied formulations is kava extract WS 1490. The dose of WS 1490 is 100 mg TID. This extract is standardized to 70% kavapyrones. The dose of 1:1 fluid extracts is 1-3 ml. BID-TID.

Side Effects/Drug Interactions

Moderate use can lead to a yellow scaly rash (often seen using > 9 gms/day). Heavy use can lead to increased liver enzymes, decreased albumin and increased cholesterol. Case reports of disorientation (and one coma) in patients who take kava in addition to a benzodiazepine. No safety data in pregnancy and lactation are available. Conflicting data exist on whether alcohol potentiates the effects of kava or vice versa.

Research

Volz HD et al., Kava-kava extract WS1490 versus placebo in anxiety disorders - a randomized placebo-controlled 25-week outpatient trial (1997) Pharmacopsychiatry 30(1)1-5.

25 week double blind, placebo-controlled study with WS 1490. 101 patients with anxiety disorders were studied. Patients reported significant relief of their anxiety symptoms starting at week 8.

Ginseng

Asian: Panax ginseng American: Panax quinquefolius

***used as tonic for increased vitality and coping with stress**

***remarkably safe**

Folk History and Traditional Use

Ginseng, the "elixir of life," has been used in Chinese medicine for almost 5000 years to maintain a general state of well-being, prolong life, improve sexual function, and invigorate the body. It was also a cure for problems with the digestive, nervous, cardiovascular, and pulmonary systems. The scientific name, Panax, is derived from the Greek word pan (all) and akos (healing).

Current Uses/Mechanism of Action

Athletic Performance: a recent study of 31 healthy men showed no improvement in their treadmill performance while taking ginseng.

Sexual Effects: preliminary studies showed an enhancement of fertility and erectile dysfunction in men. In one report of 46 men, the ginseng-treated group was found to have increased sperm counts, sperm motility, and levels of testosterone. Ginseng has been reported to have weak estrogenic activity in women. There are case reports of vaginal bleeding and mastalgia with regular use of ginseng. Women use ginseng for relief of menopausal symptoms, but there is inadequate data to support this use.

Immune-modulating effects: in vitro ginseng can increase PMN chemotaxis, phagocytosis, and NK cell activity.

Active Ingredients/Plant Information

Ginseng is a perennial plant that takes 5 to 7 years to mature. Older roots are considered to be of higher quality because they contain a higher concentration of active ingredients. Over-harvesting has made wild ginseng rare and very expensive. Most Asian ginseng is being cultivated in NE China and most American ginseng is grown in Wisconsin and Canada. American ginseng is prized in China for its "cold" qualities (it is believed to be less stimulating). Asian or Korean ginseng is felt to be more "hot" and can increase blood pressure, sexual desire, and stimulate the body. Siberian ginseng is not a true ginseng of the species panax. It was discovered by the Russians in the 1930s and is believed to be useful for increasing energy and athletic performance. The believed active ingredients are ginsenosides. Different species of ginseng have varying amounts of this active ingredient.

Preparations/Dosage/Pharmacokinetics

The root is dried prior to preparation. If the ginseng root is air-dried, it retains its slightly yellow color and is called White Ginseng. If the root is steamed before it is dried, it turns red. Standard dose is 0.5 to 2 grams of dried ginseng root or 200-600 mg/day of the extract. The standardized extract has 4-7% ginsenosides (dose is 100 mg capsules BID, or as a tincture 10-30 drops/day in divided doses).

Side Effects/Drug Interactions

Most of the reports of toxicity before the 1990's have been traced to mislabeled or adulterated products. At high doses (> 3 grams/day) ginseng can cause hypertension, nervousness, sleeplessness, rash, and diarrhea. No safety data during pregnancy or lactation are available. A case report indicated a possible interaction with coumadin, and another with digoxin (Cupp, Amer Fam Physician 1999). In general, however, ginseng has established a record of remarkable safety.

Research

Over 3000 articles have been written about ginseng, many written in Chinese. Eight English-language RCTs are indexed in Medline over the last 20 years.

