

Clinical Uses of Herbal Medicines

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***Botanical Supplement
Industry at the Crossroads***

***Quality, Safety, and
Clinical Proof of Efficacy***

***Botanical Supplement
Industry at the Crossroads***

***Herbal Supplements vs.
Herbal Drugs***

Dietary Supplement and Health Education Act of 1994

- The dietary supplement industry organized to present the Health Freedom Act in 1992 (championed by Senator Orrin Hatch).***
- It became the largest constituent issue before Congress since the Vietnam War and was passed in the waning hours of the 103rd Congress at 3 a.m. on Oct. 7, 1994 and the Senate at 12:27 a.m. on Oct. 8 and then signed into law by President Clinton***
- Designation of “dietary supplement” covers vitamins, minerals, amino acids, herbs, glandulars, etc.***

DSHEA

- *Definition of “dietary supplement” – an herb or other botanical or a concentrate, constituent, extract or combination of any botanical that is intended for ingestion as as a tablet, capsule or in liquid form and is not represented for use as a conventional food or as a sole item of a meal of the diet and is labeled as a dietary supplement*
- *This includes new drugs that were marketed as botanical prior to such approval but does not include a botanical approved as a new drug (or authorized for investigation as a new drug) for which substantial investigations have begun or made public which was not previously marketed as a dietary supplement.*

“Regardless of the regulatory or legal advantages that may be gained by calling them something else, whenever herbs are used to diagnose, cure, mitigate, treat, or prevent disease, they are, by definition, drugs.”

Varro Tyler, PhD

“We see the position which medicinal plants should hold in modern medicine: before the major chemotherapeutic agents, and indeed before surgery, in any case in their own position and in their own right. The sequence also establishes the degree of seriousness and danger of the different interventions, being a progression from the least invasive to the most invasive.”

Rudolf Fritz Weiss, M.D.

Healthcare Solution Continuum

Treat disease Treat disease "naturally" Fundamental Cure

Conventional

- *Acute disease*
- *Injury*
- *Major infection*
- *Life-threatening*

Herbal Medicine

- *More natural*
- *Less toxic*
- *Less expensive?*
- *Still symptomatic*

Natural Medicine

- *Health promotion*
- *Well-being*
- *Disease resistance*
- *Disease reversal*

Barriers to Wider Acceptance of Herbal Medicines

- How much evidence is enough?***
 - Is our data up to the standards expected by mainstream medicine?***
 - Can we get other research than RCT accepted?***
- Safety data – what's necessary?***
- Lack of consensus among opinion leaders***
- Paucity of U.S. research***
- Difficulty/expense in detailing/educating Health care professionals***
- How do we go about getting herbal medicines accepted within standards of care?***

What are Health Professionals Looking For?

- *First and foremost concern is SAFETY!!!*
- *Has a company provided sufficient warnings and cautions on labels and related product materials that reflect an accurate view of safety issues based on an expert opinion(s) of existing product/ingredient information reflecting:*
 - *Contraindications (e.g. pregnancy and lactation, pediatric use)*
 - *Known Adverse Effects/Side Effects*
 - *Potential Drug Interactions*
- *Sources of safety data include:*
 - *Preclinical toxicology, clinical trials, pharmacovigilance*

New Regulations Update

- At the end of last year, a Dietary Supplement Adverse Event Reporting law was passed by congress – focus in on “serious or life-threatening” AERs***
- It finally appears that the dietary supplement GMPs mandated by DSHEA will go into effect this year***

***Prevalence of Dietary
Supplement Use, AERs, and
Concomitant Use with Rx
Drugs***

Trends in Dietary Supplement Use

- ***The NHANES III (1988-1994) found that approximately 40% of the U.S. population aged 2 months and older used a dietary supplement.***
- ***1999 survey of 2,000 U.S. adults found that 85% of respondents had used one or more supplement in the past 12 months (Arch Intern Med 2001;161:805-10).***
- ***Eisenberg, et al – Comparing data from 1990 and 1997 surveys, the largest increase was use of herbal supplements (380% vs. 180% for megavitamin use). An estimated 15 million adults took Rx medicines concurrently with herbal or nutritional supplements (18.4% of all prescription users). (JAMA 1998;280:1569-75.)***

2002 Health and Diet Survey Sponsored by the FDA

- National telephone survey to track trends of consumer awareness, attitudes, and practices related to health and diet issues. This version asked about dietary supplement use and if any health problems were attributed to their use. Population was 2, 743 English speaking non-institutionalized adults aged 18 years or older.***
- 73% of those surveyed reported taking a dietary supplement in the previous 12 months and 4% of them had experienced an AE they believed was related to supplement use.***

2002 Health and Diet Survey Sponsored by the FDA, cont.

- 85% of all users reported taking multivitamin/multimineral supplements, 77% a specialized single ingredient vitamin or mineral supplement and 42% any kind of herb or other dietary supplement during the past 12 months***
- Significantly higher use of supplements in older age groups and by women (with the exception of greater use of herbs by men)***
- In the nonvitamin/nonmineral supplement group, most commonly used were echinacea, garlic, ginkgo, ginseng, glucosamine/chondroitin, fish oil, and St. John's wort.***

2002 Health and Diet Survey Sponsored by the FDA, cont.

- Users with self-reported AEs was 87 – 29.3% ages 18-34 yrs; 47.7% 35-54 yrs; 23% >54 yrs. Characteristics compared to those without AEs included a higher proportion of women and annual household income >\$50,000.***
- 75 of 87 persons with AEs listed only one supplement, 10 listed two and the remaining two persons listed three.***
- Multivitamins accounted for 13.3% of the AEs followed by “Xenadrine” (6.7%), vitamins/minerals (5.4%), iron (5.1%), ginkgo (4.6%), vitamin C (4.6%).***

2002 Health and Diet Survey Sponsored by the FDA, cont.

- Of the AEs self-reported, the most common were:***
 - Heart problem or chest pain (12.6%)***
 - Abdominal pain (8%)***
 - Headache (8%)***
 - Rash (7%)***
 - Allergy/reaction (6%)***
 - “Other” (29.7%)***
- What actions did they take?***
 - 90% stopped the product***
 - 48% saw a doctor***
 - 25% reported the incident to a health authority***
 - 12% went to the emergency room***
 - 9% complained to the manufacturer or place of purchase***

J Am Diet Assoc 2006;106:1966-74.

Serious AERs?

- *One 1998 study of 11 poison-control centers in the U.S. found that 1/3 of all AEs reported for dietary supplements were associated with “severe” symptoms.*
- *These included seizures, coma, myocardial infarctions, arrhythmias, coagulation disorders, hepatic disease, anaphylaxis, and death.*

Drug Safety 2000;23:87-93.

Dietary Supplement Use Among Rx Medication Users

- Analyzed data from the 2002 National Health Interview Survey (adults >18 years) regarding use of Rx medication with “nonvitamin dietary supplements” (NVDS). 21% of adults Rx med users reported using NVDS in the prior 12 months. 69% of these did not discuss the use with a conventional medical practitioner.***
- Among those reporting concomitant use, the most commonly used supplements were echinacea, ginseng, ginkgo, garlic, and “glucosamine chondroitin”.***

Dietary Supplement Use Among Rx Medication Users, cont.

- Highest rates of NVDS use were among Rx med users with menopause (33%) and GI disorders (28%). Lowest was among Rx users with coronary heart disease and history of myocardial infarction (12% each). Interestingly, elderly respondents were less likely to use NVDS. 26% of patients with liver disease and 19% with kidney disease were using NVDS and Rx meds.***

Arch Intern Med 2006;166:1968-74.

Conclusions/Comments from NVDS/Rx Findings

- ***“.....physicians need to be cognizant of potential adverse effects or interactions associated with any prescribed medication or NVDS.”***
- ***“Dietary supplements have complex mechanisms of actions and complicated pharmacokinetics, which need to be better understood.”***
- ***“Health care professionals must regularly ask their patients with chronic conditions and prescription medications about NVDS use.”***
- ***“More research on drug-herb interactions and postsurveillance studies are critically needed.”***

Survey of VA Hospital Patients Los Angeles and Pittsburgh

- 458 patients (average age 58 years and 92% were male) – an average of 6.5 oral Rx meds per pt. Most common supplements were vitamins/minerals, garlic, ginkgo, saw palmetto, ginseng, glucosamine, chondroitin, St. John's wort, DHEA, echinacea, and "other" which was not specified.***
- Potential interactions were defined as "a pharmacological or clinical response to a drug and dietary supplement combination different from the anticipated effects of the two agents when given alone, and in which co-administration might result in an antagonistic, synergistic, or idiosyncratic effect."***

Survey of VA Hospital Patients Los Angeles and Pittsburgh, cont.

- ***Most of the potential interactions in patients were with ginseng, garlic, ginkgo and coenzyme Q10. However, few of these interactions were documented by even one case report, and even fewer were identified as probable by at least 3 case reports or any safety data from a clinical trial. Of the 89 potential supplement-medication interactions, 5 (6%) were classified as “documented probable” and potentially severe.***
- ***The vast majority of patients (97.5%) who took dietary supplements, however, were either at little or no risk of supplement-medication interactions. Only 2.5% of patients reporting use of supplements and prescribed medications together could be considered to be at high risk for a potentially severe interaction.***

Arch Intern Med 2004;164:630-6.

