

Herbal Medicine -An Evidence- Based Approach

Botanical Medicine

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Botanical Medicine

- In 1850, 80% of all medicines in US and Europe were derived from plants.
- Knowledge of chemistry increased with the synthesis of aspirin. Single constituents were highly valued as they could be analyzed and dosed more precisely.
- The use of herbal medicines declined rapidly after WWII.

Botanical Medicine

- The sale of dietary supplements and herbal medicines is a multi-billion dollar business.
- Consumers are confused about what supplements to use and do not know who to ask.
- Health care providers are not adequately prepared to answer questions regarding the use of these substances.

Botanical Medicine

- Safety must be the number one concern.
- There is no question that many of the herbs commonly consumed in our diets and used medicinally have a low risk of toxicity when used appropriately.
- However, long-term use of very potent medicinal plants in humans is not well studied.

Botanical Medicine

- Acute vs. chronic toxicity – most potent medicinal herbs were used when needed, not taken daily. Be cautious with extended use of botanicals.
- Use during pregnancy – many herbs have not adequately been tested for safety during pregnancy and breastfeeding. Consult an expert before using.

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- Herb-drug interactions – there is simply no way to know with 100% certainty if an interaction will occur.
- Check with your health care provider or pharmacist before using any new OTC medications or supplements.

Botanical Medicine

- High fiber diets reduce digoxin bioavailability by 20%.
- Grapefruit juice interactions
 - Calcium channel blockers
 - Benzodiazepines
 - Cyclosporine
 - Estrogens
 - Caffeine
 - Quinidine

Botanical Medicine

- Trying to purchase a quality product can be a daunting task.
- Purchase from reputable companies who have been around awhile.
- Look for the USP or NSF certification marks that will be on products beginning the end of 2001 or beginning of 2002. This will help to assure you that the product is free of contaminants and meets label claims.

Black Cohosh (*Cimicifuga racemosa*)

- Nine clinical trials conducted on black cohosh. All but one have showed beneficial effect upon menopausal complaints, superior to placebo.
- Mechanism of action is unclear. The herb is not believed to have any significant estrogen activity.

Black Cohosh

- Black cohosh extract did not stimulate the growth of estrogen receptor positive breast cancer cells. This study is consistent with previous German research.

Zava DT, Dollbaum CM, Bien M. Estrogen and progestin bioactivity of foods, herbs, and spices. *Proc Soc Exp Biol Med* 1998; 217:369-78.

Black Cohosh

- Most recent study failed to find significant benefit over placebo in menopausal women with a history of breast cancer taking tamoxifen therapy. No change in serum hormone level noted.

Jacobson JS, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001; 19: 2739-45.

Black Cohosh

- The dose of standardized extract is 40 mg. BID (contains 2.5% triterpenes).
- The dried root is taken in doses of 250-500 mg BID
- Tincture (1:5) is taken in doses of 2-3 ml. BID
- Herbalists often combine black cohosh with St. John's Wort, motherwort and/or kava.

Echinacea

(*Echinacea* spp)

- Echinacea was entered into the NF in the early 1900's and by 1920 was one of the most popular pharmaceutical remedies sold in the US.
- Its use as an anti-ineffective agent declined with the introduction of antibiotics.
- Popular once again, sales topped \$300 million in 1998.

Echinacea

- A recent review of the clinical trials found that eight of the treatment trials for acute upper respiratory infection (URI) reported positive results, while 3 of 4 prevention trails found only marginal benefit for preventing URIs.
- If you are going to use it – use it early and take enough for effectiveness.
- Barrett B, Vohmann M, Calabrese C. Echinacea for upper respiratory infection. *J Fam Pract* 1999; 48(8): 628-635

Echinacea

- The assessment of effectiveness of echinacea is complicated by the fact that different products are used in the clinical trials; different plant parts are used; different extraction methods are employed and some preparations are combined with other herbs or homeopathic remedies – making comparisons between trials difficult.