Valerian Root (Valeriana officinalis)

*** used as a sleeping aid**

*** no good data on safety, effectiveness, drug-herb interactions**

Clinical Vignette: 28 year-old medical student with agitated depression had been on an SSRI but stopped it. He now decides to try a preparation containing valerian root, kava kava and SJW. Soon after starting the pill, he develops nausea and dizziness.

Questions: Can this combination pill cause these symptoms?

How do you proceed?

Folk History and Traditional Use

Dioscorides and Galen wrote about this herb that that has been used for thousands of years as a tranquilizer and calmative in cases of nervousness and hysteria. It has also been used for nervous stomach, nausea and poor digestion, as well as for muscle pains and dysmenorrhea.. Folk stories claim that the volatile oil found in the root of the plant attracts rodents. It is rumored that the Pied Piper of Hamlin sewed the root to this multi-colored coat and lured the rats out of the city.

Current Uses

Sleeping aide, anxiolytic, and treatment for irritable bowel syndrome.

Active Ingredients/Plant Information

The root of the tall perennial European variety of this herb is used. A strong unpleasant odor is caused by isovaleric acid which is formed by the breakdown of valepotriates in the dried roots of the plant. More than 100 constituents have been identified, but it is not clear which is responsible for the sedative qualities.

Mechanism of Action

Studies in lab animals show that valerenic acid decreases the degradation of GABA, the inhibitory neurotransmitter in the brain believed to play a role in stress and anxiety. Animal studies show that aqueous extracts of valerian root do indeed increase levels of synaptic GABA by inhibiting its re-uptake.

Preparation/Dosage/Pharmacokinetics

There are numerous formulations: capsules/tablets (250, 400, 450, 493, 530 and 550 mg, standardized to 0.8% valerenic acid), tinctures, teas and combinations. For sleep: 400-900 mg qhs, 2-3 gm dried root in a tea, or 4-6 cc of a 1:5 tincture.

Side Effects/Drug Interactions

Headache and morning drowsiness have been reported. One case report of valerian overdose describes fatigue, cramping, and tremor in a patient who took 20 times the recommended dose. No drug interactions are well characterized, but it may be wise not to combine valerian with benzodiazepines and other sedative-hypnotics. No data on safety during pregnancy and lactation are available.

Research

Leathwood PD et al. Aqueous extract of valerian root improves sleep quality in man (1982) Pharmacology Biochemistry and Behavior 17:65-71.

128 patients were given 450 mg of valerian, an over-the-counter remedy and placebo on non-consecutive nights. Questionnaires were used to assess quality of sleep each night. There were statistically significant decreases in sleep latency, awakenings and improved sleep quality in patients taking valerian versus when they ingested the placebo.

Leathwood PD and Chaufford F. Aqueous extract of valerian reduces latency to fall asleep in man (1985) Planta Medica 144-148.

8 subjects with mild insomnia were given 400 mg or 900 mg of a valerian extract versus placebo during an 8 day period. Sleep movements were recorded using a wrist band. Onset of sleep was defined as the first 5 minutes after "lights out" without movement. Results showed sleep latency was decreased from 15 minutes in the placebo group to 9 minutes in those taking 450mg valerian. No additional benefit was noted by increasing the dose to 900 mg.

Selected Journal Articles

General:

Eliason BC, Kruger J et al Dietary supplement users: demographics, product use and medical system interaction (1997) J Am Board Fam Prac 10:265-271.

Ernst E. Harmless Herbs? A review of the recent literature (1998) Amer J Med 104:170.

Gertner E, Marshall PS, Filandrinos D, Potek AS, and Smith TM. Complications resulting from the use of Chinese herbal medications containing undeclared prescription drugs (1995) Arth Rheum 38(5):614-617.

Gordon DW, Rosenthal G, Hart J, Sirota R and Baker AL. Chaparral Ingestion. The broadening spectrum of liver injury caused by herbal medications (1995) JAMA 273(6):489-490.

Johnston B. One-third of nation's adults use herbal remedies: market estimated at $3.24 billion (1997) HerbalGram 40:49.

Ko RJ. Adulterants in Asian Patent Medicines (1998) NEJM 339(12)847.

Laliberte, L. and Villeneuve, J.-P. Hepatitis after the use of germander, a herbal remedy (1996) Can Med Assoc J 154(11):1689-1692.

