Chapter 4: Overview of Herbal Supplements

5 Contact Hours

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Learning objectives

- Define what an herbal supplement is in the United States.
- Discuss the extent of use worldwide of herbal medicine.
- Outline suggested reasons patients do not disclose their use of herbal supplements to their health care providers.
- Explain why all health care providers should incorporate use of herbal supplements into the patient's medical and medication histories.
- Itemize factors that have an effect on the quality and therapeutic efficacy of herbal products.
- Describe the differences between U.S. regulatory review processes for drugs and herbal products.
- List the information required and prohibited by the FDA on herbal supplement labels.
- Generally discuss the issues and problems associated with scientific testing and reporting of research results on herbal supplements.
- Discuss the historical and current uses for 13 common herbal supplements.
- Discuss side effects and recommended dosages of 13 common herbal supplements.
- Give examples of common herbal supplements that interfere with medical lab tests.
- Give examples of common herbal supplements that affect blood coagulation and aggregation.
- Give examples of common herbal supplements that interfere with liver enzymes, liver function, and drugs metabolized in the liver.

Introduction

There are numerous health risks and misconceptions associated with herbal supplements, e.g., potential adverse effects, drug-drug interactions, lab test interactions, and dose-to-dose content variability, to name a few. More often than not, patients and health care practitioners are unaware of these potential problems. The physician may even be unaware that the patient is taking them at all, either because the patient does not voluntarily disclose the information or because the health care practitioner does not ask.

Thus, it is important for those involved in each step in the continuum of patient care to be aware not only of the extent and type of problems they may encounter when patients consume herbal medicines, but also to consistently obtain such information from patients and be able to discuss the benefits and dangers associated with these commonly used health aids.

This course provides an overview of herbal medications and the regulatory process associated with their manufacture and marketing. With some of the more frequently used herbals, it further provides specific information on safety, effectiveness, interactions and side effects.

Today, more than ever, patients receive information from and have access to a variety of medications, some of which may dramatically affect the success or failure of the medical treatment they receive. This lesson emphasizes how important it is for health care providers to inquire and for patients to disclose what herbal medications the patient is taking and to be able to discuss and explain the potential risks and benefits associated with them.

Herbal supplement use [14, 32, 34, 35, 64, 82, 100, 122, 147, 160-162, 184]

Compounds extracted from plants, animals, or microorganisms have been used to treat or prevent disease for centuries. Examples include digitalis, reserpine, morphine, penicillin, and vinca alkaloid anti-cancer drugs. Plants having medicinal or therapeutic properties, flavor, and scent used to maintain or improve health are often called herbal products, botanical products, or phytomedicines.

As defined by Congress in the Dietary Supplement Health and Education Act of 1994, a dietary supplement is a product (other than tobacco) that:

- Is intended to supplement the diet.
- Contains one or more dietary ingredients (e.g., vitamins, minerals, herbs or other botanicals, amino acids, or essential fatty oils).
- Is intended to be taken by mouth as a pill, capsule, tablet, or liquid.
- Is labeled on the front panel as being a dietary supplement.

Recently, the World Health Organization estimated that 70-80 percent of people worldwide rely on herbal medicines for some part of their primary health care, but only 23-40 percent of these people tell their physician. Statistics reveal that the likelihood of consuming herbal medicines is higher in persons of higher education and income.

Possible explanations for patients' non-disclosure include:

- The belief that natural medicines have no adverse effects.
- The belief that over-the-counter and non-mainstream medicines are irrelevant to their doctor's overall treatment plan and outcome.
- Their concern about a negative reaction from their practitioner.
- The belief that the physician lacks interest or knowledge about herbals.
- Not being asked by their practitioner about taking herbals.
- Their use of herbals is a cultural mainstay of therapy and they do not even think to disclose it.
- A lack of awareness that herbal medicines can interact with and alter the therapeutic efficacy of conventional medications.

To further complicate the issue, detailed information on herbal supplements is often outside the general knowledge base of medical prescribers, either because of limited formal training or inaccurate or biased information sources. In addition to physicians and nurses who don't ask patients about their use of herbal medicines, some community pharmacists who on a daily basis are in a key position to assess interactions with conventional drugs also may rarely ask patients about their use of herbals.

Thus, because of the prevalent use, misconceptions, invalid assumptions, and lack of patient information, it is critical to educate patients and all those in the health care delivery chain on the effects that herbal medicine can have on therapeutic outcomes.

Pharmacology of herbal supplements [30, 75, 82, 101, 109, 127, 162]

In the United States, current good manufacturing practices (cGMPs) applicable to food manufacturing are the only quality-control regulations on herbal medicines. The final marketed product, however, is impacted by more than just satisfying current good manufacturing practices.

Other factors that influence the quality and thus the potential for reliable therapeutic effectiveness of herbals include:

- Identification and collection of the botanical source (e.g. leaf, root, flower).
- Isolation, purification, and concentration of one or more active ingredients.
- Contaminants, e.g., pesticides and micro-organisms.
- Active ingredient source substitution.
- Preparation process of specimens (e.g., solutions, desiccation, trituration).
- Excipients used.
- Storage conditions.
- Final product formulation (e.g., solution, suspension, powder, tablet, capsules).

The impact of these factors is best explained by understanding how drugs work in our bodies. Pharmacokinetics, pharmacodynamics, and bioavailability are terms used to explain this process.

Pharmacokinetics is the study of the processes of drug absorption, distribution, biotransformation, and ultimate elimination of drugs and their metabolites in the body. Regardless of route of administration, all drugs undergo pharmacokinetic processes in one form or another while in the body. In addition to a drug's chemical properties, pharmacokinetics depends on patient-related factors, such as renal function, genetic makeup, sex, and age. These factors are often used to predict how a drug will affect a specific population.

Pharmacodynamics can be simply explained as what a drug does to the body. It involves receptor binding and sensitivity, post-receptor effects, and chemical interactions. Physiologic changes caused by disorders, aging, or other drugs can affect a drug's pharmacodynamics. The pharmacologic response depends on the drug binding to its target. The concentration of the drug at the receptor site influences the drug's effect.

Bioavailability refers to the extent and rate at which the drug or metabolite enters systemic circulation, thereby accessing the site of action. Bioavailability of a drug is determined by the properties of the dosage form, the product's design, and its method of manufacture. Differences in bioavailability among formulations of a given drug can have clinical significance, so knowing whether drug formulations are equivalent is essential.

Chemical equivalence means that the drug products contain the same active compound and in the same amount. Inactive ingredients in drug products may differ. Bioequivalence means that when the drug is given to the same patient in the same dosage regimen, equivalent concentrations of drug in plasma and tissues are achieved.

Therapeutic equivalence means that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects.

Herbal supplement interactions [13, 15, 28, 29, 31, 41, 42, 44, 62, 65, 79, 126, 128, 130]

Herbal supplements can interact with drugs, other herbs, foods and alcohol, and can affect lab results. These interactions can affect absorption, distribution, metabolism, excretion, and interfere with a drug's ability to reach and exert its effect on a receptor site. That many herbal products contain more than one active ingredient further complicates the process of ascertaining the source responsible for any unwanted biological event.

Pharmacokinetic interactions

Pharmacokinetic interactions can enhance or diminish the therapeutic properties of a drug, thereby evoking an unanticipated, and often unwanted, clinical response. Examples of this type of interaction include:

- **The dose-dependent inhibitory effect**
  Grapefruit and grapefruit juice affect the liver enzyme known as CYP3A4 and result in abnormally high and potentially lethal serum levels of interacting drugs. Prescription drugs such as the statins, antianxiety drugs, methadone, and calcium channel blockers are in this group. For example, goldenseal, commonly used as a topical antiseptic and orally for menstrual pain and gastrointestinal distress, also inhibits CYP3A4, so when taken with the antibiotic erythromycin, an abnormally elevated level of the antibiotic may occur.

- **The inducer effect**
  - For example, St. John's wort increases the speed of degradation and elimination of drugs transformed by CYP3A4, leading to blood levels that fall quickly below therapeutic levels. Drugs interacting in this manner with St. John's wort include cyclosporine and alprazolam.

Pharmacodynamic interactions

Pharmacodynamic interactions result from actions on molecular targets that mediate different physiological responses, with results being an inhibition or potentiation of response.

Examples of pharmacodynamics interactions include:

- St. John's wort inhibits the serotonin reuptake when taken in conjunction with other drugs, such a fluoxetine and paroxetine, that act similarly, resulting in an abnormally high level of serotonin at the nerve synapse. This creates the possibility of "serotonin syndrome," a collection of symptoms characterized by confusion, restlessness, high blood pressure, fever, and muscle spasms.
- Herbals such as red and sweet clovers when taken in conjunction with drugs used for their anti-coagulation or anti-platelet action, such as warfarin, heparin, aspirin, dipyridamole, and fibrinolytics, such as alteplase and reteplase, affect the ability of these drugs to reliably perform their intended effect as blood thinners or as an inhibitors of platelet aggregation.

Herbals and lab test interactions

The Natural Medicines Comprehensive Database identifies more than 200 different herbs and supplements that may affect lab test results. Below is an abbreviated compilation of some common herbal supplements, some of which are addressed in detail later on in this lesson (Table 1).

Regulatory approval process comparison [26, 27, 35, 123, 124]

In the U.S., the drug approval process is strictly controlled and involves highly detailed safety and efficacy scrutiny prior to marketing. The process entails preclinical stages, wherein drugs aimed at specific diseases and biological targets are identified and tested in vitro and in animals under controlled conditions to determine their potential therapeutic benefit.

Once a potential therapeutic benefit is revealed, an investigational new drug application (IND) may be submitted to the FDA for review and approval. The IND application must include the following information:

- Composition of the drug.
- Source of the drug.
- Manufacturing information.
- In vitro and animal studies data.
- Plans for proposed human clinical trials.
- Background information of the clinical trial investigators.

If approved, human clinical studies are then conducted in four phases (I, II, III, and IV).

Phase I is aimed at establishing drug safety, dosage, and pharmacokinetic properties of the drug (e.g., half-life and metabolism). These results are compared with results from the pre-clinical animal studies.

Phase II studies the effect of the drug on 100-200 volunteer patients having the disease for which the drug was developed. Toxicological studies in animals will also continue during this phase to assess toxicity.

Phase III comprises double-blind or crossover studies to evaluate drug efficacy in a larger groups of patients. If the results from Phase III meet the goals initially established, a new drug application (NDA) may be submitted to the FDA containing the data from the human trials. Upon review of the NDA, the FDA may approve, disapprove or request further testing of the drug. If approved, the drug proceeds to market and to **Phase IV.**

Phase IV includes post-marketing surveillance and adverse event reporting.

In the U.S., herbal medications are not considered drugs, but instead are categorized as dietary supplements regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. Whether a product is classified as a dietary supplement, conventional food, or drug is based on its intended use, gleaned from information that the manufacturer provides on the product label or in accompanying literature.

Dietary supplements are *not* approved by the government for safety and effectiveness before they are marketed. If the dietary supplement contains a new ingredient, that ingredient will be reviewed by FDA before marketing, but only for safety, not effectiveness.

The quality of a dietary supplement product cannot be discerned from its label. The degree of quality control depends on the manufacturer and others involved in the production process. In 2007, the FDA issued Good Manufacturing Practices (GMPs) for dietary supplements, a set of requirements and expectations by which dietary supplements must be manufactured, prepared, and stored to ensure quality. Manufacturers are now expected to guarantee the identity, purity, strength, and composition of their dietary supplements.

The GMPs aim to prevent the inclusion of the wrong ingredients, to determine ranges for the quantity of the dietary ingredient, the possibility of contamination by pesticides, heavy metals such as lead, and bacteria, and to prevent improper packaging and labeling of a product. Manufacturers are also required to report all serious dietary supplement adverse events or illnesses to FDA. FDA can take dietary supplements off the market if they are found to be unsafe, adulterated, or if the claims on the products are false and misleading.

Labeling

Unlike drugs, dietary supplements cannot claim that their product will diagnose, cure, mitigate, treat, or prevent a disease. A dietary supplement label may only contain a health claim, nutrient content claim, or structure/function claim.