Echinacea

- No serious side effects have been reported with over 2.5 million prescriptions per year in Germany and more than 150 years of reported use in the United States, with the exception of rare allergic reactions.

Mengs U, et al. Toxicity of *E. purpurea*: acute, subacute and genotoxicity studies. *Arzneim-Forsch/Drug Res* 1991; 41: 1076-81.

Echinacea

- A prospective study of 206 pregnant women found no increased risk for major malformations when echinacea was ingested during pregnancy, including the first trimester.

Gallo M; Sarkar M; Au W; et al. Pregnancy outcome following gestational exposure to Echinacea: a prospective controlled study. *Arch Intern Med* 2000; 160: 3141-43.

Echinacea

- Allergy is rare but can occur. Two of 1032 individuals patch tested with different plant ointments reacted to *E. angustifolia*. Allergy is more likely in atopic individuals.

Bruynzeel D, et al. Contact sensitization by alternative topical medicaments containing plant extracts. *Amer J Contact Dermatitis* 1992; 27: 278-79.

Echinacea

- German health authorities recommend limiting the daily use of echinacea to 8 weeks. While use of echinacea for prolonged periods of time is not likely warranted, there does not appear to be evidence of harm with extended use.

McGuffin M, et al. *American Herbal Products Association's Botanical Safety Handbook*. CRC Press, Boca Raton; 1997; 146.

Ephedra

(*Ephedra sinica* Stapf & others)

- Used for more than 25 centuries in Asia for respiratory complaints.
- Isolated ephedrine alkaloids almost 100 years ago.
- Pseudoephedrine used OTC as a nasal decongestant.
- Today, ephedra widely used as a weight loss agent and energy supplement.

Ephedra

- In both human and animal studies, ephedrine has demonstrated an anorectic effect, promoting weight loss. This effect is enhanced when used in combination with methylxanthines, as well as aspirin, which potentiates the action of ephedrine and other compounds.

Boozer CN, Nasser JA, Heymsfield SB et al: An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *International J Obesity* 2001; 25(3):316-324.

Ephedra

- Adverse effects include anxiety, constipation, dizziness, headache, hypertension, insomnia, urinary retention, seizure, stroke and cardiac arrhythmia.
- Due to growing concerns about the safety of ephedra containing products, the FDA requested an independent review of reports of adverse events related to the use of supplements that contained ephedra alkaloids.

Ephedra

- One hundred forty reports of adverse events related to the use of dietary supplements containing ephedra alkaloids submitted to the FDA between June 1, 1997, and March 31, 1999 were reviewed to assess causation and estimate the level of risk these supplements pose to the consumer.

Ephedra

- 31% of cases were either definitely or probably related to ephedrine alkaloids, while another 31% were believed to be possibly related. Of those likely to be related, 47% involved cardiovascular symptoms and 18% involved the central nervous system.

Ephedra

- Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events resulted in death, and 13 events produced permanent disability, representing 26 percent of the definite, probable, and possible cases.

Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000 Dec 21; 343(25): 1833-8.

Ephedra

- Contraindicated in those with angina, enlarged prostate, cerebral insufficiency, narrow angle glaucoma, heart disease, anorexia, bulimia, hyperthyroidism, hypertension, pheochromocytoma, and urinary retention. It must be used cautiously in those with diabetes.

Ephedra

- A recent safety assessment and determination of a tolerable upper limit for ephedra, found that 90 mg of ephedrine alkaloids in ephedra per day is unlikely to pose a risk of adverse health effects in a generally healthy population.

<http://www.crnusa.org/cantoxoverview.html>. *Cantox Health Sciences International: Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra.*

Garlic

(*Allium sativum*)

- Used since ancient times for medicine and food.
- Pasteur first to clearly demonstrate antiseptic activity of garlic.
- Garlic has been shown to slightly lower total serum cholesterol, triglycerides, and LDL, while increasing HDL levels.

Garlic

- Two reviews (in the early 1990s) of all the randomized, placebo-controlled trials found a 9-12% decrease in cholesterol levels in patients with high cholesterol after at least 30 days treatment with 600-900 mg. of garlic extract.