***Clinical Proof
of Safety
and Effectiveness***

***Accurate claims and
directions***

Standardization

Proper Stability Data

Proper Identification

Careful Testing of Raw Materials

***Consistency in Growing, Harvesting, and Proper
Storage***

Herbal Medicine Delivery Forms

- ***Teas – common in TCM to used as a decoction***
- ***Infusions***
- ***Tinctures – typically a 1:5 or 1:10 concentration – traditionally alcohol-based (glycerin is sometimes used)***
- ***Fluid Extracts – typically a 1:1 concentration***
- ***Solid Extracts – solvent has been evaporated – typically 2:1 to 8:1 concentrations***
- ***Standardized Extracts – often means expression based on a percentage of an active constituent(s)***

Nervous System Diseases

Age-Related Cognitive Decline, Dementia

- *Primary Considerations*

 - *Ginkgo*

- *Other Considerations*

 - *Huperzine A*

 - *Panax ginseng*

 - *Bacopa monnieri*

 - *Lavender oil (aromatherapy)*

Ginkgo

(Ginkgo biloba)

- ***Part used: The leaves***
- ***Major constituents***
 - ***Terpene lactones (ginkgolides, bilobalide)***
 - ***Ginkgo flavone glycosides***
- ***Mechanisms of action:***
 - ***Increase in memory performance and learning capacity (nootropic actions)***
 - ***Neuroprotective actions – especially during ischemia***
 - ***Improves circulation to the CNS and extremities***
 - ***Free radical scavenger***
 - ***Antagonism of platelet-activating factor***





Ginkgo

- *Common/Potential Clinical Uses*
 - *Mild to moderate dementia*
 - *Age-related cognitive decline (mild cognitive impairment)*
 - *Intermittent claudication*
 - *Tinnitus*
 - *Erectile dysfunction*

Ginkgo

Comparison to Cholinesterase Inhibitors

- *Detailed comparison of two EGb 761 studies with Alzheimer's disease patients (120 and 240 mg/day) with studies using the acetylcholinesterase inhibitors rivastigmine (1-4 mg/day; 6-12 mg/day), tacrine 80, 120, and 160 mg/day, metrifonate (100-180 mg/day for 2 weeks and 30-60 mg/day for 24 weeks), and donepezil (5 and 10 mg/day).*
- *While the EGb 761 studies also included patients with less severe disease, the delay in disease symptoms was greatest in the EGb 761 (120 mg/day) and donepezil studies. Similarities are also noted on response rate on the ADAS-Cog (≥ 4 points).*
- *Dropout rates were highest in the tacrine studies and high-dose rivastigmine but comparable for other drugs and EGb 761.*

Phytotherapy 2000;6:393-400

Ginkgo

Focus and Memory in the Aging

- 262 male and female subjects 60 years of age or older, with no history of dementia or significant cognitive impairment (≥ 26 on the Mini-Mental Status Examination) were given either EGB 761[®] (60 mg t.i.d.) or placebo for 6 weeks.***
- The EGb 761 group exhibited a significantly greater improvement from baseline on the delayed recall ($p < 0.04$) and recognition tasks ($p < 0.01$) used for evaluation.***

Ginkgo

Focus and Memory in the Aging, cont.

- ***On a follow-up Self-Report Questionnaire, a significant relationship was found between the type of treatment received and participants' ratings of their overall abilities to remember. Significantly more participants in the EGb 761 group (27%) rated their overall abilities to remember by treatment end as either "somewhat improved" or "much improved" compared to the placebo group (17%) (p=0.05).***
- ***Overall, more adverse events were reported by the placebo group than the EGb 761 group.***

Hum Psychopharmacol Clin Exp 2002;17:267-77.

Ginkgo

Use in healthy adults?

- *A recent meta-analysis looked at the short-term (2 days or less) and long-term (5 days and up to 2 years) effect of ginkgo on healthy/cognitively intact adults.*
- *In short-term studies, doses of 120-360 mg/day were found to be effective in improving attention, memory and speed of processing*
- *Longer studies found positive effects on cognitive function but the effect was most notable in older adults when compared to younger adults*

HerbalGram 2005;67:43–62.

Ginkgo

Recommended Use/Safety Issues

- Extract standardized to 24% ginkgo flavone glycosides and 6% terpene lactones – 120 to 240 mg/day in two or three divided doses. These extracts should be also have <5 ppm of ginkgolic acids. It may take 4 to 8 weeks to notice clinical effects.***
- Side effects are rare and may include GI upset or transient headache. At higher doses, some patient may complain of dizziness.***

Ginkgo Biloba Extract

Safety Update

- Based on at least seven reports of potential spontaneous bleeding events (120-160 mg/day for 1 week to 7 months) – possible interactions with warfarin, aspirin, and ibuprofen reported. More severe events have been in individuals >70 years of age***
- However, recent short-term pharmacological studies have found no effect of ginkgo (240 mg/day) on INR and platelet aggregation and also no interference with warfarin pharmacokinetics (British J Clin Pharmacol 2005;59:425-32)***

Ginkgo Biloba Extract

Safety Update, cont.

- ***Based on published case reports and pharmacovigilance from ginkgo extract manufacturers, researchers at the University of Exeter concluded that the ginkgo extract is unlikely to increase risk of bleeding.***
- ***In the same paper, a review of 44 clinical trials with 9,772 patients was unable to find a single case of bleeding complications after ingestion of ginkgo extract.***

Perfusion 2005;18:52-6.

Ginkgo Biloba Extract

Safety Update, cont.

- ***Ginkgo biloba Extract EGb 761 Does Not Affect Bleeding Time in Elderly Patients***
 ÿ Blood Coagul Fibrinolysis 2005;16:349-53.
- ***Ginkgo Extract EGb 761 Does Not Appear to Inhibit the Cytochrome P450 Isoenzyme (CYP2C9) Responsible for Metabolizing Warfarin***
 ÿ J Clin Pharmacol 2006;46:21-21.

Nutritional Supplement Considerations

Acetyl-L-carnitine

Phosphatidylserine

Vitamin B12 (deficiency only)

Vitamin B6

Vitamin B1

Vitamin E

Anxiety

- *Primary Considerations*

 - *Kava*

- *Other Considerations*

 - *Passion Flower*

 - *Valerian*

 - *Blue Skullcap*

Kava

(Piper methysticum)

- **Part used: The rhizome**

- **Major Constituents**

 - **Kava lactones (also called kava pyrones)**

- **Mechanisms of Action:**

 - **Anxiolytic - kava exerts a relaxing effect on the CNS. It is also associated with improving sleep quality. When used at recommended amounts, it is not associated with addiction or impaired reaction times.**





Kava

- *Common/Potential Clinical Uses*
 - *Mild to moderate anxiety*

Kava Extract

Anxiety

- *Multicenter, randomized, placebo-controlled trial in 101 adults with anxiety and tension of non-psychotic origin. Randomized to receive either 100 mg of kava extract (70% kava lactones) or placebo daily for 24 weeks.*
- *From the 8th week on, there was a significant improvement in the HAMA score in those taking kava ($p=0.02$) that reached greater significance by week 24 ($p<0.001$). Similar differences were noted on the CGI and patient self-reporting measures. AEs reported were primarily mild GI upset.*
Pharmacopsychiatry 1997;30:1-5.

Kava Extract

Comparison to Benzodiazepines

- ***Patients with mild to moderate anxiety (n=172) were randomized to receive either 100 mg of kava extract (70% kava lactones), 5 mg of oxazepam, or 3 mg of bromazepam tid for 6 weeks.***
- ***Improvement on the HAMA was statistically equal in all groups with a slightly better response reported for bromazepam on the CGI.***
- ***Adverse events were not reported to kava and low in the benzodiazepine groups (primarily fatigue).***

Healthnotes Rev 1999;6:265-70 (translation/reprint from the German)

Kava Extract

— Recommended Use/ Contraindications

• Extracts standardized to 30-70% kava lactones – the daily extract dosage should supply 140 to 240 mg of kava lactones in two or three divided dosages

• Kava is contraindicated during pregnancy and lactation.

Kava Extract

Safety Update

- ***Side effects have included gi upset, skin rash, and sebaceous reaction following long-term ingestion (J Am Acad Dermatol 1998;38:104-6). Large amounts of traditional preparations have resulted in drowsiness and impaired reaction time.***
- ***Kava should not be used concomitantly with anxiolytics, antidepressants, or neuroleptics. There is one case study of over-sedation and grogginess (not a “coma” as reported in literature) in a person combining alprazolam with kava (Arch Inter Med 1996;125:940-1).***
- ***Kava may potentiate the CNS effects of alcohol.***

Kava Extract Hepatotoxicity

- ***Reports from late 2001 have indicated that kava may be associated with liver damage.***
- ***Until additional information clarifies the extent of the risk involved, it is strongly recommended that all individuals consult their physician before taking kava. In addition, based on the available information, it seems that people with liver disease and those taking medications that have the potential to damage the liver should not take kava.***

***Reuters, Nov. 19, 2001. <http://www.reutershealth.com/frame2/eline.html>
BMJ 2001;322:139.***

Dtsch Med Wochenschr 2001;126:970–2.

Dtsch Med Wochenschr 1998;123:1410–4.

Ann Intern Med 2001;135:68–9 [letter].

Depression

- *Primary Considerations*

 - *St. John's wort*

- *Other Considerations*

 - *Ginkgo*

St. John's Wort ***(Hypericum perforatum)***

- ***Parts used: The flowering top***
- ***Major constituents***
 - ***Hyperforin***
 - ***Hypericin***
 - ***Flavonoids***
- ***Mechanisms of action***
 - ***In vitro studies suggest possible inhibition of the reuptake of serotonin, norepinephrine, and dopamine. Others suggest GABA-receptor binding.***



St. John's Wort

- *Common/Potential Clinical Uses*
 - *Mild to moderate depression*
 - *Dysthymia*

St. John's Wort Extract Placebo-Controlled Trial

321 male and female subjects aged 18 to 65 years with a major depressive episode of at least two weeks duration and a total score on the HAM-D between 18 and 25. After a single-blind run-in period, patients were randomized to either 300 mg of St. John's wort extract WS 5570 or placebo tid for 6 weeks.

Total score for the HAM-D decreased by a mean of 9.9 points for the WS 5570 group and 8.1 in the placebo group. In the intention to treat study group, the percentage of responders was significantly higher for WS 5570 (52.7%) than for placebo (42.3%) ($p < 0.05$). The percentage of patients with remission was significantly higher for the WS 5570 group (24.7%) than for placebo (15.9%) ($p = 0.03$). 30.6% of patients taking WS 5570 experienced adverse events compared to 37% in the placebo group.

Ann J Psychiatry; 2002;159:1361-66.

St. John's Wort Extract Comparison with Paroxetine

- ***251 adult patients with moderate to severe depression were randomized to receive either St. John's wort (300 mg tid) or paroxetine (20 mg/day) for 7 weeks. After 2 weeks of treatment, non-responders doubled the dose of their medication. Higher doses were given to 57% of the SJW group and 48% of the paroxetine group.***
- ***After 7 weeks of treatment, the HAMD score decreased by an average of 14.4 ± 8.8 points in the SJW group and 11.4 ± 8.6 points in the paroxetine group (56.6% and 48.8% of baseline value, respectively). Significantly more patients in the SJW group experienced "remission" of their depression ($p=0.02$). More AEs were reported in the paroxetine group.***
BMJ 2005;330:503-5.