- **Health claims** describe a relationship between a food, food component, or dietary supplement ingredient that may reduce the risk of a disease or health-related condition.
- **Nutrient content claims** describe the relative amount of a nutrient or dietary substance in a product.
- **A structure/function claim** describes how a product may affect the organs or systems of the body, but cannot mention any specific disease. FDA approval is not required for structure/function claims, but the manufacturer must submit the text of the claim to FDA within 30 days of marketing and must include the following disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

Supplement	Interactions with lab tests
Aloe dried juice.	Discolors alkaline urine and can interfere with diagnostic tests that depend on a color change. May deplete serum potassium concentrations and alter test results.
Bee pollen.	Bee pollen may increase alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, total bilirubin, prothrombin time, and alter test results.
Black cohosh.	Black cohosh might reduce serum luteinizing hormone concentrations and alter test results.
Coenzyme Q-10.	CoQ-10 doses in excess of 300 mg. per day can elevate SGOT and LDH concentrations and affect thyroid T4/T8 ratio in normal patients and some HIV-positive patients.
Evening primrose oil.	Evening primrose oil may interfere with laboratory tests measuring bleeding time and cholesterol levels, possibly causing false test results.
Green tea.	The caffeine in green tea can cause false-positive serum urate test results, can increase urine creatine levels, can cause a slight increase in urine catecholamines and vanillylmandelic acid levels, resulting in a false-positive test for pheochromocytoma and neuroblastoma.
Kava.	Kava can cause liver damage and increase liver enzymes. Liver toxicity is primarily associated with prolonged use of high doses, but has been seen with short-term use as well. Liver function tests affected include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, total and conjugated bilirubin, and gamma-glutamyltransferase.
Lemongrass.	May elevate levels of serum bilirubin and amylase.
Licorice.	Licorice can increase serum-hydroxyprogesterone concentrations and alter test results. Excessive use of licorice can cause hypokalemia and can decrease serum testosterone concentrations, affecting both lab test results.
Melatonin.	Melatonin supplementation can increase human growth hormone serum levels, can decrease serum luteinizing hormone levels and can produce dose-dependent changes in plasma oxytocin and vasopressin concentrations and alter test results.
Red yeast.	Due to lovastatin content, red yeast may increase serum levels of liver transaminase and serum creatine kinase.
Rose hip.	The vitamin C in rose hip can cause false negative urine results with methods based on hydrolysis and formation of an indophenol blue chromagen, can cause a false increase in results of serum tests relying on color reactions, can cause a false increase in serum test results measured by Technicon SMA 12/60 or colorimetric methods, can cause falsely increased serum assay results measured by Ames ARIS method, can cause a false increase in serum creatinine or urine test results, and can cause false increases in urine glucose test results measured by copper reduction methods and false decreases in results measured by glucose oxidase methods. Three to six grams of vitamin C daily can cause a true increase in urinary calcium and a true decrease in urinary sodium and alter test results. The vitamin C in rose hip can cause a false decrease in LDH measured by Technicon SMA 12/60 and Abbott 100 methods, may cause false negative guaiac results to occur with 250 mg or more of vitamin C per day, can cause falsely decreased theophylline serum assay results when measured by the ARIS system or Ames Seralyzer photometer, can cause a true decrease in serum uric acid concentrations, and a false increase in test results with assays based on other methods.
Senna.	Senna, due to its anthraquinone content, can discolor urine, interfering with diagnostic tests that depend on a color change. Excessive use of senna can cause potassium depletion, reducing serum potassium concentrations and alter test results.
Soy.	Soy can inhibit thyroid hormone synthesis, resulting in increased secretion of thyroid stimulating hormone.
Sweet clover.	Sweet clover might increase liver enzymes and test results.

Table 1. Common herbal supplements.

The FDA requires the following information on all herbal product labels:

- Product name, including the word "supplement."
- Net quantity of contents.
- Name and place of business of manufacturer, packer, or distributor.
- Directions for use.
- Serving size.
- List of dietary ingredients.
  - Amount per serving size (by weight).
  - Percent of daily value (percent DV), if established.
- If the dietary ingredient is a botanical, the scientific name of the plant or the common or usual standardized name and the plant part name.
- If the dietary ingredient is a proprietary blend (i.e., a blend exclusive to the manufacturer), the total weight of the blend and the components of the blend in descending order by weight.
- Non-dietary ingredients, such as fillers, artificial colors, sweeteners, flavors, or binders, listed in descending order by weight using common name or proprietary blend.

Standardization [29, 54, 85, 94, 112, 123]

Standardization is a method of quality control used to manufacture a consistent product, e.g., batch-to-batch consistency and identification of chemical markers. Some studies show that absence of standardization may affect the reliability of clinical results because of the variability of active constituents in the dosage forms used in the trials.

Other studies reveal that chemical compositions of several commonly used herbals were reasonably consistent with their labeled quantities. A greater consistency of composition marker compounds, however, was observed for samples purchased over-the-counter than for those purchased by mail order, with saw palmetto and St. John's wort being the least variable, (77-106 percent and 88-110 percent respectively) and ginseng and echinacea the most variable (44-261 percent and 78-173 percent, respectively).

At this time, the National Institute of Standards and Technology (NIST) in collaboration with the National Institutes of Health Office of Dietary Supplements, the Center for Drug Evaluation and Research

(CDER), and the Center for Food Safety and Applied Nutrition at the FDA are developing procedures for the standardization of active ingredients and chemical contaminants in dietary supplements and natural health products.

Standardization may result in greater consumer confidence and acceptance of these alternative and complimentary therapy options by larger numbers of conventional health care providers.

Commonly used herbal supplements

Considering the immense number of available herbals, it is beyond the scope of this lesson to review them all. Some of the most commonly used herbal supplements used in the United States will be reviewed on their use, effectiveness, safety, interactions, side effects, and dosage.

BLACK COHOSH [125, 129-141]

Background

Black cohosh is a perennial plant, a member of the buttercup family native to North America. Preparations are made from its roots and underground stems. Extracts of black cohosh are standardized to 26-deoxyactein content, a member of the group of chemicals known as saponins. Commercially available preparations of black cohosh usually contain 1 mg of total triterpene saponins in each 20-mg dose of extract.

Uses

Historically, black cohosh was used for malaise, gynecological disorders, kidney disorders, malaria, rheumatism, sore throat, colds, cough, constipation, hives, backache, to induce lactation, rheumatism, as a diuretic, and to bring on menstruation.

Today, black cohosh is primarily used for hot flashes and other menopausal symptoms. In 2001, the American College of Obstetricians and Gynecologists stated that black cohosh may be helpful in the short term (six months or less) for women with vasomotor symptoms of menopause.

Efficacy and clinical studies

In a randomized, double-blind, placebo-controlled trial, 69 breast cancer survivors took 20 mg twice daily of black cohosh for two months to determine the effect on hot flashes, excessive sweating, palpitations, headaches, poor sleep, depression, and irritability. Fifty-nine subjects were using the anti-estrogen drug tamoxifen for breast cancer, distributed almost equally between the treatment and control groups. The frequency and intensity of hot flashes and other symptoms decreased in both groups, with no statistical difference between the groups. Excessive sweating decreased significantly more in the treatment group than the placebo group.

A randomized, double blind, placebo-controlled trial in 80 menopausal women compared 8 mg/day of a black cohosh extract with placebo or conjugated estrogens (0.625 mg/day). At 12 weeks, Kupperman index and Hamilton anxiety scale scores were significantly lower in the treated groups than in the placebo group. Daily hot flashes decreased from 4.9 to 0.7 in the black cohosh group, 5.2 to 3.2 in the estrogen group, and 5.1 to 3.1 in the placebo group.

Study results are conflicting on whether black cohosh helps relieve menopausal symptoms. This could be due to lack of rigor in study design, short study duration (six months or less), use of different amounts of black cohosh from different sources, and use of different outcome measures.

Physiologic effects

Effect on hormone levels
Post-menopausal women generally have lower levels of estrogen and higher levels of two other hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), than do pre-menopausal women. Three of four studies show that black cohosh does not affect LH or FSH.

Effect on the vagina
The decrease in estrogen level in post-menopausal women alters the structure and activity of vaginal and uterine tissues. Study results are mixed on whether black cohosh affects vaginal epithelium.

Effect on the uterus
Menopause is associated with a thinning of the uterine lining. No human studies have adequately evaluated the effect of black cohosh on the uterine lining.

Side effects

Few adverse events have been reported, however, long-term safety data is not available. Stomach discomfort, headaches, heaviness in the legs, and weight problems are the main side effects noted.

Safety, cautions and warnings

Black cohosh is customarily not used for long periods, i.e., six months or less. A large study involving postmenopausal women taking combined estrogen and progestin for an average of 5.2 years showed a small, but significant increase in the risk of certain diseases. This study demonstrates the importance of long-term studies in assessing overall risks. If black cohosh is estrogenic, long-term use may adversely affect uterine or breast tissue. No studies have been published on long-term safety in humans.

Liver damage has been reported in a few individuals using black cohosh. Despite millions of uses without apparent adverse health effects, the U.S. Pharmacopeia (the standards-setting organization for foods and drugs) advises that black cohosh products be labeled with the following cautionary statement: “Discontinue use and consult a health care practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice.”

Black cohosh should only be used under medical supervision during pregnancy.

Women with breast cancer may want to avoid black cohosh until its effects on breast tissue are understood.

COENZYME Q-10 [125, 176-183]

Background

Coenzyme Q-10 is also referred to as CoQ-10. It is a vitamin-like substance primarily found in the heart, liver, kidney, and pancreas. Coenzyme Q-10 was first identified in 1957. Coenzyme Q-10 is manufactured by fermenting beets and sugar cane with special strains of yeast. Time and smoking use up the body's natural stores of coenzyme Q-10.

Uses and efficacy

Natural Medicines Comprehensive Database effectiveness ratings for Coenzyme Q-10 are as follows:

- **Likely effective in**:
  - Inherited or acquired disorders that limit energy production in the cells of the body (mitochondrial disorders), but improvement is slow, often exceeding six months.
- **Possibly effective for**:
  - Congestive heart failure (CHF) only when used in combination with other heart failure medications and treatments.
    Patients with chronic heart failure (CHF) have low plasma concentrations of coenzyme Q-10, which is associated with low-density lipoprotein cholesterol. Studies in the 1990s concluded that coenzyme Q-10 reduced oxidation of these low-density lipoproteins. One study of 236 patients with CHF found coenzyme Q-10 to be an independent predictor of mortality.
    The Q-SYMBIO trial is a randomized, controlled trial involving 422 patients with chronic heart failure to determine the benefits of coenzyme Q-10, with an endpoint including survival. Although not yet published, after two years of study, investigators reported at the Heart Failure 2013 Congress that patients in the coenzyme Q-10 group had a death rate half of what the patients in the placebo group had.
  - Lowering risk of additional heart problems in people who have had a recent heart attack when started within 72 hours of the attack and taken for one year.
  - Preventing blood vessel complications and damage from by heart bypass surgery.
  - Lowering high blood pressure, alone or with other medications.
    A 2007 meta-analysis of 12 clinical trials (362 patients) for hypertension concluded that coenzyme Q-10 has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mm and diastolic blood pressure by up to 10 mm without significant side effects.
  - Preventing migraine headaches.
    Coenzyme Q-10 can decrease the frequency of headaches by about 30 percent and the number of days with headache-related nausea by about 45 percent in adults. It can take up to three months. It is not effective once a migraine headache has developed.
  - Slowing the physiological decline in Parkinson's disease, but does not seem to improve symptoms in patients with mid-stage Parkinson's disease.
  - Enhancing the immune system of HIV/AIDS patients.
  - Improving physical performance in some muscular dystrophy patients.
- **Possibly ineffective for**:
  - Decreasing high cholesterol or triglycerides.
- **Likely ineffective for**:
  - Improving athletic performance.
  - Treating periodontal disease.
- **Insufficient evidence to rate effectiveness for**:
  - Cyclic vomiting syndrome.
  - Lowering blood sugar.
  - Breast cancer.
  - Improving sperm motility and density in some infertile men.
  - Improving exercise tolerance in patients with chest pain (angina).
  - Increasing feeling of wellness and reducing fibromyalgia pain.
  - Reducing heart wall thickness, shortness of breath and fatigue in patients with hypertrophic cardiomyopathy.
  - Reducing statin-induced myopathic pain.
  - Preventing pre-eclampsia.
  - Reducing or preventing warfarin-induced hair loss.