Litovitz TL, Clark LR and Soloway RA. 1993 Annual Report of the Association of Poison Control Centers Toxic Exposure Surveillance System (1994) Am J Emerg Med 12:46-85.

Nadir A., Agrawal S., King P.D., and Marshall, J.B. Acute hepatitis associated with the use of a Chinese herbal product, Ma-huang (1996) Amer J Gastroenterology 91(7):1436-1438.

Slifman NR, Obermeyer WR, et al. Contamination of botanical dietary supplements by Digitalis lanata (1998) NEJM 339 (12):806-811.

Woolf GM, Petrovic LM, Rojter SE, Wainwright S, Villamil FG, et al. Acute hepatitis associated with the Chinese herbal product Jin Bu Huan (1994) Ann Intern Med 121: 729-735.

Zink T and Chaffin J. Herbal "health" products: what Family physicians need to know (1998) Amer Fam Phys 58 (5):1133-1140.

Women and Herbs:

Hudson T. Women's Encyclopedia of Natural Medicine (1998) Los Angeles: Keats Publishing.

Israel D and Youngkin E. Herbal Therapies for Perimenopausal and Menopausal Complaints (1997) Pharmacotherapy 17(5):970-984.

Taylor M. Alternatives to conventional HRT (1999) Contemp OB/GYN. May:23-54.

Seidl MM. Alternative treatments for menopausal symptoms. Systematic review of scientific and lay literature (1997) Can Fam Phy 44:1299-1308.

Herbal References Resource List and Evaluation

Quality information on herbs is often not in English, not based on human data, and is not of high quality when human subjects are used. However, there is a growing body of evidence-based literature in peer reviewed journals. This is a constantly changing field and new articles and web sites are becoming available on a regular basis.

There are a variety of books, newsletters, and databases for physicians and here are the ones providing the best quality information and that are also easy to use for busy practicing physicians.

1. Robbers J. and Tyler V. Tyler's Herbs of Choice-The Therapeutic

   Use of Phytomedicinals. The Haworth Herbal Press, New York, 1998.*****

   This is a new, fully referenced, excellent general herbal guide for physicians. Varro Tyler is an expert in the field and has written a number of high quality textbooks. This book is the easiest to read and arguably the best. This book stresses the pathophysiology of certain disease states and shows the mechanism of how these herbs work. Cost is $49.95.

2. Feltrow and Avila. Professional's Handbook of Complementary and Alternative Medicines. Springhouse, 1999.

   The best pocket reference to keep with you in your office. Cost is about $39.

3. Schulz V, Hansel R, and Tyler V.E. Rational Phytotherapy: A Physician's Guide to Herbal Medicine. Springer, 1998.

   This is an excellent, well-referenced book that includes articles and references from non-English journals. It has an easy to follow format - organized by general medical symptoms and diseases, followed by discussions on herbs used for those particular diseases and organ systems. For example, there is a section on the Cardiovascular System. The chapter goes through, in detail, subcategories such as Hypertension, Atherosclerosis, and Heart Failure. The herbs that have been the most studied and with the most proven efficacy are discussed in each of subcategory sections. There is also a very thorough section on the types of herbal preparations and what they mean, including teas, tinctures, pills, and powders. The downside of this book is that it misses several of the commonly used women's herbs that patients ask about including cranberry and blue cohosh. Overall, one of the best sources around for the physician interested in more detailed discussion of herbal therapies and the research that has been internationally published on those particular herbs. Cost is $49.95.

4. Tyler V. The Honest Herbal. Fourth Edition, Pharmaceutical Products Press, 1999.

   This is a good basic reference for the physician who is not as interested in evidence-based herbal medicine. This is the most basic excellent reference to keep on hand in your office as well as at home. The cost is $28.00.