Garlic

- A recent meta-analysis of 45 randomized trials found that garlic reduced total cholesterol levels by 17.1 mg/dL after 8-12 weeks of treatment. Triglyceride and low-density lipoprotein levels were reduced by 19.1 mg/dL and 6.2 mg/dL, respectively. There were no significant changes in high-density lipoprotein levels.

Ackermann RT, Mulrow CD, Ramirez G, et al. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 2001; 161: 813-24.

Garlic: Blood Pressure

- Blood pressure was monitored in most studies. A mild reduction (5-7%) in both systolic and diastolic pressures were noted in most cases. (Silagy C, Neil A. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens* 1994; 12:463-468.)
- While beneficial, the effect is too mild and the studies insufficient to endorse garlic as a primary treatment for hypertension.

Garlic

- Animal and in vitro studies have demonstrated anticarcinogenic activity with garlic.
- Epidemiologic studies suggest that a high intake of raw and cooked garlic may exert a protective effect against stomach and colorectal cancers.

Fleischauer AT, et al. Garlic consumption and cancer prevention: meta-analyses of colorectal and stomach cancers. *Am J Clin Nutr* 2000; 72(4): 1047-52.

Garlic

- Bottom line: If you like garlic – it's probably a good idea to continue eating it as it appears to be beneficial to the cardiovascular and gastrointestinal systems.
- For the treatment of high cholesterol, however, it should only be considered sole therapy in very mild cases as part of a complete lifestyle approach.

Ginger

(Zingiber officinale)

- Four of six human studies have demonstrated the anti-emetic effects of ginger for motion sickness.
- Two trials have positively demonstrated its efficacy in preventing post-operative nausea and vomiting.

Ginger

- Ginger was found to be superior to placebo for the relief of hyperemesis gravidarum at doses of 250 mg. QID. No adverse outcomes were noted in mothers or babies.
 - Fisher-Rasmussen W, et al. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 1990; 38:19-24.
 - Vutyavanich T, Kraissarin T, Ruangsri RA. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. *Obstet Gynecol* 2001; 97: 577-82.

Ginger

- Questions of safety in pregnancy are due to inhibition of thromboxane synthesis. However, there appears little reason to worry with doses limited to 1 gram/day.
- Large doses (>2 g/d) may increase bleeding time in those taking anti-coagulants.
- Due to its cholagogue effect, those with active gallstone disease should avoid ginger.

Ginkgo (Ginkgo biloba L.)

- Ginkgo leaf has been used for centuries in Asian medicine for a variety of complaints including asthma, congestion and promotion of longevity.
- Patients with peripheral vascular disease and cerebrovascular insufficiency have been treated with ginkgo biloba extracts for more than 30 years.

Ginkgo & Dementia

- Nine clinical trials reviewed to evaluate the efficacy of ginkgo for dementia. Authors noted that none of the studies were ultimately convincing – although, they concluded that there is compelling evidence in favor of ginkgo's use in dementia.

Ernst E, Pittler MH. *Clinical Drug Investigations* 1999; 17(4): 301-08.

Cerebrovascular Insufficiency

- Cerebrovascular insufficiency is a non-official diagnostic term that covers a group of symptoms that occur primarily in elders:
 - Dizziness
 - Tinnitus
 - Difficulties with concentration and memory
 - Depressive mood
 - Headaches

Ginkgo & Cerebrovascular Insufficiency

- Symptoms are thought to be associated with impaired cerebral circulation or early indications of dementia.
- Forty controlled studies conducted on ginkgo for cerebrovascular insufficiency – eight of good quality. All but one showed benefit over placebo for afore-mentioned symptoms.

Ginkgo & Intermittent Claudication

- Fifteen controlled trials conducted on intermittent claudication – only two of good quality.
- All trials, including the two best, showed positive results in increased pain-free walking distance compared to placebo.

Kleijnen J, et al. *Lancet* 1992; 340: 1136-39.