St. John's Wort Extract Comparison with Fluoxetine

- 135 patients with a diagnosis of major depressive disorder were randomized to receive either St. John's wort (300 mg tid), fluoxetine (20 mg/day), or placebo for 12 weeks.***
- At the end of the 12-week treatment period, the SJW group showed lower HAM-D scores (n = 45; mean ± SD, 10.2 ± 6.6) compared with the fluoxetine group (n = 47; 13.3 ± 7.3; p < 0.03) and a trend toward a similar finding compared to the placebo group (n = 43; 12.6 ± 6.4; p = 0.096). There was a trend toward higher rates of remission (a HAMD of < 8) in the SJW group (38%) compared to the fluoxetine group (30%).***
- There were no AE-related treatment discontinuations in the LI 160 or placebo group, whereas the fluoxetine group had two patients drop out due to side effects.***

J Clin Psychopharmacol 2005;25:441-7.

Low Dose St. John's wort maybe effective

- *332 male and female outpatients (18–65 years old) with an episode of mild or moderate depressive episodes (single or recurrent) were randomized to receive either placebo (n=82) or 600 mg (n = 123) or 1200 mg (n = 127) St. John's wort (WS 5570)*
- *After 6 weeks of treatment, mean \pm standard deviation decreases in HAM-D total scores of 11.6 ± 6.4 , 10.8 ± 7.3 , and 6.0 ± 8.1 points were observed for the 600 mg/day, 1200 mg/day, and placebo groups, respectively.*

Low Dose St. John's wort maybe effective

- The differences between both WS 5570 groups was significant compared to placebo at 6 weeks ($p < 0.001$). No significant difference was noted between the two WS 5570 groups on the HAM-D total scores.***
- The responder rates were approximately 70% and 61% in the 600 mg and 1200 mg groups compared to 32% in the placebo group ($p < 0.001$). The number of patients in remission was 33% in the 600 mg group, 40% in the 1200 mg group, and 15% in the placebo group ($p = 0.004$ for the 600 mg group; $p < 0.001$ for the 1200 mg group). The most frequently reported adverse events were related to gastrointestinal tract disorders***

BMC Med 2006;4:14 [published online: doi: 10.1186/1741-7015-4-14]

St. John's Wort

Recommended Use/Side Effects

- Standardized extract – 600 to 1800 mg/day. It may take 2 to 4 weeks to note clinical results.***
- Side effects include mild GI upset, dry mouth, nervousness, and erythematous rash.***
- SJW may make the skin and eyes more photosensitive. Persons exposed to sunlight while taking SJW should take appropriate precautions.***
- The use of SJW during pregnancy remains controversial although recent studies suggest use during lactation may be safe***

St. John's Wort Extract

Safety Update

- ***Advise patients not to take SJW with SSRIs - there have been several cases of serotonin syndrome reported in the literature that may have been caused by concomitant use.****
- ***Warnings about use of SJW with anesthesia may be unfounded due to the fact that the herb has no in vivo MAOI activity. *****

****Clin Psychiatr News 1998;26:28.
Am Family Phys 1998;57:950.
Pharmacother 2000;20:568-74.***

*****Annals Pharmacother
1999;33:502.***

St. John's Wort Extract Safety Update

- ***Two separate publications report on a total of 5 case reports of patients showing the onset of mania following the use of St. John's wort extract for depression.***
- ***As is the case with other antidepressants, health care professionals should screen patients for a history of hypomania or mania before prescribing St. John's wort***

Biol Psychiatry 1999;46:1707-8.

J Clin Psychopharmacol 2000;20:115-7.

St. John's Wort Extract

Potential Drug Interactions

— **Case reports and/or pharmacological studies have indicated that SJW may reduce serum levels of the following drugs (most likely due to induction of CYP3A4 and P-glycoprotein):**

• **Indinavir (Crivaxin®) (*Lancet* 2000;355:547-8)**

• **Cyclosporine (*Lancet* 2000;355:548-9; *Lancet* 2000;355:1912; *J Hepatology* 2000;33:853-5; *Ann Pharmacother* 2000;34:1013-6).**

• **Tacrolimus (immunosuppressant) (*Nephrol Dial Transplant* 2003;18:819-22).**

• **Theophylline (*Ann Pharmacother* 1999;33:502)**

• **Digoxin, warfarin, oral birth control pills (*Eur J Clin Pharmacol* 1999;55:A22; *Clin Pharmacol Ther* 1999;66:338-45; *Lancet* 1999;354:2014-6; *J Clin Pharmacol* 2003;56:683–90).**

• **Irinotecan (chemotherapeutic drug) (*J Natl Cancer Inst* 2002;94:1247–9).**

• **Gleevec (chemotherapeutic drug – U. of Florida report)**

Ginkgo and SSRI SEs

- *Fluoxetine-induced genital anesthesia relieved by GBE*

(J Clin Psychiatry 1998;59:4).

- *J Sex Marital Therapy 1998;24:139-45.*

- *33 women and 30 men (presumably elderly) - all but 15 taking SSRIs*

- *Unspecified GBE given at a dose of 80-120 mg daily and titrate dose to 120 mg bid*

- *Effective in alleviating sexual side effects in 91% of women and 76% of men*

- *Many patients experienced improved cognitive function and increased energy.*

Nutritional Supplement Considerations

Folic acid (for folate deficiency)

Iron (for iron deficiency)

Vitamin B12 (for B12 deficiency)

Vitamin B6 (with oral contraceptives)

5-HTP

DHEA

L-phenylalanine/DLPA

Melatonin

SAMe

Valerian

(Valeriana officinalis)

- ***Parts used: The root***
- ***Major constituents***
 - ***Volatile oils***
 - ***Valepotriates***
 - ***Lignans***
- ***Mechanisms of action***
 - ***In vitro studies suggest possible GABA-receptor binding – new data focused on lignans***



Beezer

Valerian

- *Common/Potential Clinical Uses*

- *Insomnia*

- *Mild anxiety*

Valerian Insomnia

- ***20 clinical trials have investigated the use of valerian either alone or in combination with herbs such as lemon balm or hops***
- ***Although trials have varied greatly in the quality of sleep measure, most suggest that valerian reduces sleep latency, improves quality of sleep, and does not lead to morning grogginess.***

Source: *The ABC Clinical Guide to Herbs*

Valerian and Lemon Balm Dyssomnia in Children

- 918 children (> 12 years old; average age of 8.3 years) suffering from pathological restlessness and/or nervous dyskoimesis (difficult falling asleep) received tablets containing 160 mg of valerian root dry extract and 80 mg of lemon balm fro 4 weeks.***
- The mean dosage at the start of the study was 3.5 tablets per day with the maximal dosage chosen for 74.6% of the participants. In the course of the study, the dosage was modified in 68 participants.***

Valerian and Lemon Balm Dyssomnia in Children

- ***Dyssomnia improved from “moderate” and “severe” in 77.1% of participants at baseline to 76.6% reporting “absent” or “mild” at the end of the study. During the study, “improvement in total” was found to be 70.4% for restlessness and 80.9% for dyssomnia.***
- ***“Tolerability” was judged by the investigators to be “very good” or “good” for 96.7% of the participants. Only two adverse events occurred during the study and neither was judged to be due to the herbal combination.***

Phytomedicine 2006;13:383–7.

Valerian

Recommended Use/Safety Issues

- Concentrated root extract (5:1) containing no less than 0.5% volatile oils – 300 to 500 mg 30 to 60 minutes before hs. Dried valerian root – 2 to 3 grams as an equivalent dose.***
- Side effects include mild GI upset and occasional drowsiness.***
- European monographs list no contraindications to use during pregnancy or lactation although WHO does recommend avoidance***
- Caution should be advised regarding concomitant use with benzodiazepines***

Migraine Headache

- *Primary Considerations*

 - *Feverfew*

 - *Butterbur root extract*

- *Nutritional Supplements*

 - *Magnesium – 400-600 mg/day*

 - *Riboflavin – 400 mg/day*

Feverfew

(Tanacetum parthenium)

- ***Part used: The leaves***
- ***Major constituents***
 - ***Sequiterpene lactones – primarily parthenolide***
- ***Mechanisms of action***
 - ***Inhibits platelet aggregation and serotonin release***
 - ***May also inhibit prostaglandin synthesis***



Feverfew

- *Common/Potential Clinical Uses*
 - *Migraine Headache*
- *Clinically studied products commercially available - None*

Feverfew

- *Meta-analysis of studies with migraine patients found five studies that met inclusion criteria – 3 positive and 2 negative (Cephalagia 1998;18:704-8).*
 - *Positive studies have suggested that prophylactic use of dried feverfew leaves (50 to 200 mg/day) reduced the severity and incidence of migraines. Studies are criticized for small sample size and unclear reporting or randomization and blinding methods.*
 - *Of the two negative studies, one is only reported in abstract form. The second used a dried alcoholic extract of feverfew (143 mg/day) and found no effect on migraine severity and incidence although less pain medication was used in the feverfew group.*

Feverfew

Recommended Use/Safety Issues

- Feverfew dried leaf extract with a standardized parthenolide content of at least 250 mcg per daily dose. Continuous use is recommended for at least 3 months.***
- No long-term studies have been performed to assess the safety of feverfew. Side effects include nervousness and mild GI upset. Chewing the leaves may cause mouth ulcerations.***
- Contraindicated during pregnancy and lactation and not recommended for children under 2 years of age.***
- No known drug interactions.***

Standardized Butterbur Extract

- The butterbur plant (*Petasites hybridus*) is a member of the Asteraceae family of plants***
- It has been used medically for centuries, including to treat plague and fever in the Middle Ages***
- In modern times, a standardized butterbur extract has been clinically studied for the prevention of migraines***

Indications

- *Prevention and treatment of migraine headaches*
- *Indications being researched:*
 - *Allergic rhinitis*
 - *Asthma*

Butterbur Extract for Migraine Headache

- A randomized, double-blind, placebo controlled trial compared the effects of 150 mg and 100 mg of standardized butterbur extract per day to a placebo for the prevention of migraine attacks***
- This study included 202 participants who suffered from at least 3 migraine attacks per month, and had experienced at least 2 attacks during the month before the study began.***
- The study duration was 16 weeks***

Neurol 2002;58(Suppl 3):A472

Butterbur Extract for Migraine Headache

- Both the 100 mg and the 150 mg per day of the standardized butterbur extract groups experienced a reduction in the number of migraine attacks compared to placebo but only significant in the 150 mg group***
- The 150 mg per day group had a higher reduction rate in the number of migraine attacks than the 100 mg group***
- After four months of treatment, the percent of patients showing a 50% or greater reduction in migraine attacks was 68% for the 150 mg group***