Safety

Coenzyme Q-10 is likely safe to use in most adults when taken orally or when applied directly to the gums. Toxicity is not usually observed even with high doses of coenzyme Q-10. A daily dosage up to 3,600 mg was well tolerated by healthy as well as unhealthy persons.

Coenzyme Q is possibly safe for children, but should only be used under medical supervision.

Because there is insufficient information, use of coenzyme Q-10 should be avoided while pregnant or breast-feeding.

Side effects

Coenzyme Q-10 is well tolerated in most people. Common side effects include stomach upset, loss of appetite, nausea, vomiting, diarrhea, and allergic skin rashes. Dividing the total daily dose into smaller increments taken more frequently can reduce side effects.

Cautions and warnings

Coenzyme Q-10 may lower blood pressure and may increase the effects of medications used to lower blood pressure. If the patient has blood pressure problems, avoid use of coenzyme Q-10 except under medical supervision.

Use of coenzyme Q-10 should be discontinued at least two weeks before any scheduled surgery.

Interactions

Because coenzyme Q-10 is an antioxidant, there is some concern that it may decrease the effectiveness of some cancer drugs. Research is unclear in this regard.

Coenzyme Q-10 may help the blood clot, thus may decrease the effectiveness of warfarin and increase the risk of dangerous clots.

If taking coenzyme Q-10, the dose of warfarin needs to be closely monitored, and warfarin dosage may need adjustment.

Red yeast might reduce coenzyme Q-10 levels.

There are no known interactions with foods.

Oral dosage

Dosage ranges from 100-3,600 mg per day in 2-4 divided doses have been studied.

CRANBERRY [125, 163-167]

Background

Cranberry is a small, evergreen shrub prevalent throughout North America. The red berries are used to produce beverages and many other food products, as well as dietary supplements in the form of extracts, capsules, or tablets. Cranberry juice is marketed unsweetened or sweetened with either sugar or artificial sweeteners.

Uses and mechanism of action

Cranberry has a long history of use primarily for preventing urinary tract infections, but also for neurogenic bladder, to deodorize urine in people with difficulty controlling urination, to increase urine flow, to kill germs, to speed skin healing, and to reduce fever. Some people use cranberry for type-2 diabetes, chronic fatigue syndrome, scurvy, pleurisy, and even cancer. More recently, cranberry has been used as a folk or traditional remedy for Helicobacter pylori (H. pylori) infections that can lead to stomach ulcers, or to prevent dental plaque. Cranberry has also been reported to have antioxidant and anti-cancer activity.

It was previously thought that cranberry acidified the urine, making it inhospitable for the growth of bacteria. Current research supports the notion that some of the chemicals in cranberries keep bacteria from sticking to the lining of the urinary tract where they multiply. Cranberry, however, is not able to release bacteria already adhering to the lining, which may explain why cranberry is possibly effective in preventing urinary tract infections but also possibly ineffective in treating them.

Cranberry contains significant amounts of salicylic acid that can reduce swelling, prevent blood clots, and can have antitumor effects.

Efficacy

- **Possibly effective for**:
  - Preventing urinary tract infections, particularly repeat infections.
- **Possibly ineffective for**:
  - Lowering blood sugar in type 2 diabetes.
- **Insufficient evidence to rate effectiveness for**:
  - Benign prostatic hyperplasia (BPH).
  - Reducing urinary odor in people with bladder control problems.
  - Skin healing.
  - Pleurisy.
  - Cancer.
  - Chronic fatigue syndrome.

Safety

Cranberry juice and extracts are likely safe for most adults and children.

Side effects

Drinking too much cranberry juice may cause mild stomach upset and diarrhea.

Cautions and warnings

Cranberries and cranberry juice are safe to consume during pregnancy and breast-feeding. It is not known, however, whether dietary supplements containing cranberry are safe to use during pregnancy and breast-feeding.

Because cranberries contain significant amounts of salicylic acid, caution should be used before consumption in patients allergic to aspirin (acetylsalicylic acid).

Diabetics should avoid the sugar-sweetened cranberry products.

Cranberry juice and extracts contain a large amount of oxalate. Because kidney stones are composed of oxalate combined with calcium, consumption of cranberry juice or extracts may increase the risk of kidney stones.

Cranberry should be consumed only under the supervision of a health care provider if the patient is on anticoagulants. The dosage of the anticoagulant may need to be monitored and adjusted.

Interactions

Cranberry may impede the elimination of warfarin from the body and thus may increase the likelihood of bruising and bleeding. The dose of warfarin may need to be adjusted.

Cranberry may inhibit certain enzymes in the liver necessary for the metabolism of certain drugs, possibly increasing their therapeutic effects and side effects. Patients should consult with their health care provider before taking cranberry while on any of the following medications: amitriptyline, diazepam, zyleutin, celecoxib, diclofenac, fluvastatin, glipizide, ibuprofen, irbesartran, losartan, phenytoin, piroxicam, tamoxifen, tolbutamide, torsemide, warfarin, and others.

Cranberry has no known interactions with foods or other herbs and supplements.

Oral dosage

Studies have used the following doses:

- To prevent urinary tract infections:
  - Adults: 1-10 oz. per day of cranberry juice.
  - Children: 5 ml/kg daily as 30 percent cranberry concentrate.
- As a urinary deodorizer: 3-6 oz. per day of cranberry juice.

ECHINACEA [12, 21, 33, 37, 38, 59, 60, 67-69, 78, 83, 88, 92, 97,102, 103, 142, 168-175]

Background

Echinacea, also known as coneflower or black-eyed susan, is prevalent in North America and thrives in temperate climates. The aboveground parts of the plant and roots of echinacea are used fresh or dried to make teas, juice, extracts, or topical preparations.

Historical and current use

Echinacea was used by Native Americans for toothaches, gingivitis, stomach pain, colds, infections, as a topical disinfectant and for wound healing. The German Commission E approved echinacea extracts for use orally in relieving cold symptoms, upper respiratory infections, urinary tract infections, and topically for superficial wounds. Research discloses that echinacea may help treat, but not prevent, cold symptoms.

Pharmacology

Echinacea's complex chemical makeup is not fully understood. It contains phenols, such as caffeic acid, that act to scavenge tissue-damaging free radicals. Also present are alkylamides that inhibit cyclooxygenase and 5-lypoxygenase, that explain its anti-inflammatory properties. Echinacea is also thought to have immunostimulatory properties as demonstrated by its action in macrophage proliferation, interleukin-1 and interferon stimulation, and to increase the numbers of T lymphocytes.

Uses and efficacy

Research results are conflicting and inconclusive about whether echinacea has therapeutic value in the prevention and treatment of the common cold. It is noteworthy, though, that a meta-analysis of three randomized, double-blind and placebo-controlled trials involving almost 400 subjects found that the risk of developing a cold was 55 percent higher in the placebo than in the echinacea-treated group, a statistically significant difference.

There is limited and inconclusive data as to whether echinacea has other therapeutic applications, e.g., as an immunostimulant, anti-infective, or in wound healing.

As with other herbals, the absence of standardized methods of preparation, the inadequacy of species identification, product contamination, and dose-to-dose variability between marketed products on the amount and type bioactive components add to the conflicting therapeutic efficacy results found in the scientific literature.

Adverse effects

The most common adverse reactions seen with the use of echinacea are allergic rash, nausea, vomiting, abdominal pain, mild drowsiness, and headache.

Safety and cautions

Echinacea is generally well-tolerated. Both in vitro and in vivo studies suggest that even when administered in doses several-fold higher than customarily used, echinacea is devoid of toxicity. Although women who took echinacea during the first trimester of pregnancy showed no difference in fetal health than those who did not, the absence of definitive data in this group dictates that echinacea should be avoided during the first trimester of pregnancy.

Interactions

Echinacea might decrease how quickly the body breaks down caffeine. This may cause an accumulation of caffeine in the bloodstream increasing the potential side effects, e.g., jitteriness, headache, and rapid heartbeat.

Echinacea might change how the body breaks down some medications categorized as cytochrome P450 substrates. Taking echinacea along with such a medication might increase its effects and side effects. Some of these cytochrome substrate medications include the statins customarily used to lower high cholesterol, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, triazolam, clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, theophylline, zileuton, and zolmitriptan.

Medications that depress immune response are known as immunosuppressants. Echinacea can increase the immune response. Thus, taking echinacea with some medications that decrease immune response might undermine the effectiveness of the immunosuppressants and may lead to serious medical complications, possibly including organ rejection in transplant patients. Some of these immunosuppressants include azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate, tacrolimus, sirolimus, prednisone, and corticosteroids.

Echinacea increases the absorption of midazolam and thus might increase its effects and side effects as well.

Dosage

There is no established dosage for echinacea. Studies conducted to determine whether echinacea is effective to treat cold symptoms and upper respiratory infections have used a dosage range of 300-1,000 mg for five to seven days.

EVENING PRIMROSE OIL [15, 43, 125, 142, 161]

Background

Evening primrose oil is obtained from the seed of the evening primrose plant and contains fatty acids. Essential fatty acids are required by the body for growth and development, and must be obtained from the diet. In foods, evening primrose oil is used as a dietary source of essential fatty acids. In manufacturing, evening primrose oil is used in soaps and cosmetics.

Uses

Evening primrose oil has been used for skin disorders, such as eczema, psoriasis and acne; rheumatoid arthritis; osteoporosis; multiple sclerosis; cancer; high cholesterol; heart disease; dyspraxia; intermittent claudication; alcoholism; Alzheimer's disease; schizophrenia; chronic fatigue syndrome; asthma; diabetic peripheral neuropathy; neurodermatitis; hyperactivity; and attention deficit-hyperactivity disorder; weight loss; whooping cough; irritable bowel syndrome; peptic ulcer disease; pre-eclampsia; shortening or starting labor; preventing late deliveries; premenstrual syndrome; breast pain; endometriosis; and hot flashes.

Efficacy

The effectiveness ratings for evening primrose oil are:

- **Possibly effective for**:
  - Breast pain, but not long-term, severe breast pain.
  - Osteoporosis, in combination with calcium and fish oils.
  - Rheumatoid arthritis pain.
  - Shortening labor, pre-eclampsia, or preventing late deliveries.
  - Sjogren's syndrome (an autoimmune disorder in which the glands that produce tears and saliva are destroyed).
- **Possibly ineffective for**:
  - Symptoms of premenstrual syndrome.
  - Attention deficit-hyperactivity disorder.
  - Reducing symptoms associated with eczema.
  - Menopausal hot flashes and night sweats.
  - Cancer.
  - Acne.
  - Multiple sclerosis.
  - Heart disease.
  - High cholesterol.
  - Alzheimer's disease.
- **Insufficient evidence to rate effectiveness for**:
  - Chronic fatigue syndrome.

Safety and cautions

Evening primrose oil is likely safe for most people.

It is only possibly safe during pregnancy and if breast-feeding, so consumption should be avoided because there is a lack of reliable studies in the patient population.

Evening primrose oil may increase the chance of bruising and bleeding. Use in patients with a clotting or blood disorder should be avoided unless under direct supervision of a health care provider.

Evening primrose oil consumption should be stopped at least two weeks before any scheduled surgery.

Evening primrose oil may make seizures more likely in people with a history of seizures, so use should be avoided. Seizures have been reported in people with schizophrenia treated with phenothiazine drugs, GLA (gamma linolenic acid, a chemical found in evening primrose oil), and vitamin E.

Side effects

Side effects are generally mild and include upset stomach, nausea, diarrhea, and headache.

Interactions

Evening primrose oil contains GLA (gammalinolenic acid) that may slow blood clotting, thus increasing the chances of bruising and bleeding. Use of evening primrose oil without prescriber approval is discouraged in patients taking any of the following medications that also slow blood clotting: aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, naproxen, dalteparin, enoxaparin, heparin, warfarin, and others.

Evening primrose oil when taken with phenothiazines (chlorpromazine, fluphenazine, trifluoperazine, thioridazine) may increase the risk of having a seizure.

Using evening primrose oil with other herbs, e.g., angelica, clove, danshen, garlic, ginger, ginkgo, red clover, and turmeric that can slow blood clotting could increase the risk of bleeding in some people.

There are no known interactions with foods.