Mechanism of Action

- Due to numerous constituents – two key substances are:
 - Flavonoids (ginkgo-flavone glycosides)
 - Terpenoids (ginkgolides and bilobalide)

Products are generally standardized to these two components: 24-25% flavonoids and 6% terpenes.

Mechanism of Action

- The flavonoid fraction is a potent anti-oxidant. In reperfusion injury – free radical levels are increased – the radical scavenging capacity of ginkgo inhibits formation of nitric dioxide radicals from nitric oxide (NO), leaving NO to activate guanyl cyclase, increasing cGMP concentration – leading to vasodilation.

Mechanism of Action

- Ginkgo also increases relaxation of blood vessels due to increased synthesis of prostacyclin.
- Ginkgolides are potent platelet-activating-factor (PAF) antagonists. PAF thought to be involved in regulation of blood pressure, anaphylaxis and inflammation after ischemic injury.

Ginkgo

- For further review of clinical trials and mechanisms of action of ginkgo, the following is an excellent resource:
 - Lawson LD, Bauer R. *Phytomedicines of Europe: Chemistry and Biological Activity*. ACS Symposium Series 691. Washington DC: American Chemical Society 1998: 210-220.

Ginkgo

- Dose of standardized extracts of ginkgo are generally 60-240 mg/d.
- Four case reports of spontaneous bleeding have been reported in patients taking ginkgo alone (2), aspirin (1), warfarin (1).
- If a cause-effect relationship is established – this complication is extremely rare given the millions of doses taken.

Kava-kava

(Piper methysticum)

- A recent systematic review found that kava extract is an effective treatment for anxiety when compared to placebo.
- Two trials were conducted in menopausal women complaining of irritability, anxiety and sleep disturbance. Kava was found to be more effective than placebo in relieving these symptoms.

Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. *J Clin Psychopharmacol* 2000; 20: 84-89.

Kava

- Kava produces relaxation of skeletal muscle both *in vitro* and *in vivo*.
- Sedative effects have been noted *in vivo*.
- Isolated kavapyrones and extract of whole rhizome have been shown to induce sleep in animals.

Kava

- Kava dermopathy, an abnormal skin condition, can occur with chronic and excessive consumption of kava but is very rare with normal use.
- The cause is unknown but may be related to interference with cholesterol metabolism.
Complete resolution of the rash occurs after kava is discontinued.

Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol* 1994; 31: 89-97.

Kava

- Interaction with alcohol is controversial. When twenty healthy adult volunteers were given 100 mg kava extract TID for eight days, no additive effects were noted when alcohol was administered on days 1, 4, and 8 in doses sufficient to achieve blood alcohol levels of 0.05%.

Herberg KW. Effect of kava-special extract WS 1490 combined with ethyl alcohol on safety-relevant performance parameters. *Blutalkohol* 1993; 30: 96-105.

Kava

- Adverse effects include stomach complaints, restlessness, drowsiness, and headache.
- Four cases of probable dopamine antagonism have been reported in the literature. Check with your doctor if you are taking any type of neurological or psychiatric medications.

Schelosky L, Raffauf C, Jendroska K, et al. Kava and dopamine antagonism. *J Neurol Neurosurg Psychol* 1995; 58: 639-40

Kava

- German Commission E allows kava to be recommended for “conditions of nervous anxiety, stress, and restlessness.”
- The dose is based upon kavalactone content. For a 30% kavalactone product the dose is 100-200 mg. TID.

Milk Thistle

(*Silybum marianum*)

- Approved by the German Commission E for the treatment of chronic liver disease and cirrhosis.

(Blumenthal M, Gruenwald J, Hall T, Rister RS, eds. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicine*. Boston: Integrative Medicine Comm. 1998.)

Milk Thistle

- A protective effect on the liver has been demonstrated when silymarin was administered alongside known hepatotoxins: carbon tetrachloride, ethanol, thioacetamide, acetaminophen and the toxins from death cap mushroom (*Amanita phalloides*).

Morazzoni P, Bombardelli E. *Silybum marianum* (Carduus marianus)
Fitoterapia 1995; 66: 3-42.