Side Effects/Contraindications

- *Standardized butterbur extract is generally well tolerated*
- *The clinical trials reported occasional gastrointestinal upset. Taking butterbur extract with meals generally alleviates this problem.*
- *Because of smooth muscle relaxing effects, standardized butterbur extract is not recommended for pregnant or nursing women. New concerns arising about potential hepatotoxicity.*

Cardiovascular Disease

Atherosclerosis

***See Hyperlipidemia for Primary and
Other Considerations***

Garlic

(Allium sativum)

- ***Part used: The bulb***
- ***Major Constituents: The sulfur compound allicin – produces other compounds such as allyl sulfides, ajoene, and the vinyldithiins***
- ***Mechanisms of action***
 - ***Mildly decreases serum lipid levels***
 - ***Increases fibrinolysis***
 - ***Decreases platelet aggregation***
 - ***Increases activity of nitric oxide***
 - ***Decreases LDL-cholesterol oxidation***
 - ***Mild antihypertensive action***



Garlic

- *Common/Potential Clinical Uses*
 - *Prevention of atherosclerosis*
 - *Mildly elevated serum cholesterol and/or triglycerides*
 - *Mild hypertension*

Garlic

Antiatherosclerotic Actions

- *Randomized, double-blind, placebo-controlled trial examined the effect of 900 mg/day of garlic (Kwai) on atherosclerotic plaques in 280 male and female volunteers (age 44-74 years) with ultrasound verification of advanced atherosclerotic plaques in the carotid bifurcation and/or the femoral arteries. 152 persons completed the 48 month study.*
- *Taking all participants into consideration, the placebo group had a 15.6% increase in plaque volume compared to a 2.6% decrease in the garlic group. In men, plaque volume increased by 5.5% in the placebo group compared to 1.1% in those taking garlic. In women, plaque volume increased by 53.1% in the placebo group compared to a decrease of 4.6% for the garlic group. The effect was most notable between 50-80 yrs.*

Atherosclerosis 1999, 144:237-49.

Aged Garlic and Atherosclerosis

- ***One-year pilot study (placebo-controlled) at UCLA found that AGE (Kyolic) reduced plaque formation by more than 50% in high-risk coronary artery patients with a history of open-heart by-pass surgery***
- ***Daily dose was approx. 1.2 g (4 mL)***
- ***Interestingly, it also reduced serum homocysteine***

Budoff M, et al. Experimental Biology Meeting, 4/15/03, San Diego

Garlic

Lipid Lowering or Not?

- **Majority of studies have used the Kwai product that is standardized to alliin content (1.3%) and allicin potential. The daily dose has ranged from 600 to 900 mg/day for 12 to 24 weeks.**
- **Negative Trials**
 - *Arch Intern Med* 1998;158:1189–94.
 - *J Royal Coll Phys* 1996;30:329–34.
 - *Atherosclerosis* 1995;113:219–25.
- **Positive Trials**
 - *Arzneimittelforschung* 1990;40:1111–6.
 - *Br J Clin Pract* 1990;44(Suppl 69):7–11.
 - *Am J Med* 1993;94:632–5.

Garlic

Lipid Lowering – Probably Not

- 192 adults (ages 30 to 65 years old) with fasting LDL-C concentrations of 130 to 190 mg/dL triglyceride level less than 250 mg/dL and body mass index of 19 to 30 were entered in this 6-month study***
- Following a two-week run-in phase, subjects were randomized to one of four treatment arms: 1) 4.0 g of blended raw garlic (an average-sized clove crushed in a blender; 2) 4 Garlicin tablets (350 mg each tablet supplying 3200 mcg of allicin; 3) 6 Kyolic-100 aged-garlic tablets (300 mg per capsule with no allicin yield; 4) 4 or 6 placebo tablets.***

Garlic

Lipid Lowering – Probably Not, cont.

- *There were no statistically significant effects of the three forms of garlic on LDL-C concentrations. The 6-month mean (SD) changes in LDL-C concentrations were + 0.4 (19.3) mg/dl (+ 0.01 [0.50] mmol/L), + 3.2 (17.2) mg/dL (+ 0.08 [0.44] mmol/L), + 0.2 (17.8) mg/dL (+0.005 [0.46] mmol/L), and – 3.9 (16.5) mg/dL (– 0.10 [0.43] mmol/L) for raw garlic, Garlicin, Kyolic, and placebo, respectively. There were no significant changes in any group for TC, HDL-C, TG, or TC/HDL ratio for any group.*
- *No serious adverse event occurred.*
Ann Intern Med 2007;167:346–53.

Garlic

Recommended Use/Safety Issues

- **Standardized garlic powder products containing 1.3% alliin and providing 5,000 to 6,000 mcg of allicin potential daily – 600-900 mg/day**
- **Side effects are rare at the above doses – heartburn and flatulence may be experienced by persons sensitive to garlic. There are rare reports of hypersensitivity to garlic.**
- **Should not be used concomitantly with anticoagulant or anti-platelet aggregation medications. Use cautiously with other nutrients or herbs that may affect bleeding time (e.g. ginger, vitamin E).**

Hyperlipidemia

- *Primary Considerations*

 - *Red Yeast Rice*

 - *Policosanol*

 - *Fenugreek (primarily in diabetic patients)*

 - *Psyllium*

- *Other Considerations*

 - *Garlic*

 - *Guggul*

 - *Polymethoxylated Flavones/Tocotrienol
Combination*

Red Yeast Rice

Hyperlipidemia

- **83 persons (ages 34-78 years) with hyperlipidemia were randomized to receive either red yeast (*Monascus purpureus*) rice supplement (1.2 g bid, Cholestin) or placebo for 8 weeks. All subjects were placed on the American Heart Association Step I diet.**
- **Between baseline and 8 weeks, total serum cholesterol was significantly reduced ($p < 0.05$) in the Cholestin group. This difference was also significant ($p < 0.05$) at 4 wks post-treatment. LDL-cholesterol levels were also significantly lower at weeks 8 and 12 ($p < 0.001$). Triacylglycerol concentrations were significantly lower at week 8 ($p = 0.05$) but not week 12. HDL-cholesterol concentrations did not differ between groups.**

Am J Clin Nutr 1999;69:231-6.

Policosanol

Ineffective for Hyperlipidemia

- 143 participants (18 to 80 years old) with hypercholesterolemia or combined hyperlipidemia. Inclusion criteria included an LDL-C level of at least 150 mg/dl and either none or one cardiovascular risk factor other than known coronary heart disease, or baseline LDL-C levels of between 150 and 189 mg/dl and two or more risk factors.***
- After an open-label 6-week placebo and diet run-in phase, subjects were randomized to one of 5 groups: 10, 20, 40, or 80 mg/day of policosanol or placebo. Treatment duration was 12 weeks.***

Policosanol

Ineffective for Hyperlipidemia, cont.

- The per-protocol analysis was completed on 129 patients (placebo, n = 25; 10 mg policosanol, n = 26; 20 mg, n = 25; 40 mg, n = 24; 80 mg, n = 29). LDL-C levels did not decrease by more than 10% of baseline in any of the five treatment groups. No statistically significant difference was found between placebo and any of the four policosanol groups.***
- There were no significant effects for policosanol on any of the secondary measures including ratio of TC or LDL-C to HDL-C.***
- Policosanol was well tolerated with out any serious adverse events.***

JAMA 2006;295:2262-9.

Policosanol Ineffective for Hyperlipidemia – Two more studies

- ***Kassis AN, Jones PJH. Lack of cholesterol-lowering efficacy of Cuban sugar cane policosanols in hypercholesterolemic persons. Am J Clin Nutr 2006;84:1003–8.***
- ***Cubeddu LX, Cubeddu RJ, Heimowitz T, et al. Comparative lipid-lowering effects of policosanol and atorvastatin: A randomized, parallel, double-blind, placebo-controlled trial. Am Heart J 2006;152:982.e1–982.e5 [electronic publication].***

Psyllium

Adjunctive Use with Statins

- *68 patients (18 to 80 years) who met the National Cholesterol Education Program ATP III criteria for drug treatment of hyperlipidemia were randomized to receive one of the following treatments for 12 weeks: (1) simvastatin (20 mg/day) plus placebo; (2) low-dose simvastatin (10 mg/day) plus placebo; or (3) low-dose simvastatin plus psyllium soluble fiber (5.1 g of psyllium husk and 3.6 g of soluble fiber per day). The placebo powder was Tang®.*
- *The study consisted of a 4-week diet stabilization (NCEP Step 1 Diet) period that included a 2-week baseline evaluation phase, followed by an 8-week treatment period.*

Psyllium

Adjunctive Use with Statins, cont.

- *At the end of 8 weeks, TC had dropped by 66 mg/dL (26%) in the low-dose simvastatin/psyllium group and 61 mg/dL in the 20 mg simvastatin group compared to baseline ($p = 0.33$). LDL-C levels dropped 63 mg/dL (36%) in the low-dose simvastatin/ psyllium group, which was similar to that seen in the 20 mg simvastatin group.*
- *Reductions in Apo-B were more pronounced with the combination therapy (50 mg/dL; 32%) compared with 43 mg/dL (29%) with 20 mg of simvastatin ($p < 0.05$). Triglyceride and HDL-C levels were not significantly changed from baseline in any of the treatment groups.*
- *61% of the patients taking the low-dose simvastatin/ psyllium combination achieved their LDL-C goal compared with 50% of those receiving 20 mg of simvastatin (comparison with the low dose simvastatin-only group is not given).*

Arch Intern Med 2005;165:1161-6.

Nutritional Supplement Considerations

Pantethine (best for high triglycerides)

Fish Oil

Beta-glucan

Beta-hydroxy-beta-methylbutyrate (HMB)

Chromium

Glucomannan

Sitostanol

Soy

Vitamin B3 (niacin only)

Vitamin B5 (pantethine only)

Vitamin C (protection of LDL cholesterol)

Coenzyme Q10

Potential Clinical Applications

- Cardiovascular diseases***
 - Cardiomyopathy***
 - Congestive heart failure***
 - Angina***
 - Myocardial Infarction (angina, arrhythmias)***
 - Hypertension***
- Neurological disease***
 - Parkinson's Disease***
 - Huntington's disease***
- Diabetes (deficiency)***
- Periodontal Disease***

Coenzyme Q10

Co-Administration with Statin

Drugs

- *Statin drugs inhibits 3-hydroxy-3-methyl glutaryl (HMG)-CoA reductase, required for synthesis of cholesterol as well as CoQ10.*
- *In 17 men treated with simvastatin (2-4 mg/d for a mean of 4.7 years), discontinuation of the drug for 4 wks increased CoQ10 levels by 32%; resumption of simvastatin caused CoQ10 levels to decrease by 25%.*

Eur J Clin Pharm 1994;46:313-7.