Oral dosage

There is no established dosage for evening primrose oil. Use for breast pain has been in the range of 3-4 grams daily.

GARLIC [1, 2, 3, 6, 17, 36, 44-46, 51, 57-59, 70, 79, 80, 83, 84, 89, 95, 110, 117, 125]

Background and historical uses

Garlic, also known as allium, is related to chives and onions. Garlic is the edible bulb from the plant, used as both a medicine and a spice for thousands of years. Historically, garlic has been used for high cholesterol, heart disease, high blood pressure, and cancer prevention, e.g., stomach and colon cancers. Garlic cloves can be eaten raw or cooked. They may also be dried or powdered and used in tablets and capsules. Raw garlic cloves can be used to make oils and liquid extracts.

Pharmacology

More than 20 sulfur compounds have been identified in garlic. These compounds include allinin and the peptides, steroids, terpenoids, flavonoids, and phenols.

Methyl-allyl trisulfide, an allicin derivative, inhibits cyclooxygenase activity and prostaglandin synthesis that may explain the anti-thrombotic and anti-platelet aggregation properties of garlic.

Garlic has also been studied for potential use in the treatment of stomach and colorectal cancer. This potential use may arise from the presence in garlic of diallyl trisulfide, a sulfur compound that is a potent inhibitor of colon and lung cancer cell proliferation.

Clinical trials

Reliable and consistent evidence of medicinal benefits of garlic are few.

In one study, garlic lowered total cholesterol levels by 8 percent to 15 percent (lowering low-density lipoprotein and triglycerides, but with no change in high-density lipoproteins). A meta-analysis, however, found the reduction to be only 4 percent to 6 percent and was not statistically significant after a six-month period.

Garlic has also been shown to inhibit platelet aggregation, as expected by its inhibitory effects on cyclooxygenase and prostaglandin synthesis. The effective dosages have not been established, and it is unknown how garlic compares to anti-platelet drug therapy. Because of reports associating garlic with bleeding incidents, co-administration of garlic with anti-platelet aggregation drugs (e.g., aspirin) or anticoagulants (e.g., warfarin), should be avoided.

Epidemiological studies suggest that regular consumption of garlic may lower risk of developing gastric and colorectal cancers, but more investigation is needed before a definitive answer can be formulated.

Efficacy

The efficacy rating for garlic is as follows:

- **Possibly effective for**:
  - High blood pressure.
  - Hardening of the arteries (atherosclerosis).
  - Preventing colon cancer, rectal cancer, and stomach cancer.
  - Preventing tick bites.
  - Fungal skin infections.
- **Possibly ineffective for**:
  - Diabetes.
  - Treating H. pylori, a bacterium that can cause ulcers.
  - High cholesterol.
  - Breast cancer.
  - Lung cancer.
  - Treating peripheral arterial occlusive disease.
- **Insufficient evidence to rate effectiveness for**:
  - Treating high cholesterol in HIV/AIDS patients.
  - Common cold or flu.
  - Benign prostatic.
  - Hyperplasia.
  - Arthritis.
  - Allergies.
  - Traveler's diarrhea.
  - Pre-eclampsia.
  - Male urinary tract problems.
  - Preventing prostate cancer.
  - Chronic fatigue syndrome.
  - Warts and corns.

Interactions and adverse effects

The interaction between garlic and anticoagulants and anti-platelet aggregation agents such as warfarin, heparin, ticlopidine, and clopidogrel is clinically significant in that a potentiation of the activity of these drugs occurs when co-administered with garlic.

Garlic also reduces by 50 percent the plasma concentration of the protease inhibitor/HIV drug saquinavir. This is a dangerous interaction, so in an abundance of caution, use of garlic in patients taking any protease inhibitor is not recommended.

The most common adverse effects reported are bad breath and body odor. Other side effects include dyspepsia, flatulence, dermatitis, and respiratory difficulty in hypersensitive patients.

Safety

Garlic is safe in most populations at customary doses. Patients allergic to garlic, chives, onions, leeks, or lilies should avoid use of garlic.

Dosage

There is no established dosage for garlic; however, studies have been conducted using garlic preparations having 1.3 percent allinin or 0.6 percent allicin that are administered at 600-900 mg per day (approximately equal to one small clove of fresh garlic).

GINKGO [4, 9, 20, 22, 23, 33, 45, 47-50, 53, 56, 66, 71, 83, 116, 119, 163]

Background and historical uses

Ginkgo (Ginkgo biloba), also known as kew tree, is an herb from which the leaves are generally used to make extracts. Ginkgo extracts have been used for centuries in traditional Chinese medicine to treat disorders such as asthma, allergies, premenstrual syndrome, tinnitus, cognitive impairments, and central and peripheral vascular insufficiencies.

Pharmacology

More than 40 chemical compounds have been isolated from ginkgo and include flavonoids, terpenoids, flavones, catechins, sterols, and organic acids. Ginkgo biloba extracts available in Europe and North America are standardized to 24 percent flavonoids and 6 percent terpenoids.

Because of the complex interactions among chemical components, it is difficult to establish a well-defined cause-effect relationship between specific elements and biological effects. Nevertheless, it is now known that flavonoids have antioxidant properties and are free-radical scavengers.

Flavonoids also provide a protective effect against apoptosis and beta-amyloid neurotoxicity of Alzheimer's disease and help prevent neuronal degeneration in Parkinson's disease. Terpenoids prevent platelet aggregation, have anti-inflammatory properties, and prevent contraction of smooth muscles in the respiratory tract.

Efficacy

The effectiveness ratings for ginkgo are as follows:

- **Possibly effective for**:
  - Improving symptoms of Alzheimer's, vascular, or mixed dementias.
  - Ginkgo biloba extract stimulates receptor expression and neurotransmitter concentrations in the brain, particularly acetylcholine.
  - Improving short-term visual memory and speed of mental processing in nondemented people with age-related memory loss.
  - Improving thinking skills in healthy young to middle-aged people.
  - Reducing the number of painful attacks in people with Raynaud's syndrome.
  - Increasing the distance people with poor blood circulation in their legs can walk without pain, and may reduce the need for surgery.
  - Reducing symptoms associated with dizziness and balance disorders.
  - Relieving PMS-related breast tenderness.
  - Improving pre-existing visual field damage in people with normal tension glaucoma.
  - Improving color vision in diabetics.
- **Possibly ineffective for**:
  - Treating ringing in the ears.
  - Treating depression in those suffering seasonal affective disorder.
  - Treating sexual problems related to antidepressant medicines.
  - Preventing symptoms of altitude sickness.
- **Likely ineffective for**:
  - Reducing the chance of having a heart attack, chest pain, or stroke.
- **Insufficient evidence to rate effectiveness for**:
  - Reducing age-related macular degeneration.
  - Decreasing symptoms of anxiety in adults with generalized anxiety disorder or adjustment disorder with anxious mood.
  - Reducing anxiety, hyperactivity and impulsiveness symptoms in patients with attention deficit-hyperactivity disorder.
  - Improving clot-related stroke recovery.
  - Recovering short-term hearing loss from unknown causes.
  - Reducing pain of fibromyalgia.
  - Reducing the negative effects of radiation exposure on the body.
  - Decreasing high cholesterol.
  - Preventing atherosclerosis.
  - Reducing likelihood of blood clots.
  - Preventing heart disease.
  - Preventing or treating colorectal or ovarian cancers.
  - Reducing symptoms of chronic fatigue syndrome.
  - Treating coughs.
  - Improving symptoms of asthma and bronchitis.
  - Treating digestive disorders.
  - Preventing and treating urinary problems.

Allergies and side effects

Ginkgo can cause some minor side effects, such as headache, nausea, dizziness, constipation, and forceful heartbeat. Ginkgo fruit and pulp can cause severe allergic skin reactions and irritation of mucous membranes. There also may be ginkgo cross-allergenicity in people who are allergic to poison ivy, poison oak, poison sumac, mango rind, or cashew shell oil.

Safety

Ginkgo leaf extract is likely safe when taken orally in appropriate doses in adults and children for up to six months.

Ginkgo is possibly unsafe when used during pregnancy and may cause early labor or extra bleeding during delivery. Although in vivo studies did not disclose any embryotoxic or teratogenic effects, ginkgo extract should be avoided during pregnancy and breast-feeding.

In animals, extremely high doses of ginkgo leaf increased the risk of liver and thyroid cancers, but there is insufficient information on humans.

Ginkgo leaf extract may increase the risk of bruising and bleeding and decreases the blood's ability to form clots. Bleeding into the eye and brain and excessive bleeding following surgery have been observed in a few patients.

The roasted ginkgo seed or crude ginkgo plant is possibly unsafe when taken by mouth. Eating more than 10 roasted seeds a day can cause difficulty breathing, weak pulse, seizures, loss of consciousness, and shock. The fresh seed is poisonous, and may cause seizures, loss of consciousness, and death.

Cautions and warnings

Ginkgo may:

- Affect blood sugar levels.
- Cause seizures. Avoid use in seizure patients.
- Impede conception.
- Worsen bleeding disorders.
- Slow blood clotting, resulting in excessive bleeding during and after surgery. Ginkgo should be stopped at least two weeks before any scheduled surgery.

Interactions

Ginkgo interacts with almost 500 drugs and drug combinations. Because of the sheer quantity of interactions, it is wise to consult a comprehensive database, such as *http://www.drugs.com/drug-interactions/ginkgo,ginkgo-biloba-index.html#S*, for a clearer picture.

In light of the quantity of potential interactions, this will address the more frequently encountered and more serious ones.

Ginkgo may decrease the effects of antiviral agents, such as efavirenz and indinavir, used to treat HIV.

Ginkgo may increase or decrease the therapeutic action of drugs that are metabolized by certain specific enzymes in the liver. Some of these drugs that are changed by the liver include clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, theophylline, zileuton, zolmitriptan, amitriptyline, carisoprodol, citalopram, diazepam, lansoprazole, omeprazole, phenytoin, celecoxib, diclofenac, lovastatin, fluvastatin, glipizide, ibuprofen, irbesartan, losartan, piroxicam, tamoxifen, tolbutamide, torsemide, warfarin, codeine, desipramine, donepezil, fentanyl, flecainide, fluoxetine, meperidine, methadone, metoprolol, ondansetron, tramadol, trazodone, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, and triazolam.

Ginkgo might increase or decrease insulin and blood sugar in type 2 diabetics, so it is wise to monitor blood sugar closely. Diabetes medication might need to be changed or the dose adjusted.

Do not take ginkgo with medications that lower the seizure threshold and thus increase the chance of having a seizure. These drugs include propofol, mexiletine, amphotericin, penicillin, cephalosporins, imipenem, bupropion, cyproheptadine, cyclosporine, fentanyl, methylphenidate, and theophylline.

Ginkgo slows clotting, so taking it with anticoagulants or anti-platelet drugs that also slow blood clotting may increase the chances of bruising and bleeding. Some medications that slow blood clotting include aspirin, clopidogrel, dalteparin, enoxaparin, heparin, indomethacin, ticlopidine, and warfarin. Some herbs and supplements, such as angelica, clove, danshen, garlic, ginger, and Panax ginseng, can also slow blood clotting, thereby increasing the risk of bleeding in some people. Ginseng should not be taken with these herbals.

Ginkgo can also affect chemicals in the brain in a way that may possibly decrease the effectiveness of medications used to prevent seizures. Some medications used to prevent seizures include phenobarbital, primidone, valproic acid, gabapentin, carbamazepine, and phenytoin.

Ginkgo can alter the blood pressure-lowering effect of hydrochlorothiazide, which can lead to elevated blood pressure.

Ginkgo and other herbals that can increase the risk of seizure should not be taken together. Herbs and supplements that can increase seizure risk include butanediol, cedar leaf, Chinese club moss, EDTA, folic acid, gamma butyrolactone (GBL), gamma hydroxybutyrate (GHB), glutamine, huperzine A, hydrazine sulfate, hyssop oil, juniper, L-carnitine, melatonin, rosemary, sage, and wormwood.

There are no known interactions of ginseng with foods.