Monographs on Herbs

German Commission E Monographs First*** and Second Edition*****

These herbal monographs were translated from German to English and published in 1998. There is a new edition out this year. Recommendations for herbal therapies are based on a Health Commission in Germany that existed from 1978-1994. The recommendations for herbal use are based on more than just randomized controlled data. Historical/folk use, anecdotal information, case reports, and unpublished data were all used to make recommendations about herbal products. The major drawbacks of the first edition are that there are no references and only data up until 1994 is used. Also, the information is often specific to products available only in Europe, and approval does not necessarily mean unconditional safety. This is not the top book to buy on herbal therapies. Cost is $189. The book can be purchased through the herb education catalog from the American Botanical Council. The number to call is 1-800-373-7105.

The second edition just came out and lookds better, it is smaller, and would be an excellent reference book.

The Review of Natural Products/Facts and Comparisons *****

An expensive but worthwhile purchase. Monographs on herbs are updated and published in a style similar to Scientific American. The monographs are concise with helpful information on use, dosing, and referenced with animal and human data. This might be a resource you might want to purchase with other colleagues given the expense. The initial cost for a large book containing pages on individual herbs is $195, for yearly updates the cost of the subscription is $139. The toll free number to call is 1-800-223-0554.

ESCOP ****

The European Scientific Cooperative of Phytotherapy was established in 1989. They have compiled 50 monographs that are fully referenced. This is a relatively brief herbal monograph and does not seem to offer more than The Review of Natural Products/Facts and Comparisons. The cost is $179.

WHO Monographs on Selected Medicinal Plants ***

These are fully referenced and are available through the American Botanical Council. The first volume is available with 26 herbs included and the cost is $82.80. Credit card orders: 1-800-373-7105, customer service: 512-926-4900.

The Prescriber's Letter, Natural Medicines Comprehensive Database ***

From the editors of the Prescriber's Letter. Excellent book with an option to get a web version as well. Currently there is a half price offer for the book and the web version for $66. Great, concise and has a good section on potential drug/herb interactions. Call 1-800-995-8712.

Newsletters

1. **Alternative Medicine Alert *****

   A newsletter that focuses on the clinical use of alternative medicine. This is an easy to read, well-researched newsletter on complementary topics. Articles are thorough, well referenced but brief. The newsletter won a recent first place Newsletter Publication Award. The current cost is $189/year (12 issues). The newsletter also offers CME credits. More information is available on 1-800-688-2421.

2. **The Integrative Medicine Consult ****

   This newsletter also contains excellent reviews on a variety of complementary topics. This newsletter is as expensive as Alternative Medicine Alert, and does not have as many subscribers. It costs $189/year. The address to order is: IMC 1029 Chestnut Street Newton, MA 02464.

3. **FACT/ Focus on Alternative and Complementary Therapies ******

   This newsletter is published at the University of Exeter, Exeter, England. It is another great source for brief reviews of current literature, and books, as well as occasional systematic reviews. It has a more open viewpoint on several complementary medicine fields that are more widely accepted in Europe than in the United States. More information is available from www.ex.ac.uk/FACT/ . Cost is $89 per year, 4 issues are published per year. You can order by fax: 212-686-7993 or you can write to: Pharmaceutical Press c/o CABI Publishing, CAB International, 10 East 40th Street, Suite 3203, New York, New York 10016

Special Reports/Theme Issues on Alternative and Complementary Medicine

Various journals have dedicated entire theme issues to Alternative and Complementary Medicine. Their articles are not only about herbal medicine, but include other topics including homeopathy and acupuncture.

- WJM, September 1999
- JAMA, November 11, 1998
- Archives of Internal Medicine, November, 9, 1998
- Archives of Neurology, November 1998
- Archives of General Psychiatry, November 1998
- Archives of Pediatrics and Adolescent Medicine, November 1998
- Archives of Surgery, November 1998
- Archives of Family Medicine, November 1998

Free Databases

There are a number of databases that physicians can access in their office. These are the free ones. However, there are several expensive databases that physicians may want to learn more about. These include Napralert, Embase, The Cochrane Library, and Phytodok.

1. Pubmed *****
   This is Medline's publicly available search service of the entire 9 million-citation database. Drawback: The medline-indexed journals do not include a large volume of botanical scientific information, especially foreign journals.

2. HerbMed *****
   This is a new electronic evidence-based resource for herbal information, with hyperlinks to clinical and scientific publications. It is designed for the needs of physicians and pharmacists. This site is clearly organized into 6 categories for each herb: evidence for activity, warnings, preparations, mixtures, mechanism of action, and other.