Coenzyme Q10

Co-Administration with Statin Drugs, Cont.

- **Reduction in CoQ10 also noted in the following studies:**
 - **Lovastatin – Patient reports and rat studies (*Proc Natl Acad Sci USA* 1990;87:8931-4).**
 - **Simvastatin – study compared hyperlipidemic pts treated with drug and diet or using just diet alone – those taking simvastatin had significantly lower plasma CoQ10 (*J Clin Pathol* 1993;46:1055-7).**
 - **Hyperlipidemic patients treated with either pravastatin or simvastatin (20 mg/d) or placebo for 3 months – 40% reduction in CoQ10 levels for those taking statins. This was confirmed in a study with healthy volunteers as well (*J Clin Pharmacol* 1993;33:226-9).**

Coenzyme Q10

Recommended Use/Safety

- Doses used in clinical trials have ranged from 90 to 390 mg/day. Typically, 100-200 mg/day is recommended for patients taking statin drugs.**
- Although still in the experimental phase, doses for neurological indications have ranged from 300 to 1200 mg/day.**
- Extremely safe with mild gi upset occasionally reported.**
- Only one report of a woman developing less responsiveness to warfarin after taking CoQ10 (*Ugeskr Laeger* 1998;160:3226-7).**

Fish Oil and Statins

- ***Small clinical trial comparing fluvastatin (40 mg/day) alone or in combination with fish oil (3 g/day) for 8 weeks***
- ***Fluvastatin alone led to a significant decrease of total and LDL-cholesterol (25% and 35%, respectively; $p < 0.05$). Serum triglycerides were reduced by 12% ($p < 0.01$). No sig. effect on HDL-C or blood pressure***
- ***Addition of fish oil resulted in TC being reduced by an additional 6%, LDL-C by an additional 9%, and triglycerides by an additional 32%. In addition, HDL-C was increased by 11% and systolic and diastolic BP was reduced by 6% and 8%, respectively ($p < 0.05$).***

Prostaglandins Leukotrienes Essential Fatty Acids 2005;72:379–80 [Letter].

Congestive Heart Failure

- ***Primary Considerations***

 - ***Hawthorn***

- ***Other Considerations***

 - ***Terminalia arjuna – 500 mg tid***

Hawthorn Leaf & Flower Extract

- Standardized to oligomeric procyanidins***
- Strengthen heart function (increase in left ventricular ejection fraction)***
- Particularly useful for***
 - Early stage Congestive Heart Failure***
 - Angina***
 - Post myocardial infarction***



Hawthorn Extract

CHF

- A randomized, double-blind, placebo-controlled clinical trial was designed to study the efficacy of a standardized hawthorn in 209 patients with congestive heart failure (NYHA] class III). Following a four week single-blind run-in phase, patients were randomized to take either 450 mg WS 1442, 900 mg WS 1442, or placebo two times per day for 16 week.***
- After the 16 weeks of treatment, the maximum tolerated workload showed a statistically significant increase in the 1,800 mg WS 1442 group when compared to both the 900 mg WS 1442 group ($p = 0.01$) and placebo ($p = 0.013$). Percentage of patients with improvement in maximal workload tolerated was 52.2% of the 1,800 mg group, 34.3% for the 900 mg group, and 42.9% in the placebo group.***

Hawthorn Extract

CHF, cont.

- *Deterioration of maximal workload was reported in 5.8% of the 1,800 mg group compared to 12.9% and 17.1% for the 900 mg and placebo groups, respectively. Heart failure symptoms as rated by the patients were reduced to a significantly greater extent in both WS 1442 groups as compared to placebo ($p = 0.004$ for the 1,800 mg group and $p = 0.04$ for the 900 mg group).*
- *Twice as many adverse events were reported in the placebo group compared to both WS 1442 groups. Ten percent of patients in the placebo group complained of dizziness or vertigo while only 4.3% of patients in the 900 mg WS 1442 group and 1.4% of patients in the 1800 mg WS 1442 group complained of these symptoms.*

Am Heart J 2002;143:910–5.

Hawthorn Extract SPICE Trial

- ***A randomized, placebo-controlled trial is taking place in seven European countries to study the influence of WS 1442 on the mortality of class II and III CHF patients.***
- ***Billed the “SPICE” study (Survival and Prognosis: Investigation of *Crataegus* extract WS 1442 in Congestive Heart Failure), the trial will randomize up to 2,300 class II or III CHF patients to receive either 900 mg/day of WS 1442 or placebo for 24 months while continuing any preexisting drug therapy for CHF.***
- ***This will provide not only long-term data on efficacy and safety (including potential drug interactions) for WS 1442 therapy but also provide its influence on cardiac endpoints such as sudden death, non-lethal myocardial infarction, and hospitalization due to progression of heart failure.***
Eur J Heart Failure 2006;2:431-7.

Hawthorn Extract SPICE Trial - results

- WS 1442 had a neutral effect on the primary end point, a composite of sudden cardiac death, death due to progressive heart failure, fatal MI, nonfatal MI, or hospitalization due to HF progression, measured at 24 months. The rates were statistically similar, at 28% for actively treated patients and 29% for controls.***
- Patients taking WS 1442 showed significant relative-risk reductions in the secondary end point of cardiac mortality after six months (by 41%, $p=0.009$) and 18 months (by 20%, $p=0.046$) but not at the 12-month or 24-month follow-ups (by 18% and 10%, respectively).***

Hawthorn Extract SPICE Trial – results, cont.

- The rates of adverse events and of serious adverse events were about 68% and 40%, respectively, for both groups.***
- In a prospectively planned subgroup analysis, patients who received WS 1442 and had an LVEF from 25% to 35% showed a significantly reduced risk of sudden cardiac death from month 12 to month 24; no such signal emerged for patients with the poorest ventricular function. The protection was significantly stronger among the 70% of patients with ischemic disease.***

Results reported at the American College of Cardiology 2007 Scientific Sessions on May 28, 2007.

Hawthorn - Mild Hypotensive Effect in Type 2 Diabetics

- 80 patients (mean age 62 years old) with type 2 diabetes and hypertension (DBP 85-95 mmHg and SBP 145-165 mmHg). Hypotensive drugs were used by 71% of the study population with a mean intake of 4.4 hypoglycemic and/or hypotensive drugs. Randomized to receive 600 mg of a 3:1 hawthorn flowering tops extract standardized to 2.2% flavonoids or placebo b.i.d. for 16 weeks.***
- The hawthorn group had a significantly greater decrease in mean DBP (85.6 mmHg at baseline to 83.0 mmHg at 16 weeks) compared to the placebo group (84.5 mmHg to 85.0 mmHg) ($p = 0.035$).***

Hawthorn - Mild Hypotensive Effect in Type 2 Diabetics

- ***There was no significant difference in mean SBP decrease between groups from baseline (3.6 and 0.8 mmHg for hawthorn and placebo, respectively).***
- ***No herb-drug interactions were found in the hawthorn group. Subjective well-being scores found no significant adverse events in either group.***

British J General Practice 2006;56:437-43.

Hawthorn Extract Recommended Use

- 900-1800 mg/d of a standardized leaf-and-flower extract (18.75% oligomeric procyanidins or 2.2% total flavonoids) for stage II CHF patients and stable angina. New data suggest higher dose may be more efficacious for more advanced disease.***
- There is a theoretical interaction with digitalis and other cardiac glycosides. Concomitant use should be closely monitored.***

Nutritional Supplement Considerations

Magnesium

Propionyl-L-carnitine

Taurine

Arginine

Coenzyme Q10

Coenzyme Q10

CHF

- *A Danish meta-analysis identified 14 controlled trials using 60-200 mg/d of CoQ10 – 8 met criteria for analysis – 7 found a significant improvement in ejection fraction, stroke volume, cardiac output, cardiac index, and end diastolic volume (Ugeskr Laeger 1997;159:7302-8).*
- *However, two more recent small DBPC using 99 mg/d and 200 mg/d found no significant effect on heart function in CHF pts.*

J Am Coll Cardiol 1999;33:1549-52.

Ann Intern Med 2000;132:636-40.

Chronic Venous Insufficiency

- *Primary Considerations*
 - *Horse chestnut seed extract*
- *Other Considerations*
 - *Butcher's Broom*
 - *Gotu Kola*
 - *Pycnogenol*
 - *Red Vine Leaf extract*
 - *OPCs*

Horse Chestnut

(Aesculus hippocastanum)

- ***Part Used: The seeds***
- ***Major constituents***
 - ***Aescin (escin) – a complex mixture of saponins***
- ***Mechanisms of action***
 - ***Veinotonic (vascular strengthening)***
 - ***Vasculotropic (diminished vascular permeability)***
 - ***Antiedema and anti-inflammatory actions***



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Aesculus hippocastanum 4627

Horse Chestnut

- *Common/Potential Clinical Uses*
 - *Chronic venous insufficiency*
 - *Varicose veins*
 - *Hemorrhoids*

Horse Chestnut Chronic Venous Insufficiency

— ***A systematic review and critique of the clinical studies on the use of horse chestnut extract for chronic venous insufficiency (CVI). In trials administering 100 to 150 mg of aescin, significant improvement was noted in edema, calf spasm, pain, and other symptoms of CVI. The placebo-controlled RCTs found a decrease in leg circumference at the calf and ankle with the use of HSCE. Adverse events included gastrointestinal symptoms, dizziness, nausea, headache, and pruritis. The authors conclude that HSCE is a safe and efficacious treatment for CVI and that future studies should include the use of HSCE with compression therapy for the long-term management of CVI.***

Arch Dermatol 1998;134:1356-60.