Dosage

The following oral doses of ginkgo leaf extract have been studied and used for:

- Dementia syndromes: 120-240 mg per day divided in 2-3 doses.
- Cognitive function improvement in healthy young people: 120-600 mg per day.
- Raynaud's disease: a dosage of 360 mg per day divided into 3 doses.
- Peripheral vascular disease: 120-240 mg per day divided into 2-3 doses.
- Vertigo: 120-160 mg per day divided into 2-3 doses.
- Premenstrual syndrome (PMS): 80 mg twice daily, starting on the 16th day of the menstrual cycle until the fifth day of the next cycle.
- Normal tension glaucoma: 40 mg 3 times daily up to four weeks.

For all uses, it is advisable to start at a dose not more than 120 mg per day to avoid gastrointestinal (GI) side effects. Increase to higher doses as needed. Dosing may vary, depending on the specific formulation used.

GINSENG (PANAX) [7, 21, 33, 52, 55, 61, 72, 93, 98, 106-108, 113, 115, 120, 125]

Background

Ginseng is a perennial herb that has been used for medicinal purposes in Asian countries for centuries. It is harvested in autumn and prepared from the root of plants that are generally 5-6 years old.

American ginseng (Panax *quinquefolius*) is native to the rich hardwood forests of Canada and the eastern half of the United States. Asian ginseng is obtained from Panax ginseng. Japanese ginseng is from Panax japonicas. Siberian (Russian) ginseng is from E. senticosus, a plant that is not considered a true ginseng.

The different types should not be interchanged because they have different medicinal effects. Because of vast harvesting arising from its immense popularity and multiple uses, wild American ginseng is becoming rare. As a result, some states list it as an endangered plant species.

Historical uses

American ginseng has been used for stress, to boost the immune system, as a general tonic and stimulant, to help prevent colds and flu and reduce severity of symptoms when infections occur, for dysentery, for pseudomonal infections in cystic fibrosis patients, to improve digestion, for loss of appetite, vomiting, colitis, gastritis, anemia, diabetes, insomnia, nerve pain, erectile dysfunction, fever, hangover symptoms, attention deficit-hyperactivity disorder (ADHD), blood and bleeding disorders, cancer, painful joints, dizziness, headaches, convulsions, fibromyalgia, atherosclerosis, memory loss, and as an anti-aging aid.

Oils and extracts made from American ginseng are used in soaps and cosmetics.

Pharmacology

American ginseng contains a variety of saponins called ginsenosides that affect insulin levels, lower blood sugar, lower blood pressure, and improve cognitive performance. The concentration of the various ginsenosides varies among species, plant age, and season of harvest. Ginseng also contains polysaccharides that may affect the immune system.

Both in vitro and in vivo rodent studies have shown that ginseng extracts have a neuroprotective effect useful in some types of Parkinsonism.

Well-designed scientific studies of ginseng are limited and have generally failed to support historical use claims, except possibly some clinical trials on ginseng's hypoglycemic properties.

It should be noted that different American ginseng products may differ in effect because of varying amounts of ginsenosides.

Efficacy

The effectiveness ratings for American ginseng are as follows:

- **Possibly effective for**:
  - Lowering post-prandial blood sugar in type 2 diabetics. Taking 3 grams of American ginseng by mouth, up to two hours before a meal, can significantly lower blood sugar after a meal, but larger doses don't seem to lower blood sugar more.
  - Preventing and reducing symptom severity in adult respiratory tract infections, e.g., influenza and common cold.
- **Insufficient evidence to rate effectiveness for**:
  - Attention deficit-hyperactivity disorder (ADHD).
  - Breast cancer.
  - Athletic performance. Ginseng may decrease muscle damage during exercise.
  - Stress.
  - Anemia.
  - Insomnia.
  - Gastritis.
  - Impotence.
  - Fever.
  - HIV/AIDS.
  - Fibromyalgia.

Safety, cautions and warnings

American ginseng is possibly safe in adults and children when used short-term.

American ginseng is possibly unsafe in pregnancy because of the possibility of birth defects. American ginseng should be avoided in pregnancy. Because there is insufficient evidence about it, American ginseng should be avoided if breast-feeding.

Adverse reactions and side effects

American ginseng may lower blood sugar and has been linked to insomnia.

Patients suffering from estrogen-sensitive conditions, such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids, should not take American ginseng unless the ginsenosides have been removed or if the preparation contains only low concentrations of ginsenosides.

Common side effects seen with use of American ginseng include diarrhea, itching, insomnia, headache, nervousness, rapid heartbeat, blood pressure alterations, breast tenderness, and vaginal bleeding.

Uncommon side effects that have been reported include liver damage, Stevens-Johnson syndrome, severe allergic reaction, and estrogen-like effects in men, e.g., reduced libido and gynecomastia.

Interactions

Long-term use of American ginseng has been reported to induce the hepatic enzyme CYP450 that increases the metabolism of warfarin by the body. This enzymatic effect decreases the effect of warfarin, thereby increasing the risk of clotting. In an abundance of caution, American ginseng should not be consumed by patients taking anticoagulant medications. In contrast, the anticoagulant properties of ginseng may also account for a few instances of nose and vaginal bleeding.

Ginseng has been shown to potentiate action of many anti-hypertensive medications. Thus, ginseng should be avoided in patients taking blood pressure medications absent physician supervision.

Use of American ginseng with monoamine oxidase inhibitors, e.g., phenelzine and tranylcypromine, used for depression, may result in enhanced side effects such as anxiousness, headache, mood disorders, nervousness, restlessness, and insomnia.

There are no known interactions with food, herbs or other supplements.

Safety

Ginseng preparations are generally safe and well tolerated when administered within the recommended dosage. Nevertheless, ginseng should be avoided during pregnancy and breast-feeding. One respiratory tract infection study in Canada involving 75 pediatric patients showed ginseng to be safe when given at standard and low doses, but additional research is needed before use in children can be recommended.

Dosage

Purified ginseng extracts are generally standardized to 4 percent or 7 percent ginsenoside contents. The usual oral dose of standardized 4 percent extract is 100-200 mg once or twice daily, for up to 12 weeks. Dried ginseng root in amounts equivalent to 200-600 mg of standardized extract has been used for years in China.

Long-term use of ginseng should not exceed 1 g/day (dry root) or 400 mg/day (extract). A ginseng treatment schedule of 2 to 3 weeks on, then 1 to 2 weeks off, may be repeated for several months.

KAVA [5, 18, 33, 42, 44, 73, 83, 87, 90, 143, 163]

Background

Kava, a plant native to the South Pacific, is a member of the pepper family. It is also known as kava-kava, kawa, or ava pepper. The root is used for medicine. Whole kava roots are chewed for their medicinal value. Kava is available as liquid tinctures or standardized extracts, and powdered in capsules or tablets. A tea can also be made by simmering the plant roots in water.

The main active ingredients in kava root are kavalactones (kavapyrones). These chemical compounds have been extensively studied and found to reduce convulsions, promote sleep, and relax muscles in animals. They also have pain-relieving properties, which may explain why chewing kava root causes some temporary numbness and tingling sensation on the tongue. Kava also contains antioxidant flavonoids and alkaloids.

Historical and current uses

Kava is used to relieve anxiety, stress, restlessness, and treat sleep problems. It has also been used for attention deficit-hyperactivity disorder (ADHD), epilepsy, psychosis, depression, migraines and other headaches, chronic fatigue syndrome, respiratory tract infections, tuberculosis, muscle pain, cancer prevention, urinary tract infections, pain and swelling of the uterus, venereal disease, menstrual discomfort, and to arouse sexual desire.

Kava has been used topically on skin diseases, including leprosy, to promote wound healing and as a painkiller. As a mouthwash, it is used for canker sores and toothaches.

Efficacy

The effectiveness ratings for kava are as follows:

- **Possibly effective for**:
  - Anxiety.
    Review of seven scientific studies concluded that a standardized kava extract was significantly more effective than placebo in treating anxiety. Another study found symptoms improved after only one week of treatment. Kava may be as effective as some prescription antianxiety medications. Another study involving kava and diazepam showed similar brain wave activity changes, suggesting that they may work in the same ways to calm the mind. There is also evidence that 300 mg of kava may improve mood and cognitive performance. This is significant because benzodiazepines (e.g., diazepam and alprazolam), used to treat anxiety often decrease cognitive function. Anxiety-related research on kava has decreased because of reports of liver toxicity.
  - Insomnia.
    Preliminary evidence suggests that kava may help improve sleep quality and decrease the amount of time needed to fall asleep. Because of safety concerns, other herbs and drugs to treat sleeplessness should be considered before using kava.
- **Insufficient evidence as to effectiveness for**:
  - Cancer prevention.
  - Restlessness.
  - Attention deficit-hyperactivity disorder (ADHD).
  - Epilepsy.
  - Psychosis.
  - Depression.
  - Chronic fatigue syndrome.
  - Headaches.
  - Colds and respiratory tract infections.
  - Tuberculosis.
  - Chronic bladder infections.
  - Sexually transmitted diseases.
  - Menstrual problems.

Safety and warnings

There are some big safety concerns arising from many cases of liver damage and deaths in patients with previously healthy livers traced to kava use. Kava has been banned in Switzerland, Germany, and Canada, and several other countries are considering similar action.

Given these injuries even after short-term use (one to three months), it is impossible to say what dose of kava may be safe. The FDA has advised health care professionals of possible health risks of consuming kava. It is not recommended for use in the U.S., but if used, should only be administered under a doctor's supervision.

Kava should never be given to children.

Using kava can make you unable to drive or operate machinery safely.

In addition to liver damage, kava should not be used during pregnancy or while breast-feeding because of possible harm to the uterus and passage of its potentially dangerous chemicals into breast milk.

Kava may also worsen depression. Kava affects the central nervous system and may increase the effects of anesthesia and other medications used during and after surgery. Stop using kava at least two weeks before a scheduled surgery.

Side effects

Side effects associated with kava include allergic and contact dermatitis, dizziness, drowsiness, restlessness, stomach upset, tremors, dry, discolored skin, hair loss, partial loss of hearing, and loss of appetite. Like alcohol, kava may have intoxicating effects and should not be taken before operating a car or other machinery.

Interactions

Kava may increase:

- The effects of anti-convulsant medications, e.g., phenytoin.
- The chance of liver function impairment and damage if combined with alcohol.
- The effects of benzodiazepines, e.g., alprazolam, diazepam.
- Lorazepam, clonazepam, triazolam, and chlordiazepoxide, used for anxiety.
- The effects of barbiturates, e.g., pentobarbital, used for sleep disorders.
- The effects of diuretics, enhancing the risk of dehydration.
- The risk of side effects associated with phenothiazine medications, e.g., chlorpromazine, used for the treatment of schizophrenia, and promethazine, used as an antihistamine and anti-nausea agent.
- The risk of liver damage if combined with drugs that may also harm the liver. Some medications that can harm the liver include acetaminophen, amiodarone, carbamazepine, isoniazid, methotrexate, methyldopa, fluconazole, erythromycin, phenytoin, lovastatin, pravastatin, and simvastatin.
- The risk of harm to the liver if combined with other herbs known to detrimentally affect the liver. Some of these products include androstenedione, chaparral, comfrey, DHEA, germander, niacin, pennyroyal oil, and red yeast.

Kava may reduce the effectiveness of levodopa used to treat Parkinson's disease.

Kava affects medications that are metabolized by the liver. Some medications that are changed by the liver include clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, theophylline, zileuton, zolmitriptan, dsipramine, donepezil, fentanyl, flecainide, fluoxetine, metoprolol, meperidine, methadone, tramadol, trazodone, amitriptyline, diazepam, zileuton, celecoxib, diclofenac, lovastatin, fluvastatin, glipizide, ibuprofen, irbesartan, losartan, phenytoin, piroxicam, tamoxifen, tolbutamide, torsemide, warfarin,

acetaminophen, chlorzoxazone, ethanol, theophylline, ketoconazole, itraconazole, and fexofenadine.

Kava should be discontinued at least 24 hours before surgery because of a possible effect of anesthetics used during surgery, e.g., enflurane, halothane, isoflurane, and methoxyflurane.

Kava can cause enhanced sleepiness or drowsiness if used in conjunction with other herbs and supplements that have the same effect. Some of these herbs and supplements include 5-HTP, calamus, California poppy, Jamaican dogwood, catnip, hops, St. John's wort, skullcap, valerian, and yerba mansa.