Milk Thistle

- Sixteen placebo-controlled trials have been conducted on silymarin (the flavonoid complex in milk thistle) for the treatment of liver disease.
- Most of the studies were plagued with methodological flaws and poor study design, however, there is a beneficial trend seen in laboratory parameters in most trials.

Milk Thistle

- Dosage and Contra-indications
 - The dose used in the clinical trials in Germany for the treatment of liver disease was 420 mg./day of an extract standardized to contain 70% silymarin.
 - There are no known drug interactions.
 - Side effects are mild; GI disturbances, diarrhea.

Saw Palmetto

(*Serenoa repens* (Bart.) Small)

Saw Palmetto

- Clinical research has primarily been focused on symptomatic relief of benign prostatic hyperplasia.
- Most studies have been conducted on commercial liposterolic extracts containing fatty acids, phytosterols, and polysaccharides.

Saw Palmetto: Mechanism of Action

- The mechanism of action is not completely understood. To date, the most likely explanations include:
 - inhibition of binding of DHT to cytosolic androgen receptors in prostate tissue
 - inhibition of type 1 and 2 isoforms of 5 α -reductase
 - alpha 1-adrenergic blocking activity.

Saw Palmetto: Meta-analysis

- 1998 meta-analysis reviewed 18 studies with a total n of 2939.
- Mean duration of studies was nine weeks.
- Author's conclusions stated that saw palmetto decreased symptom scores and increased urinary flow measures compared to placebo.

Wilt TJ, *et al.* Saw palmetto extracts for treatment of benign prostatic hyperplasia. *JAMA* 1998; 280:1604-09.

Saw Palmetto: Meta-Analysis

- Summary of results for *S. repens*:
 - mean urinary flow 28% improvement vs plac
 - peak urinary flow 24% improvement vs plac
 - residual urine 43% decrease vs placebo
 - nocturia 25% improvement vs plac
 - urinary symp score 28% improvement vs plac
 - No significant difference between groups for adverse effects.

Saw Palmetto: Summary

- Conclusion by L. Marks MD to physicians
“SPE should now be considered a treatment option for men with symptomatic BPH, absent complications of the disorder. SPE is extremely safe, exerts positive effects, patients want it, and more potent remedies (drugs, surgery) are often not necessary for most BPH cases.” (*Urology Times* 1999; 27(6): 1, 42.)

Saw Palmetto:

Dosage and Contra-Indication

- The dose used in the clinical trials was 160 mg. BID of an extract standardized to contain not less than 70% lipophilic components.
- The most common side effects were gastrointestinal.
- No known herb-drug interactions.

St. John's Wort

(Hypericum perforatum)

In 1996, a meta-analysis of 23 randomized, clinical trials involving 1,757 patients with depression found SJW to be superior to placebo for mild-to moderate depression.

Linde K, et al. St. John's Wort for depression: an overview and meta-analysis of randomized clinical trials. *BMJ* 1996; 313:253-58.

St. John's Wort

- There is no evidence that St. John's Wort is effective for severe forms of depression.
- St. John's Wort has repeatedly been shown to be effective for treating mild forms of this disorder.
- Counseling (mental health professional, pastor, support group, etc) should be part of any wholistic approach to depression.

St. John's Wort

Dosage and Contra-indications

- Products are standardized to 0.3% hypericin or 3-5% hyperforin. Dose is 300 mg TID.
- Rare cases of photosensitivity. Should be used with caution with those taking photosensitizing agents.
- Side effects include GI disturbances, headache, and insomnia.

St. John's Wort

- As mentioned previously:
 - St. John's Wort appears to induce a subset of the P-450 enzymes that metabolize a number of pharmaceutical medications.
 - Talk to you doctor or pharmacist to determine if you are taking any medications that are dependent upon the p-450 system.

Thank you for allowing me to share this information on botanicals with you today.

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The significant problems we have cannot be solved at the same level of thinking we were at when we created them.

Albert Einstein