Horse Chestnut

Recommended Use/Safety Issues

- Horse chestnut seed extract standardized to 16-20% aescin – 300 mg (approx. 50 mg aescin) two to three times daily.***
- Side effects are rare and may include generalized pruritis, nausea, GI upset, and calf spasms.***
- Based on reports of i.v. aescin causing a worsening of kidney function, it should be avoided by persons with kidney disease.***
- While there have been no reports of interactions, some references suggest avoiding use of HCSE in persons taking anticoagulant medications.***

Butcher's Broom Extract

- ***Placebo-controlled trial with 148 women with CVI – 75 mg of butcher's broom extract per day (standardization not give) for 12 weeks.***
- ***Significant changes in leg volume and ankle and leg circumference were seen in the butcher's broom group compared to placebo. Quality of life did not change significantly in either group.***
- ***Other clinical trials have used one capsule, containing standardized extracts providing 15 to 30 mg of ruscogenins, tid. The amount of butcher's broom extract used in these trials is 150 mg bid or tid.***

Arzneimittelforschung Drug Res 2002;52:243-50.

Intermittent Claudication

- *Primary Considerations*

 - *Ginkgo*

- *Other Considerations*

 - *Garlic*

 - *Padma 28 (Padma Basic)*

Ginkgo

Intermittent Claudication

- ***Randomized, double-blind, placebo-controlled trial - 111 intermittent claudication). Test medication was 40 mg. Of Ginkgo biloba extract EGb 761® tid for 24 weeks.***
- ***The primary outcome measure was the difference in pain-free walking distance between baseline and after 8, 16, and 24 weeks. Secondary outcome measures were the respective differences in pain-free walking distance between the EGb 761 and placebo groups, the increase in pain free walking distance, the patients assessment of pain, and Doppler index measures for pressure in affected legs.***

Ginkgo

Intermittent Claudication

- ***At the end of the treatment period, the mean pain-free walking distances were 153.2 m in the EGb 761 group and 126.6 m in the placebo group compared to 108.5 m and 105.2 m respectively at baseline. The difference between groups was significant at all three visits—week 8 ($p = 0.017$); week 16 ($p = 0.007$); and week 24 ($p = 0.016$).***
- ***The maximum walking distance also increased significantly in the EGb 761 group compared to the placebo group at weeks 16 and 24. At week 16 it increased to 35.0 m in the EGb 761 group compared to 19.3 m in the placebo group ($p = 0.023$) and 61.1 m and 25.0 m respectively at week 24 ($p = 0.038$).***

VASA 1998;27:106–10.

Ginkgo

Intermittent Claudication

- Previous studies have found that 120 to 160 mg of ginkgo extract EGb 761 significantly improves pain-free and maximum walking distance in persons with intermittent claudication (IC).**
- In a 24-week dose comparison study, 77 patients with IC were randomized to received either 60 mg or 120 mg of EGb 761 bid.**
- At 24 weeks, both groups had an improvement in pain-free walking distance but the difference in groups favored the high-dose group ($p=0.0253$). On measures of maximum walking distance, both groups again showed clinically significant improvement at both weeks 18 and 24. However, the high-dose group again showed superior improvement at both week 18 ($p=0.0133$) and week 24 ($p=0.0112$). Both groups showed mild improvement in blood flow according to Doppler measures.**

Arzneim-Forsch Drug Res 1999;49:900-4

Padma 28

- ***The herbal preparation PADMA 28® cited in the clinical trials has been manufactured since 1969. It combines 29 herbs. In countries such as the U.S. as well as the United Kingdom, Canada, Italy, Austria, and the Netherlands, the product is sold as a dietary supplement. In these countries, the only difference in the formulation is the removal of aconite in PADMA Basic.***
- ***The clinical trials below used two tablets twice daily for 4 to 6 months***

Alternative Ther 1995;1:44–9.

J Vasular Invest 1998;4:129–36.

Angiology 1993;44:863–7.

Nutritional Supplement Considerations

Inositol hexaniacinate

Propionyl-L-carnitine

Vitamin E

Respiratory Tract Diseases

Botanical Approaches Acute Respiratory Tract Infections

— Primary Considerations

• *Pelargonium sidoides*

• *Echinacea* (and combination with *baptisia* and *thuja*)

• *Andrographis*

• CVT-E002 (COLD-fX) – American ginseng root polysaccharide extract

• Elderberry Syrup (influenza) [*Sambucol*]

— Other Considerations

• Vitamin C (prevention)

• Zinc

Echinacea

(Echinacea purpurea, E. angustifolia, E. pallida)

- Parts used: Aerial and/or root**
- Major constituents**
 - Alkylamides/polyacetylenes**
 - Caffeic acid derivatives**
 - Polysaccharides**
- Mechanisms of action**
 - Increases phagocytosis and enhances macrophage activation**
 - Increases tumor necrosis factor alpha and interleukins 1, 6, and 10**



Echinacea

- *Common/Potential Clinical Uses*
 - *Acute treatment of colds and influenza*
 - *Supportive treatment of recurrent infections (e.g. otitis media, sinusitis, vulvovaginal candidiasis)*

Echinacea

Treatment, Prevention, or Both?

- Studies looking at prevention of URIs have largely shown no effect for echinacea.***
 - Unpublished Bastyr University study (Echinaguard)***
 - Arch Fam Med 1998;7:541-5 (unspecified root products)***
 - Am J Med 1999;106;138-43 (Echinacin)***
- However, studies looking at short-term use of 10 to 14 days at the onset of a common cold have shown success in reducing the severity and duration of symptoms.***
 - Eur J Clin Res 1997;9:261-8 (Echinacin/Echinaguard)***
 - Phytomedicine 1999;6:1-5 (Echinaforce)***
 - Current Med Res Opinion 1999;15:214-27 (Esberitox)***

Echinacea

Common Cold

- *Based on research completed to date, echinacea appears best suited for acute treatment of the common cold and less likely to prevent ARIs. Successful studies are more likely to have been completed on liquid forms of the herb.*
- *May be taken at the onset of a cold or flu for a period of 7 to 10 days without interruption – traditionally it is taken every 2 hours during the first day and then three to four times daily thereafter.*

Echinacea

Common Cold

- *150 volunteers (aged 18–65 years old) with a history of two or more infections of the common cold in the previous year. Subjects were instructed to start the treatment following the onset of two symptoms of the common cold (one was rhinitis). Randomized to placebo or a standardized *Echinacea purpurea* liquid extract (40% alcohol) made from the flowering tops of the freshly harvested plants and is standardized to contain alkamides / cichoric acid / polysaccharides at concentrations of 0.25/2.5/25.5 mg/ml, respectively.*
- *Treatment consisted of eight doses the first day and three doses per day for the next 6 days. A dose was 5 ml of the echinacea extract or placebo diluted in a half glass of water. Treatment duration was 7 days.*

Echinacea

Common Cold, cont.

- In the echinacea group, there were no significant differences in Total daily symptom scores (TDSS) during the first three days but a significant decline was seen thereafter ($p < 0.05$). In the placebo group, a significant increase in TDSS from day 1 values was found at days 2, 3, and 4 of the cold ($p < 0.05$). A significant decline was not measured in the placebo group until day 7. Significant between groups differences on the TDSS were evident throughout the observation period ($p < 0.05$).*

Phytotherapy Res 2005;19:689–94.

Echinacea

Safety Issues

— Side Effects/Contraindications

- Ÿ German Commission E monograph suggests that persons with autoimmune disease such as lupus, or other progressive systemic diseases such as TB, MS, or HIV-infection/AIDS avoid use of echinacea.***
- Ÿ Persons with allergies to plants of the Asteraceae family (ragweed, asters, chrysanthemums) should avoid use of echinacea***
- Ÿ A recent Canadian study found no differences in pregnancy outcomes (including malformations) in women taking echinacea during pregnancy compared to those who didn't (Arch Intern Med 2000;160:3141-3).***
- Ÿ No known drug interactions***

Andrographis

- *Randomized, controlled clinical trials using the SHA-10 extract (300 mg qid) have limited use of the product to five days. Results in these studies have typically been noticed by the second day of use.*
- *Adverse events are not reported in these clinical trials. Use of Andrographis at dosages higher than the suggested use above has been associated with gastrointestinal upset and vomiting. Andrographis is contraindicated during pregnancy and should be used with caution by persons taking anticoagulant drugs or aspirin.*

Phytomedicine 1999;6:217–23.

Phytomedicine 1996;3:314–8.

CVT-E002

Prevention of ARIs

- 323 subjects aged 18 to 65 who had contracted at least 2 colds in the past year. Subjects were randomized to 400 mg of CVT-E002 (n=153) or placebo (n=170) daily for 4 months.**
- The mean number of colds per person was 0.68 in the CVT-E002 group compared to 0.93 in the placebo group ($p = 0.017$). The number of subjects with 1 cold was 95 (64%) in the placebo group and 71 (55%) in the CVT-E002 group—this difference did not reach statistical significance.**

CVT-E002

Prevention of ARIs, cont.

- ***However, the number of people with ≥ 2 colds was 34 (23%) in the placebo group compared to 13 (10%) in the CVT-E002 group ($p = 0.004$).***
- ***For those with Jackson-defined colds, the average duration was 16.5 days in the placebo group and 10.8 days in the CVT-E002 group ($p < 0.001$). The average total symptom score was 112.3 in the placebo group and 77.5 in the CVT-E002 group ($p = 0.002$).***

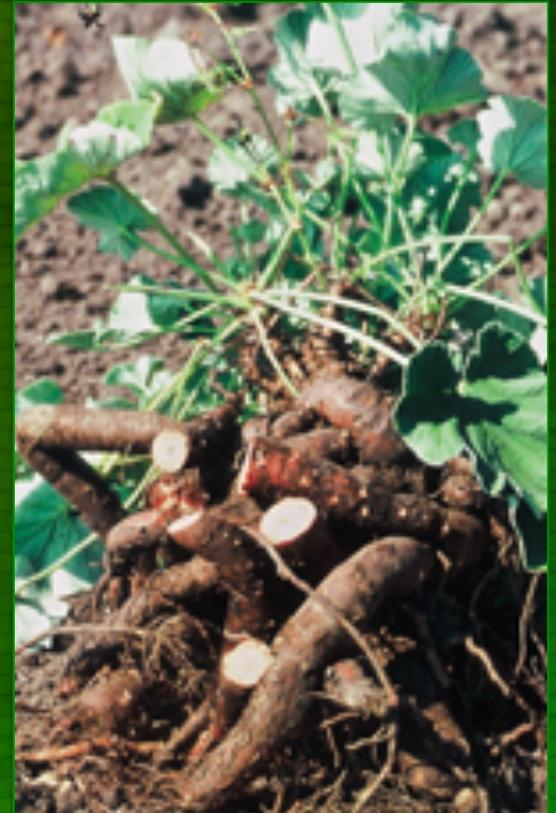
Canadian Med Association J. 2005;173:1043–1048.