Dosage

Currently, there is not enough scientific information to determine an appropriate range of doses for kava. Standardized products are, however, available, with dosages of kavalactones ranging from 120-250 mg/day. In the U.S., most formulations are standardized to 30 percent or 55 percent, i.e., a 100 mg tablet contains 30 mg or 55 mg of kavalactones, respectively. Although use is discouraged, any kava use should be limited to less than three months.

MELATONIN [125, 152]

Background

Melatonin is a naturally occurring hormone that regulates night/day cycles or sleep-wake cycles. Darkness induces the production of melatonin to prepare the body for sleep, and light decreases it to prepare for awakening. It is thought that supplementing natural stores of melatonin might help those who have difficulty sleeping.

Uses and efficacy

The effectiveness ratings for melatonin are as follows:

- **Likely effective for**:
  - Disturbed sleep-wake cycles in children and adolescents with mental retardation, autism, and other central nervous system disorders.
  - Sleep disorders in blind people.
- **Possibly effective for:**
  - Improving jet lag-related alertness, tiredness, movement coordination, and the time it takes to fall asleep.
  - Trouble sleeping.
  - Reducing the number of cluster headaches.
  - Reducing anxiety before surgery (taken sublingually).
  - Helping elderly people sleep after discontinuing use of benzodiazepines.
  - Helping reduce symptoms associated with smoking cessation.
  - Improving the effectiveness and reducing side effects of cancer medications used for tumors in the breast, lung, kidney, liver, pancreas, stomach, colon, and prostate.
  - Decreasing symptoms of a movement disorder called tardive dyskinesia.
  - Decreasing sunburn (applied topically as a cream before sun exposure).
- **Possibly ineffective for**:
  - Adjusting shift work-related sleep disorders.
- **Likely ineffective for**:
  - Depression (may actually worsen symptoms).
- **Insufficient evidence to rate effectiveness for**:
  - Menopausal symptoms.
  - Migraine headache.
    - Evidence suggests that taking melatonin at bedtime can prevent episodic migraine headache. When headaches do occur, they are milder and pass more quickly. Some researchers believe that melatonin production might be altered in migraine sufferers.
  - Insomnia caused by high blood pressure medications, e.g., beta-blockers.
  - Ringing in the ears (tinnitus).
  - Chronic fatigue syndrome.
  - Osteoporosis.
  - Irritable bowel syndrome.
  - Birth control.
  - Fibromyalgia.

Safety

Melatonin is likely safe for most adults when taken by mouth short-term or applied to the skin.

Melatonin may interfere with ovulation, making it more difficult to conceive. Not enough is known about the safety of melatonin when breast-feeding. It is advisable to avoid melatonin if pregnant, trying to become pregnant, or if breast-feeding.

Because it may affect other hormones and thus may interfere with development during adolescence, use in most children should be avoided.

Cautions and warnings

Melatonin can raise blood pressure, increase blood sugar, worsen symptoms of depression, and increase the risk of seizures. In hypertensive patients, diabetics and those who have previously experienced a seizure, caution and close monitoring is recommended.

Side effects

Side effects observed with melatonin use include daytime sleepiness, dizziness, headaches, abdominal discomfort, mild anxiety, irritability, confusion and brief feelings of depression.

Interactions

Because melatonin may cause sleepiness and drowsiness, combining it with other sedative medications such as clonazepam, lorazepam, diazepam, phenobarbital, and zolpidem may cause too much drowsiness.

Birth control pills increase the amount of melatonin the body makes, resulting in abnormally high levels of melatonin.

Caffeine may decrease the effectiveness of melatonin.

Fluvoxamine can increase the amount of melatonin that the body absorbs and thus may increase the effects and side effects of melatonin.

Melatonin can increase blood sugar and thus may decrease the effectiveness of diabetes medications such as glimepiride, glyburide, insulin, pioglitazone, rosiglitazone, chlorpropamide, glipizide, and tolbutamide.

Melatonin might decrease the effectiveness of immunosuppressants medications such as azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD, mycophenolate, tacrolimus, sirolimus, prednisone, and corticosteroids.

Taking melatonin with medications that slow clotting might increase the chances of bruising and bleeding. Medications known to slow blood clotting and impair platelet aggregation include aspirin, clopidogrel, diclofenac, ibuprofen, naproxen, dalteparin, enoxaparin, heparin, and warfarin.

Melatonin may decrease the anti-hypertensive activity of nifedipine.

Verapamil can increase the speed at which the body metabolizes melatonin, so may decrease the effectiveness of melatonin.

Flumazenil may decrease the effects of melatonin.

Melatonin may increase the effect of herbs that slow blood clotting and thus might increase the risk of bleeding. Some herbs that slow blood clotting include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, and willow.

Using melatonin along with herbs having sedative properties, e.g., 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, skullcap, valerian, and yerba mansa, may increase the effects and side effects of melatonin.

There are no known interactions of melatonin with foods.

Dosage

The following oral doses have been used in scientific studies for:

- Insomnia:
  - Adults: 0.3-5 mg at bedtime.
  - Children: 5 mg at 6 or 8 p.m.
- Jet lag:
  - 0.5-5 mg at bedtime on the arrival day, continuing 2-5 days.
- Tardive dyskinesia:
  - 10 mg daily of a controlled-release formulation.
- Solid tumors in combination with conventional therapy: 10-50 mg along with radiotherapy, chemotherapy, or interleukin. Melatonin is typically started seven days before the start of chemotherapy and continued throughout full treatment course.
- Prostate cancer that has spread to other sites (metastatic cancer) and is resistant to triptorelin used alone: 20 mg taken daily has been used in combination with 3.75 mg of triptorelin injected into the muscle every 28 days.
- Prevention and treatment of low platelets associated with cancer chemotherapy: 20 mg each evening.
- Benzodiazepine withdrawal in elderly people with insomnia: 2 mg of controlled-release melatonin taken at bedtime for six weeks. Benzodiazepine dosage is reduced 50 percent during the second week, 75 percent in weeks three and four, and stopped during weeks five and six. Therapy may continue up to six months.
- Prevention of cluster headache: an evening dose of 10 mg.
- Reducing anxiety before surgery in adults: 0.05 mg/kg under the tongue.
- Nicotine withdrawal symptoms: 0.3 mg orally 3.5 hours after stopping smoking.

SAW PALMETTO [8, 10, 11, 13, 16, 19, 24, 33, 39, 40, 74, 77, 83, 91, 104, 105, 111, 116- 118, 125, 154]

Background

Saw palmetto is a fan palm, dwarf palm or cabbage palm that grows as a tree or shrub in the warm climates of the coastal southeast U.S., from South Carolina to Florida. The plant has white flowers that produce yellow berries.

Saw palmetto's active ingredients include fatty acids, plant sterols, and flavonoids. The berries contain high molecular weight polysaccharides (sugars) that may reduce inflammation and strengthen the immune system.

Saw palmetto is commercially available as dried berries, powdered capsules, tablets, liquid tinctures, liposterolic extracts, and a tea. The product label should indicate that contents are standardized and contain 85-95 percent fatty acids and sterols.

Historical and current uses

Historically, saw palmetto has been used to treat urinary tract problems, to increase sperm production, for colds and coughs, sore throat, asthma, bronchitis, chronic pelvic pain syndrome, hormone imbalance, migraine headache, prostate hyperplasia and cancer, as a diuretic, as a sedative, as an antiseptic, and to enhance sexual drive.

Today, the primary use of saw palmetto is to treat benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland. The urethra, the tube that empties urine from the body, runs through the prostate gland. When the prostate gland is enlarged, men may have difficulty urinating.

Pharmacology

It is thought that saw palmetto may inhibit an enzyme that affects the level of testosterone, may reduce the amount of an enzyme that promotes the growth of prostate cells, and may shrink the inner lining that puts pressure on the tubes that carry urine. Saw palmetto has a mechanism of action similar to finasteride and dutasteride, two common drugs used to treat BPH. Interestingly, saw palmetto also inhibits cell proliferation and promotes programmed death of prostate cancer cells. Its anti-inflammatory properties have been linked to its inhibitory actions on cyclooxygenase and lipoxygenase. These combined mechanisms may synergistically contribute to the therapeutic efficacy of saw palmetto extracts.

Because of the short duration of the clinical studies (less than three months), it is not possible to say whether saw palmetto is truly effective in treating or preventing symptoms of BPH. Some studies show symptomatic improvement in symptoms, such as frequent urination, trouble starting or maintaining urination, and nocturnal urination. Other studies show that saw palmetto is as effective in treating symptoms as finasteride, but without the loss of libido side effects. Animal studies indicate that saw palmetto inhibits the growth of tumor cells, thus may possibly be helpful in treating prostate cancer.

Efficacy

In 2002, Wilt et.al. analyzed the results from 21 clinical trials involving more than 3,000 patients. These trials assessed the efficacy of saw palmetto versus placebo and finasteride with respect to urinary symptoms (dysuria, fullness, bladder residual volume, nocturia, urine flow rate, and prostate size). The authors concluded that men taking saw palmetto were nearly twice as likely to report improvement in symptoms than those taking placebo.

Additionally, the saw palmetto patients had responses similar to those found for finasteride with urologic symptoms and flow measures, but with a lower rate of impotence.

Another study involving more than 2,500 patients suffering from mild-to-moderate BPH compared the effectiveness of saw palmetto to tamsulosin (704 patients) and finasteride (1,098 patients), using two different doses of saw palmetto (160 mg twice a day or 320 mg once a day).

The study disclosed a better outcome for patients taking saw palmetto than those taking either of the conventional drugs. Unlike the conventional drugs, sexual dysfunction was not reported in patients treated with saw palmetto. Co-administration of saw palmetto and finasteride did not improve the treatment outcome.

The absence of efficacy of saw palmetto in some studies may be attributable to the study being conducted in moderate-to-severe BPH as opposed to mild-to-moderate BPH, the failure of the study to set appropriate dose-response parameters, or failure to increase the dose of saw palmetto to adjust for the severity of the medical condition.

Although much of the extensive research on saw palmetto is conflicting on whether saw palmetto is beneficial in treating prostate symptoms, there is enough evidence to suggest that saw palmetto is possibly effective in the treatment of mild-to-moderate BPH. It is also less expensive, better tolerated than conventional medications, and unlike finasteride and dutasteride, does not interfere with the laboratory measurements of prostate specific antigen (PSA), used to assess the progression of prostate cancer.

- **Insufficient data to support use of saw palmetto for**:
  - Treating prostate infections.
  - Chronic pelvic pain syndrome.
  - Prostate cancer.
  - Baldness.
  - Colds and coughs.
  - Sore throat.
  - Asthma.
  - Chronic bronchitis.
  - Migraine headache.
  - Increasing breast size.
  - Reducing bleeding after prostate surgery.

Side effects

Side effects are usually mild and include dizziness, headache, nausea, vomiting, constipation, diarrhea, and impotence.

Safety and toxicity

Saw palmetto is likely safe for most people. No serious toxicities have been reported in the scientific literature.

Because of its anti-androgenic properties, women should not take saw palmetto for treatment of urogenital problems if they take contraceptives, hormone replacement therapy, have breast cancer, or are pregnant. Saw palmetto is likely unsafe when used during pregnancy or breast-feeding.

Saw palmetto is not recommended for children.

Because saw palmetto might slow blood clotting and enhance bleeding, saw palmetto should be stopped at least two weeks before any scheduled surgery.

A 2008 meta-analysis found serious adverse effects (e.g., cancer, sexual dysfunction, hepatoxicity, and respiratory problems) were no more common in saw palmetto treatment groups than with placebo. In clinical trials, 3 percent of the saw palmetto subjects developed hypertension, compared to 2 percent treated with finasteride, but this difference was not statistically significant.

Interactions

Because saw palmetto may work similarly to finasteride, it is not recommended that saw palmetto be combined with finasteride or other medications used to treat BPH unless directed to by a physician.

Saw palmetto might slow blood clotting. Taking saw palmetto with medications that also slow clotting may increase the chances of bruising and bleeding. Drugs that slow blood clotting or impair platelet aggregation include aspirin, clopidogrel, diclofenac, ibuprofen, naproxen, dalteparin, enoxaparin, heparin, and warfarin.