3. IBIDS ***

   http://ods.od.nih.gov/databases/ibids.html

   The International Bibliographic Information on Dietary Supplements (IBIDS) database from the NIH Office of Dietary Supplements contains over 300,000 citations and abstracts on scientific literature, and lists over 2900 publications. The database contains citations of journal articles and includes abstracts where available. Citations on the topic of dietary supplements include vitamins, minerals, and selected herbal therapies. The database includes only the 50 or so top-selling herbal remedies in this country. Not as helpful as other sites, since a lot of the information is less clinically relevant and more agriculturally based.

General Internet Resources

1. Columbia Medical School's Rosenthal Center of Alternative and Complementary Medicine *****
   www.rosenthal.hs.columbia.edu

   This web site has been organized in an easy to use format. You can make links with PubMed, HerbMed.

2. University of Pittsburgh Alternative Medicine Homepage ***
   http://www.pitt.edu/~cbw/altm.html

   A directory of internet sites with helpful annotations. Both disease categories as well as specific alternative modalities, including herbal therapies, organize this site. This is also a good site to look up licensed professionals doing acupuncture, herbs, etc. The list includes practitioners who are licensed and in good standing with their respective discipline review boards.

Internet Resource for Reporting and Receiving Information on Adverse Reactions of Herbal Products

1. Medwatch ***
   http://www.fda.gov/medwatch

   Medwatch is the FDA's Medical Products Reporting Program and provides access to the Special Nutritionals Adverse Event Monitoring System, a searchable database reporting adverse effects and problems associated with the use of herbal products. Results are presented in a table format, showing each product's name, manufacturer, and adverse effects. The site is full of lists and only helpful as a quick reference when you are looking up potential herb-drug interactions.

2. Phytonet ****
   www.escop.com

   Phytonet is maintained by the Center of Complementary Health Studies at the University of Exeter, Exeter, England. It is designed to keep researchers up to date with the work of the European Scientific Co-operative on Phytotherapy

   (ESCOP), an organization promoting the development of therapeutic standards for herbal medicines. One of Phytonet's major functions is the collection and dissemination of information on the adverse effects of herbal preparations.

On-Line Magazines/Newsletters

1. HerbalGram *****

   http://www.herbalgram.org/herbalgram/index.html

   This herbalist magazine is published by the American Botanical Council and includes research reviews, legal issues, herb market trends, book catalogue, and features.

2. Medical Herbalism ***

   http://medherb.com/MHHOME.SHTML

   A full text clinical newsletter for the herbal practitioner. This site also links you to herbal medicine databases not found easily elsewhere, such as David Hoffman's Health World Materia Medica and Grieves Modern Herbal.

Journals

There are several journals devoted to the topic of Herbal Medicine. Journals such as Phytomedicine, Planta Medica, and Journal of Natural Products can be requested to be part of your hospital or University library. Given the large number of herbal sources, getting a

regular subscription to an herbal journal may be too much information and too cumbersome for the average clinical physician.

Worthwhile Herbal Magazines

The American Botanical Council publishes Herbalgram. It can be subscribed to and is also available on the web. It contains articles on herbs, news about herbs and all sorts of political information on herbs. It also has a large section of books that can be purchased through the American Botanical Council. If you join the Herb Research Foundation, you get a subscription to Herbalgram for free. The address is:

American Botanical Council P.O. Box 144345 Austin, Texas 78714-4345, www.herbalgram.org, phone number is 1-800-373-7105.

The address for the Herb Research Foundation is:

1007 Pearl Street, Suite 200 Boulder, Colorado 80302, www.herbs.org, phone number is 303-449-2265.

Post-Lecture Questions

1. Herbal medicines are considered drugs by the FDA and are under FDA control for safety and purity. True of False?

2. St. John's Wort can be safely used in conjunction with SSRIs. True or False?

3. Ginkgo biloba should be stopped prior to surgery. True or False?

4. Echinacea's immune effects improve as the patient continues to take the herb. True or False?

5. It is safe to prescribe aspirin to a patient taking feverfew?

1. F

2. F

3. T

4. F

5. F