Vitamin C

- ***The most recent study was a 5 year clinical trial in Japan comparing either 5 mg or 500 mg of vit. C per day in 244 adults.***
- ***The results found that the “high-dose” group had a significant reduction in the frequency of getting colds but there was no reduction in the duration or severity once a person had a cold.***

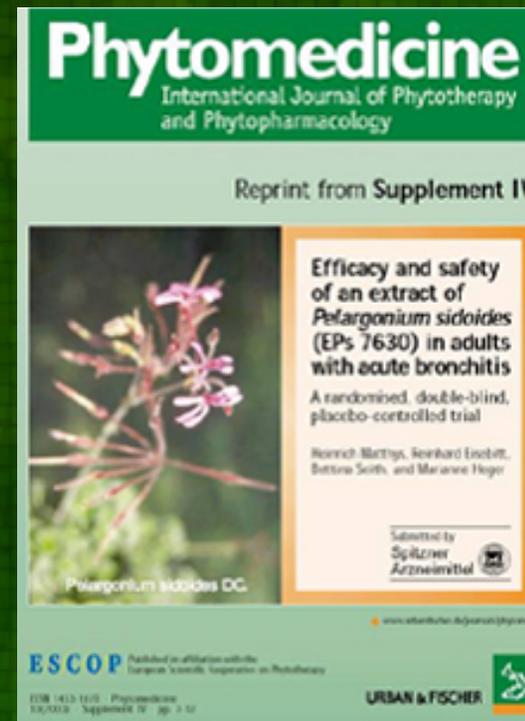
European J Clin Nutr 2006;60:9-17

Pelargonium sidoides



EPs7630

- **Over 20 clinical studies completed to date**
- **Over 7,000 persons (including over 2,500 children)**
- **Evaluated on tonsillitis, bronchitis, sinusitis, and common cold.**



Chuchalin et al., 2005

Study design: *randomized, double-blind, placebo-controlled, parallel-group, prospective and multi-center trial using a design with planned interim analyses*

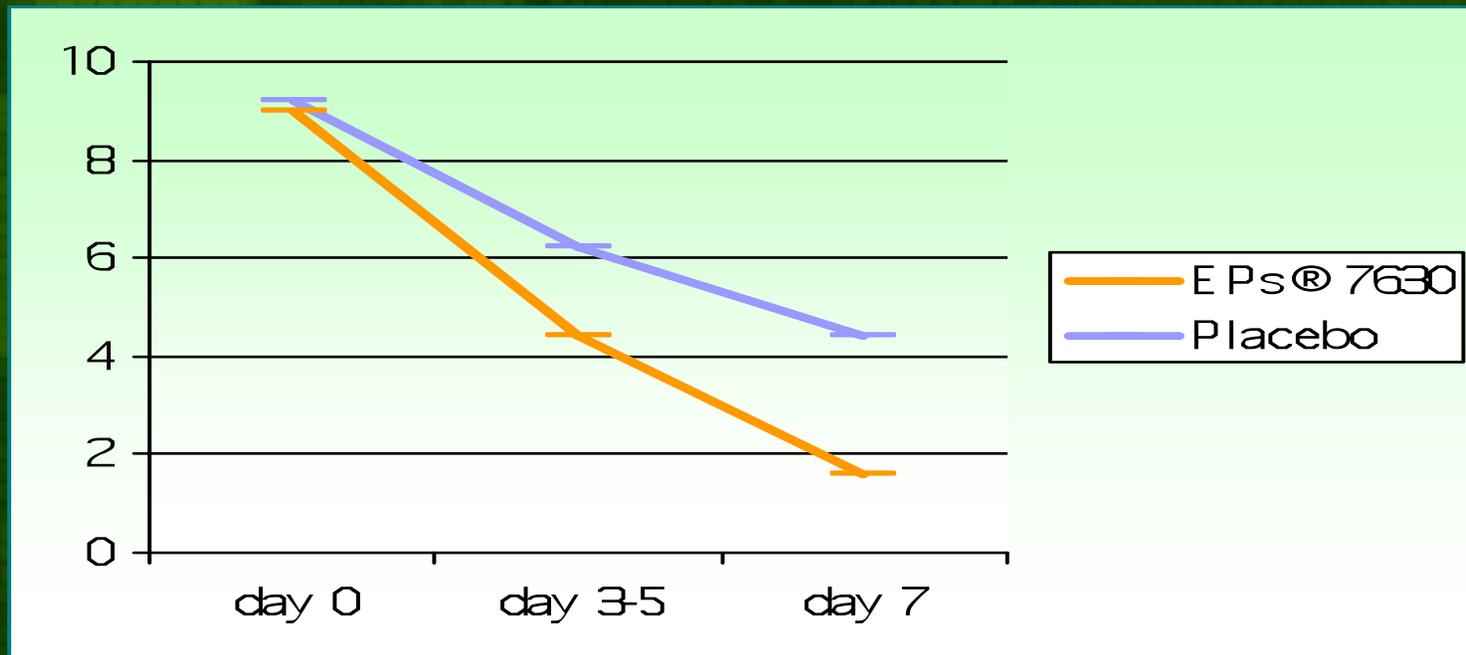
Patients: *124 adults with acute Bronchitis present \leq 48 hours, Bronchitis Severity Score (BSS) \geq 5 points, and informed consent.*

Duration: *7 days*

Dosage: *3 x 30 drops of EPs[®] 7630 or placebo before or after meal*

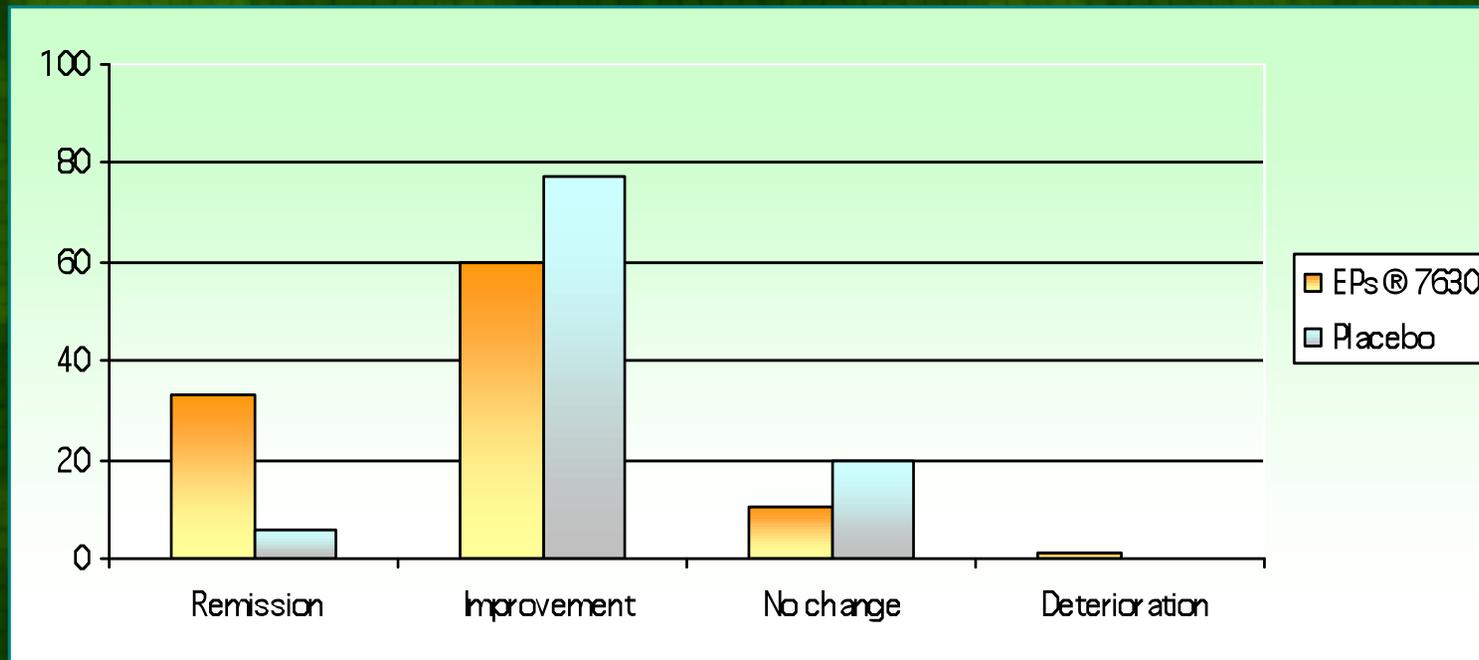
Setting: *6 outpatient clinics*

Bronchitis Severity Score (BSS)
Total score of 5 bronchitis-specific symptoms



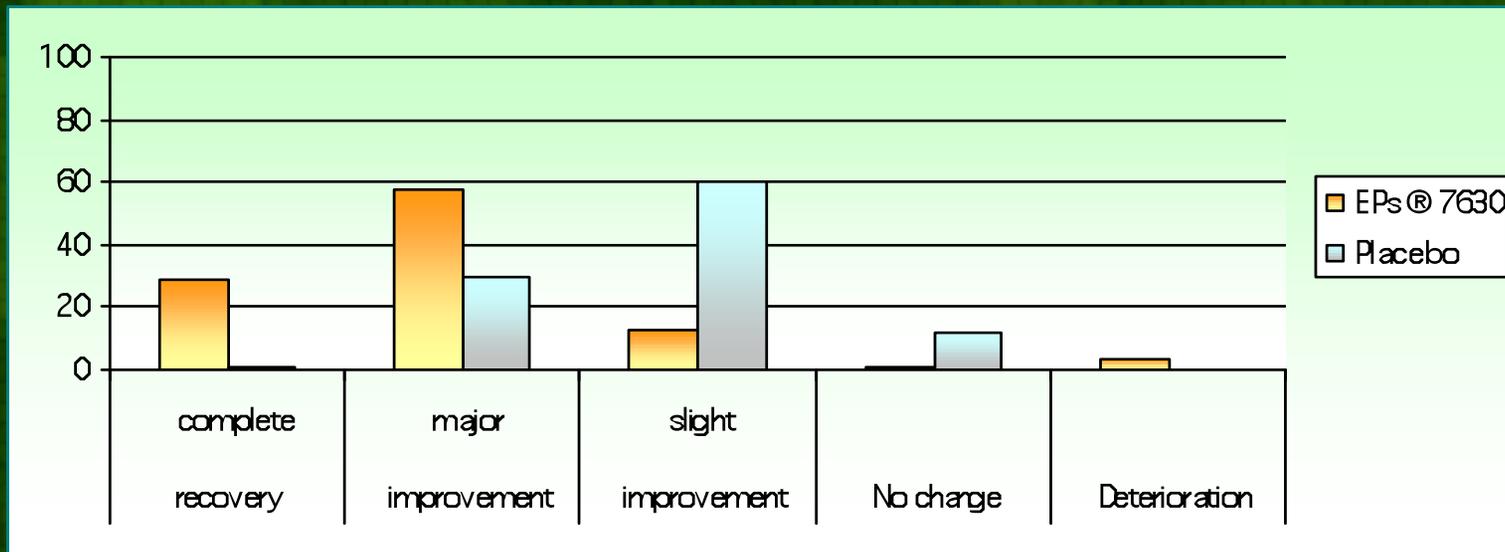
Decrease of BSS under EPs® 7630 compared with placebo (n=124, ITT analysis; EPs® 7630 n= 64/ placebo n=60)