Saw palmetto may reduce the number of estrogen and androgen receptors, possibly reducing the effectiveness of oral contraceptives and thus raising the risk of unplanned pregnancy. Taking saw palmetto along with estrogen replacement therapy, e.g., conjugated equine estrogens (Premarin), ethinyl estradiol, and estradiol, may decrease the effectiveness of these estrogen replacements.

Saw palmetto may interfere with the absorption of iron.

There are no known interactions with food, herbs or supplements.

Dosage

For benign prostatic hyperplasia (BPH): 160 mg twice daily or 320 mg once daily. Therapeutic benefits are observed within three to four weeks after the initiation of treatment, which usually lasts for three to six months. The general dosage range is 100-400 mg twice daily.

ST. JOHN'S WORT [25, 33, 46, 57, 58, 62, 63, 83, 90, 96, 109, 114, 146-150, 155-159, 163]

Background

St. John's wort is a shrubby plant with clusters of yellow flowers having oval, elongated petals. It is native to Europe, parts of Asia and Africa, Canada, and the western United States. It is commonly found in the dry ground of roadsides, meadows, and woods.

The plant gets its name because it is often in full bloom around June 24, the day traditionally celebrated as the birthday of John the Baptist. "Wort" is an old English word for plant.

Both the flowers and leaves are used as medicine.

St. John's wort is formulated in capsules, tablets, as tinctures, as a tea, oil-based skin lotions, and in chopped or powdered forms of the dried herb. Most products are standardized to contain 0.3 percent hypericin.

The active ingredients in St. John's wort are deactivated by light, so it is packaged in amber containers.

Historical uses

St. John's wort is an ancient herbal remedy popularly known as "nature's Prozac." St. John's wort was used as a medicine in ancient Greece for a range of illnesses, including various nervous disorders and for its antibacterial, antiviral, and anti-inflammatory properties, e.g., aiding with wound healing, bug bites, hemorrhoids, and burns.

Over the years, St. John's wort has been used to treat heart palpitations, moodiness, menopause symptoms, attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder, seasonal affective disorder, chronic fatigue syndrome, smoking cessation, fibromyalgia, migraine and other types of headaches, muscle pain, nerve pain, irritable bowel syndrome, cancer, HIV/AIDS, and hepatitis C.

Pharmacology

The most studied active components of both the leaves and flowers of St. John's wort are hypericin, pseudohypericin, flavonoids, and essential oils. Investigators long believed that hypericin was responsible for St. John's wort's action in depression, however, recent studies suggest that hyperforin may play a larger role in depression.

Hypericin and hyperforin both act on chemical messengers in the nervous system that regulate mood. Clinical studies closely correlate hyperforin concentrations of 2 percent to 4 percent to antidepressant activity. Both hypericin and hyperforin inhibit reuptake of serotonin at the nerve synapse like fluoxetine and paroxetine, and also inhibit reuptake of dopamine and noradrenaline, like venlafaxine.

Extracts of St. John's wort have antibacterial properties arising from hyperforin's inhibitory effect on the growth of Gram-positive bacteria, including penicillin-resistant and methicillin-resistant staphylococcus aureus. This activity may explain the antiseptic and wound-healing properties of topical St. John's wort preparations. Hyperforin, however, has no effect on Gram-negative bacteria.

Current uses and efficacy

St. John's wort is one of the most commonly purchased herbal products in the United States. It has been studied extensively as a treatment for depression. It has fewer side effects than most other prescription antidepressants. Unfortunately, it interacts with numerous medications so should be taken only under medical supervision.

Many studies find that St. John's wort works as well for mild to moderate depression as selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, citalopram, and sertraline, but without the loss of sex drive. Researchers are unsure how St. John's wort works, but have suggested that it acts similar to an SSRI, by making more of the brain chemicals serotonin, dopamine, and norepinephrine available. These neurotransmitters help improve one's mood.

The American College of Physicians-American Society of Internal Medicine suggests that St. John's wort is a viable option along with antidepressant medications for short-term treatment of mild depression. In contrast, the National Collaborating Centre for Mental Health recommends against its use in depression because of uncertainty about appropriate doses, persistence of effect, variability in content in the marketed preparations, and potential serious drug interactions.

The effectiveness ratings for St. John's wort are:

- **Possibly effective for**:
  - Premenstrual syndrome:
    - Preliminary studies suggest that St. John's wort may help relieve the cramps, irritability, food cravings, and breast tenderness associated with PMS by as much as 50 percent in some women.
  - Menopause:
    - Combined with black cohosh, St. John's wort may improve mood and anxiety during menopause.
  - Seasonal affective disorder:
    - St. John's wort has improved mood and lessened anxiety and sleep disturbances in people with seasonal affective disorder, a disorder that arises from lack of sunlight. An even greater degree of improvement is obtained when light therapy is combined with St. John's wort.
  - Eczema, wounds, minor burns, hemorrhoids:
    - St. John's wort has antibacterial and anti-inflammatory properties helpful in treating minor skin lesions. Applying St. John's wort ointment three times daily for 16 days may improve wound healing and reduce scar formation after a cesarean section.
  - Obsessive compulsive disorder:
    - One study found that 450 mg St. John's wort twice daily for 12 weeks improved OCD symptoms. But two other studies disagreed. Evidence is conflicting. The inconsistent findings could be the result of study design defects and differences in the St. John's wort products used.
- **Likely ineffective for**:
  - Attention deficit-hyperactivity disorder (ADHD).
  - Hepatitis C virus (HCV) infection.
  - HIV/AIDS.
  - Irritable bowel syndrome.
  - Diabetic polyneuropathic pain.
  - Smoking cessation.
- **Insufficient evidence for**:
  - Stomach upset.
  - Bruises.
  - Skin conditions.
  - Migraine headaches.
  - Muscle and nerve pain.
  - Sciatica.
  - Excitability.
  - Fibromyalgia.
  - Chronic fatigue syndrome.
  - Cancer.
  - Weight loss.

Safety, cautions and warnings

France has banned the use of St. John's wort based on a report issued by the French Health Product Safety Agency warning of significant drug interactions seen with St. John's wort. Japan, the United Kingdom, and Canada are in the process of including drug-herb interaction warnings on St. John's wort products. St. John's wort is available in the U.S. unrestricted and over-the-counter.

St. John's wort can also make the skin overly sensitive to sunlight. Hats, long sleeved shirts, and SPF 15 or greater sun screen are recommended in light-skinned people. Sunlamps, tanning booths, and tanning beds should be avoided. St. John's wort should also be avoided when taking drugs that produce photosensitivity. These drugs include amitriptyline, fluoroquinolone antibiotics, sulfonamides, tetracycline, and psoralen containing products.

St. John's wort may interfere with conception or worsen infertility. Women who are pregnant, trying to become pregnant, or breast-feeding should not take St. John's wort.

It may worsen ADD and ADHD symptoms, especially when combined with methylphenidate.

St. John's wort increases the risk of psychosis and mania in those suffering from schizophrenia, bipolar disorder, and major depression. St. John's wort may elevate thyroid stimulating hormone (TSH) levels.

St. John's wort may also contribute to dementia in Alzheimer's patients. Use of anesthetics in people who have taken St. John's wort for at least six months may lead to serious heart complications during surgery. Use of St. John's wort should be discontinued at least two weeks before any scheduled surgery.

Side effects

St. John's wort is generally well tolerated in recommended doses for up to three months. The most common side effects include stomach upset, hives or other skin rashes, fatigue, restlessness, sleep disturbances, vivid dreams, anxiety, headache, dry mouth, sexual dysfunction, irritability, light sensitivity, diarrhea, tingling, dizziness, and mental confusion. Side effects occur in 1-3 percent of patients, an incidence similar to placebo and less than standard antidepressant drugs.

Interactions

St. John's wort interacts with the following medications:

- Medications used to treat depression or other mood disorders.
  - St. John's wort tends to increase the side effects associated with these drugs. The combination may also precipitate a dangerous and even lethal condition called serotonin syndrome, which is characterized by one or more of the following symptoms: headache, shivering, palpitations, agitation, rapid heartbeat, heavy sweating, confusion, dilated pupils, diarrhea, muscle rigidity, elevated blood pressure, loss of muscular coordination, high fever, unconsciousness, and seizures.
  - Do not take St. John's wort with the following antidepressants:
    - SSRIs, e.g., citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine, or sertraline.
    - Tricyclics, e.g., amitriptyline, nortryptyline, or imipramine.
    - MAO Inhibitors, e.g., phenelzine, tranylcypromine, or nefazodone.
- Antihistamines such as loratadine, cetirizine, or fexofenadine. St. John's wort may reduce levels of these drugs in the body, making them less effective.
- Clopidogrel. Combining St. John's wort with clopidogrel may increase the risk of bleeding.
- Dextromethorphan (cough medicine). Taking St. John's wort with dextromethorphan, a cough suppressant, can increase the risk of side effects, including serotonin syndrome.
- Digoxin. St. John's wort may lower digoxin levels thereby inhibiting its effectiveness.
- Immunosuppressants.
  - St. John's wort can reduce the effectiveness of medications taken after organ transplant or to control autoimmune diseases. Taking St. John's wort with any of the following immunosuppressants may even lead to rejection of the transplanted organ: adalimumab, azathioprine, cyclosporine, etanercept, methotrexate, mycophenolate, or tacrolimus.
- Antiretrovirals.
  - St. John's wort appears to interact with protease inhibitors and non-nucleoside reverse transcriptase inhibitors, such as indinavir, amprenavir, nelfinavir, ritonavir, and saquinavir used to treat HIV and AIDS. The Food and Drug Administration recommends that St. John's wort not be used with any type of antiretroviral medication.
- Birth control pills.
  - Breakthrough bleeding has occurred while taking birth control pills and St. John's wort. It may be that the herb can lessen the effectiveness of birth control pills, so may lead to unplanned pregnancies.
- Aminolevulinic acid.
  - This drug makes skin more sensitive to sunlight. St. John's wort also increases skin sensitivity to light. The combination may exert a dangerous impact on skin sensitivity to the sun.
- Reserpine. St. John's wort may interfere with reserpine's ability to reduce blood pressure.
- Sedatives.
  - St. John's wort can increase the effect of drugs having a sedative effect, such as tricyclic antidepressants, alcohol, anticonvulsants e.g., phenytoin and valproic acid, barbiturates benzodiazepines, and drugs to treat insomnia, e.g., zolpidem, zaleplon, eszopiclone, and ramelteon.
- Alprazolam. St. John's wort may speed up the metabolism of alprazolam in the body, thereby reducing its effectiveness.
- Theophylline. St. John's wort can lower blood levels of theophylline, thereby reducing its ability to open airways in people with asthma, emphysema, or chronic bronchitis.
- Triptans (used to treat migraines).
  - St. John's wort increases the side effects of triptans used to treat and prevent migraine headaches, even leading to serotonin syndrome. The tripan group of drugs includes naratriptan, rizatriptan, sumatriptan, and zolmitriptan.
- Warfarin. St. John's wort reduces the blood thinning effectiveness of warfarin.
- Drugs metabolized by certain liver enzymes.
  - St. John's wort induces the expression of certain liver enzymes that play a central role in the metabolism of many drugs. Hyperforin, an abundant, lipophilic component of St. John's wort, contributes to the therapeutic effects, side effects, and drug interactions of this herb. St. John's wort might affect the speed in which the liver breaks down some medications. Taking St. John's wort along with some medications that are changed by the liver can decrease or increase the effectiveness and side effects of these drugs.
  - Caution and physician oversight is recommended before consuming St. John's wort if the patient is taking any of the following medications: clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, zileuton, zolmitriptan, amitriptyline, nortriptyline, diazepam, zileuton, celecoxib, diclofenac, anti-cholesterol statins, glipizide, ibuprofen, irbesartan, losartan, piroxicam, tamoxifen, tolbutamide, torsemide, warfarin, carisoprodol, citalopram, diazepam, lansoprazole, omeprazole, phenytoin, ketoconazole, itraconazole, fexofenadine, triazolam, and many others.
- Drugs moved by pumps in cells (P-glycoprotein substrates).
  - St. John's wort can enhance or diminish the activity of these cell pumps, thereby affecting the absorption and effectiveness

of drugs moved in this manner. Medications that are moved by these pumps include corticosteroids; vinca alkaloids, e.g., vinblastine and vincristine, vindesine; antifungals, e.g., ketoconazole and itraconazole; antiretrovirals, e.g., amprenavir, indinavir, nelfinavir, and saquinavir; H2 blockers, e.g., cimetidine and ranitidine; verapamil; diltiazem; erythromycin; cisapride; fexofenadine; cyclosporine; loperamide; etoposide; paclitaxel; and quinidine.

There are no known interactions of St. John's wort with food.

Dosage

Clinical trials have used a range of doses of St. John's wort that include:

- **Adults**: 500-1,800 milligrams of St. John's wort extract daily by mouth.
  - Most common dosage: 450 mg orally twice daily or 300 mg 3 times daily.
  - 1.5 percent hyperforin has been applied to the skin to treat atopic dermatitis.
- **Children**: 150-1,800 milligrams of St. John's wort extract by mouth daily.

It may take three to four weeks to feel any effects from St. John's wort. Abrupt cessation of St. John's wort may cause unpleasant side effects, so gradually lower the dose before stopping.

VALERIAN [2 8, 31, 76, 81-83, 86, 99, 100, 121, 122, 125, 144, 145, 153]

Background

Valerian is a perennial plant native to Europe. It has straight, hollow stems topped by umbrella-like heads, dark green leaves that are hairy on the underside, and small, sweet-smelling white, purple or pink flowers. The light grayish brown root is pressed into fresh juice or freeze-dried to form powder and used medicinally. Valerian fluid extracts and tinctures are available in alcohol or alcohol-free bases. Powdered valerian is formulated as a capsule, tablet, and as a tea.

Historical use

Valerian has been used to ease insomnia, anxiety, nervous restlessness, flatulence, urinary tract disorders, angina pectoris, congestive heart failure, and stomach cramps for almost 2,000 years. Topically, it has been used to treat acne and to aid wound healing.

Pharmacology

Various chemical compounds have been extracted from valerian, e.g., terpenes, valepotriates, amino acids, and alkaloids. No single compound seems to account for its pharmacological properties, however, the biologically active, valerenic or valeric acid, at concentration of 0.3 percent to 0.8 percent, has been selected for standardization purposes.

Scientists believe that valerian increases the amount of gamma aminobutyric acid (GABA) in the brain. GABA helps regulate nerve cells and has a calming effect on anxiety. Benzodiazepine drugs, such as alprazolam and diazepam, also work by increasing the amount of GABA in the brain. Valerian may act similarly, but has a weaker effect.

Current uses

alerian is most commonly used for sleep disorders, especially insomnia, but the evidence is conflicting. Valerian is frequently combined with hops, lemon balm, or other herbs that also cause drowsiness. Some studies show that valerian reduces the time it takes to fall asleep and improves the quality of sleep itself. These studies conflict on the time it takes to adduce any effect, ranging from almost immediately to 28 days. Unlike many prescription sleeping medications, valerian may have fewer side effects, such as less morning drowsiness.

Some people trying to withdraw from the use of "sleeping pills" use valerian to help them sleep after they have tapered the dose of the sleeping pill.

Valerian is also used for conditions connected to anxiety and psychological stress, including nervous asthma, hysterical states, excitability, fear of illness, headaches, migraine, and stomach upset.

Some people use valerian for depression, mild tremors, epilepsy, attention deficit-hyperactivity disorder (ADHD), and chronic fatigue syndrome (CFS).

Valerian is used for muscle and joint pain, menstrual cramps and symptoms associated with menopause, including hot flashes and anxiety.

Valerian can be added to bath water to help with restlessness and sleep disorders.

Valerian extracts and oil are used to flavor foods and beverages.

Efficacy

The effectiveness ratings for valerian are as follows:

- **Possibly effective for**:
  - Insomnia.
    - Valerian does not relieve insomnia as fast as sleeping pills, in some instances taking up to four weeks for a noticeable effect. Valerian seems to improve the sleep quality during withdrawal from the use of sleeping pills. Randomized clinical trials found the effectiveness of valerian in the treatment of insomnia to be inconclusive, but the studies may have been too short in duration to adequately assess effectiveness.
- **Insufficient evidence to rate effectiveness for**:
  - Anxiety. Again, there is contradictory evidence as some studies reported a reduction in stress associated with social situations, while other studies found no effect.
  - Restlessness. A valerian root extract 160 mg combined with lemon balm leaf extract 80 mg appears to reduce symptoms of serious restlessness in children under the age of 12, but additional research is needed.
  - Depression.
  - Convulsions.
  - Mild tremors.
  - Epilepsy.

- Attention-deficit hyperactivity disorder (ADHD).
- Chronic fatigue syndrome.
- Muscle and joint pain.
- Headache.
- Stomach upset.
- Menstrual pains.
- Menopausal symptoms including hot flashes and anxiety.

Safety

The United States Food and Drug Administration lists valerian as "Generally Recognized As Safe" (GRAS). Germany's Commission E approved valerian as an effective mild sedative.

Valerian is likely safe for most people when used in medicinal amounts short-term. Clinical trials have reported safe use of valerian for medicinal purposes in more than 12,000 people for up to 28 days. The safety of long-term use is unknown.

Use of valerian in children without doctor approval is not recommended. There is, however, some data that suggests valerian might be safe for use in children for up to eight weeks.

Although test studies show no harmful effects on fertility or fetal development, it is advisable to avoid valerian if pregnant or breast-feeding.

Valerian should not be used while driving, operating heavy machinery, or other activities that require alertness.

Valerian and anesthesia medications used during surgery affect the central nervous system. The combined effects might be harmful. Use of valerian should be discontinued at least two weeks before any scheduled surgery.

Side effects

Side effects that have been observed with use of valerian include allergic reactions, headache, stomach upset, uneasiness, morning sluggishness, dizziness, excitability, restlessness, sleeplessness, dilated pupils, and irregular heartbeat.

Instances of paradoxical reactions, such as anxiousness and restlessness, have occurred instead of the desired calm and sleepy effect.

In most cases, valerian does not appear to cause dependency or significant withdrawal symptoms. However, there have been a few reports of withdrawal symptoms when valerian was consumed for very long periods of time. Thus, it may be advisable to gradually lower doses of valerian, rather than stopping all at once.

Interactions

Some medications are enzymatically metabolized in the liver. Valerian might decrease how quickly these liver enzymes break down some medications and thus may increase the effects of these drugs. Some medications changed by the liver include lovastatin, fluvastatin, ketoconazole, itraconazole, fexofenadine, triazolam, and others.

Valerian can increase the effects of anti-convulsant drugs, such as phenytoin and valproic acid.

Valerian can also increase the drowsiness and sleepiness symptoms associated with drugs used in anesthesia and CNS depressants, such as alcohol, barbiturates, pentobarbital, phenobarbital, secobarbital, thiopental, fentanyl, morphine, and propofol. This also may be seen when valerian is combined with benzodiazepines, such as alprazolam, diazepam, clonazepam, lorazepam, midazolam, temazepam, and triazolam.

Valerian can also increase the effects of drugs to treat insomnia, such as zolpidem, zaleplon, eszopiclone and ramelteon, and antidepressants such as amitriptyline.

Using valerian with alcohol can increase central nervous system side effects, such as dizziness, drowsiness, difficulty concentrating, and impairment in thinking and judgment.

Valerian can also enhance the sedating effects of other herbs, such as chamomile, lemon balm, catnip, calamus, California poppy, hops, Jamaican dogwood, kava, L-tryptophan, melatonin, sage, St. John's wort, sassafras, and skullcap.

Dosage

For insomnia, valerian may be taken one to two hours before bedtime, or up to three times daily, with the last dose 30 minutes to 1 hour before bedtime. It can be consumed as a tea by pouring 1 cup boiling water over 1 teaspoonful (2-3 g) of dried root, steep five to 10 minutes; as a tincture (1:5): 1-1½ tsp. (4-6 mL); as a fluid extract (1:1): ½ to 1 tsp. (1-2 mL); or as a dry powdered extract (4:1): 250 to 900 mg.

A few weeks are generally needed to see full effects. Once sleep improves, use should be continued for two to six weeks.

For anxiety: 200 mg 3-4 times daily.

Do not use longer than one month without doctor approval. To avoid possible side effects after long-term use, the dose should be gradually reduced over a week or two before complete cessation of treatment.

Conclusion

In the past 15 years, there has been a dramatic increase in the popularity and widespread use of herbal products and dietary supplements. It is anticipated that the use will continue to rise. To complicate matters, it is estimated that 70-80 percent of the world's population takes herbal supplements, that more than 50 percent of these patients are also on conventional drug therapy, yet most do not disclose their herbal consumption to their health care practitioners.

Reasons for non-disclosure range from concern over possible negative reaction or lack of interest by the health care provider; the belief that because herbals are of natural origin, they are intrinsically safe and devoid of adverse effects or toxicity; or the belief that therapeutic inefficacy is the worst that could happen from taking herbals. Most of these reasons have been proven false.

As such, health care providers need to accommodate for this recent paradigm shift in therapy. The easiest way to do so is to stay abreast of current research into this ever-growing therapeutic area and to establish a habit of routinely and specifically asking patients open-ended, nonjudgmental questions about herbal medicine use as part of taking a medical history.

Some or all of the following questions may be helpful:

- What herbal supplements, vitamins, or other over-the-counter remedies are you taking?

- How long have you been taking these products?
- At what dose or frequency are you taking these products?
- What purpose or result are you seeking to achieve from each of these products?
- What, if any, side effects or problems have you experienced?
- What, if any, improvement in your health or condition have you observed that you attribute to the herbal medicine you take?
- Do you have any plant allergies?

Learning about patients' use of herbal medicines (and over-the counter remedies) can strengthen rapport and build trust. It also allows the physician an opportunity to consider all factors affecting the patient's health while providing medical guidance and information on uses, adverse effects, and interactions. The overall result enhances the likelihood of successful therapeutic outcome.

Finally, it is vital to the provision of optimum health care that health care providers have an understanding of the pharmacological properties and therapeutic efficacy of herbal medicines.

Health care providers must be enlightened on the U.S. regulatory framework applicable to herbals as compared to drugs; this course has provided a concise overview of some of the most common herbal medicines, including their uses, pharmacology, side effects, interactions, dosages, and the risks and benefits of their use.

This includes the urgent need to include current or past use of herbals in patients' medical history, in an effort to provide the safest and most complete health care possible.

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OVERVIEW OF HERBAL SUPPLEMENTS

Final Examination Questions

Choose the best answer for questions 1 through 5 and mark your answers online at **PharmacyTech.EliteCME.com**.

1. Approximately what percentage of people worldwide use herbal medicines as some part of their primary health care?
   a. 70-80 percent.
   b. 40-60 percent.
   c. 20-39 percent.
   d. 10-19 percent.

2. Which of the following statements about the regulatory process for herbal supplements in the United States is false?
   a. Herbal supplements are strictly controlled and must be approved by the government for effectiveness before they are marketed.
   b. Dietary supplements are not approved by the FDA for safety and effectiveness before they are marketed.
   c. If an herbal medicine contains a new ingredient, that ingredient will be reviewed by FDA before marketing, but only for safety, not effectiveness.
   d. The FDA can take herbal medicines off the market if they are found to be unsafe, adulterated, or if the claims on the products are false and misleading.

3. Which of the following is not a reason suggested for conflicting results on whether black cohosh helps relieve menopausal symptoms?
   a. Lack of rigor in study design.
   b. Overly long study duration (6 months or more).
   c. Use of different amounts of black cohosh from different sources.
   d. Use of different outcome measures.

4. Which of the following statements about saw palmetto is false?
   a. It may inhibit an enzyme that affects the level of testosterone, may reduce the amount of an enzyme that promotes the growth of prostate cells, and may shrink the inner lining that puts pressure on the tubes that carry urine.
   b. Data supports the use of saw palmetto for treating prostate cancer.
   c. In most studies, sexual dysfunction was not a frequently encountered side effect with use of saw palmetto.
   d. Saw palmetto has the same or similar mechanism of action as finasteride and dutasteride, two common drugs used to treat BPH.

5. Health care practitioners should ask patients which of the following questions as part of the medical or medication history?
   a. Are you taking herbal supplements, vitamins or other over-the-counter remedies?
   b. How long have you been taking any herbal products and at what dose or frequency?
   c. What, if any, side effects or problems have you experienced from herbal medicines?
   d. All of the above.

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