Clinical findings (bronchitis-specific symptoms) - Cough-



Comparison between day 0 and day 7 (EPs® 7630, n=64/ placebo, n=60)

Treatment outcome
- Assessment by the physician on day 7-



Treatment outcome under EPs® 7630 compared with placebo (n=124, ITT analysis; EPs® 7630 n=64/placebo n=60)

Results

Primary efficacy:

- *Decrease of BSS from baseline to day 7 was 7.2 ± 3.1 points with EPs[®] 7630 and 4.9 ± 2.7 points with placebo
→ highly significant superiority of EPs[®] 7630 compared with placebo*

Secondary efficacy:

- *BSS <5 points observed in 95.3% with EPs[®] 7630 compared with 58.3% with placebo ($p < 0.0001$)*
- *Recovery and improvement more frequently in the EPs[®] 7630 group*
- *very good or good tolerability was reported by 98.4% of patients in EPs[®] 7630 group and by 96.7% in placebo*

Explore 2005;1:437-45.

EPs7630[®] Recommended Use

- Ethanolic extract (1:9-11; 1X) of the root of *P. sidoides* (ETOH-free forms are available):***
 - Adults: 1 ml 3 to 5 times per day***
 - Children 6-12 years: 1 ml 2 to 4 times per day***
- Not recommended for pregnant or lactating women***

EPs 7630 Safety

- EPs 7630 has been found not to interact with antibiotics*
 - EPs7630 has been shown to have no effect on blood coagulation or the actions of warfarin*
 - A large observational study with 2099 patients with bronchitis ranging in age from newborns to 93 years of age (241 were ≤ 6 years of age; 78 were infants < 2 years of age)
 - Adverse events were largely minor and transitory with one case of a rash in one child. Of the total of 28 AEs were reported, 3.1% were reported in children and 3.8% in infants**
- Phytomed 2007;14:69-73.*

Musculoskeletal Diseases

Osteoarthritis

- **Primary Considerations**
 - **Ginger (combination with greater galangal)**
 - **Standardized Willow Bark Extract (Asalixx®) – chronic low back pain**
 - **Danish Rose Hips Extract**
 - **Cayenne (topical) – 0.025-0.075% cream**
- **Other Considerations**
 - **Bromelain, trypsin rutin combination**
 - **Boswellia extract**
 - **Devil's Claw**
 - **Cat's claw**

Boswellia for OA

- ***66 patients (ages 40–70 years old) with primary OA received either 10 mg of valdecoxib (Bextra®) once daily or 333 mg of *Boswellia serrata* extract t.i.d. for 6 mths. The BSE was standardized to 40% boswellic acids.***
- ***Compared to baseline, the WOMAC scores for pain, stiffness and difficulty in performing daily activities were not significantly different in the BSE group at one month ($p > 0.05$) compared to the valdecoxib group ($p < 0.001$). However, after the second month of treatment, the BSE group showed a significant decrease in symptoms ($p < 0.001$) compared to baseline.***

Boswellia for OA, cont.

- ***The significant reduction compared to baseline persisted throughout the treatment period in the valdecoxib group ($p < 0.001$). The WOMAC scores in the BSE were significantly lower at seven months compared to the valdecoxib group ($p < 0.001$).***
- ***There were no differences between the two groups on the pre- and post-treatment radiographs of the affected knee.***
Indian J Pharmacol 2006;39:27–29.

Combination of Bromelain, Trypsin, and Rutin for OA

- 96 patients (28 men and 70 women, mean age approximately 56.5 years) with radiologically confirmed and symptomatic OA in one knee were randomized to receive one enteric coated enzyme-rutoside combination (ERC), containing 90 mg bromelain, 48 mg trypsin and 100 mg rutosid t.i.d. or diclofenac sodium 50 mg b.i.d.***
- Lequesne's Functional Index decreased by a mean 26.3% (13.0 to 9.4) in the ERC group and by a mean 23.6% (12.5 to 9.4) in the diclofenac group. The mean complaint index decreased by 30.2% (4.9 to 3.5) in the ERC group and by 26.6% (4.9 to 3.6) in the diclofenac group.***

Combination of Bromelain, Trypsin, and Rutin for OA, cont.

- ***Pain at rest decreased by 41.0% in the ERC group compared to 22.5% in the diclofenac group.***
- ***Pain with motion was equally reduced by 28.6% in both groups. ERC improved restricted function by a mean 10.0%, while there was no improvement with diclofenac.***

Clin Rheumatol 2004;23:410–15.

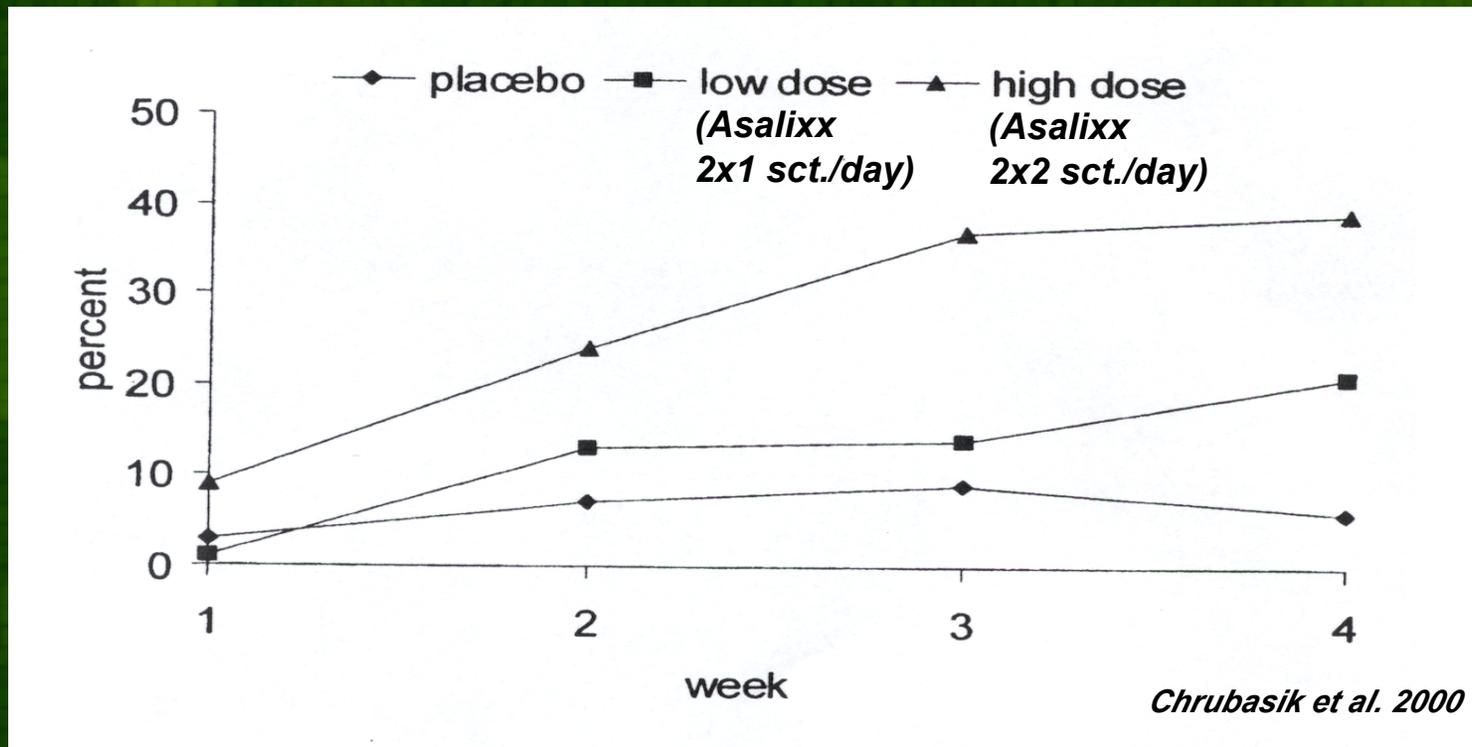
Asalixx[®]

White Willow Bark Extract

Chrubasik, Eisenberg et al. 2000:

- ***chronic low back pain***
- ***treatment: 4 weeks,***
- ***randomized, placebo-controlled, double-blind***
- ***BNO 1455 corr. to 120 mg and 240 mg salicin/day respectively***
- ***primary outcome measure: freedom from pain***
- ***secondary outcome measure: Arhuser Low Back Pain Index (pain intensity, invalidity, movement restriction); quantity of rescue medication (Tramadol drops)***
- ***n = 70 + 70 + 70***

Asalixx[®]



Percentage of patients who were free from pain without rescue medication for at least 5 days in weeks 1 to 4 in the placebo, and in the low-dose and high-dose willow bark groups

Asalixx[®]

Clinical studies on efficacy

Phytomedicine, Vol. 8(4), pp. 241–251
© Urban & Fischer Verlag 2001
<http://www.urbanfischer.de/journals/phytomed>

Phytomedicine

Potential economic impact of using a proprietary willow bark extract in outpatient treatment of low back pain: An open non-randomized study

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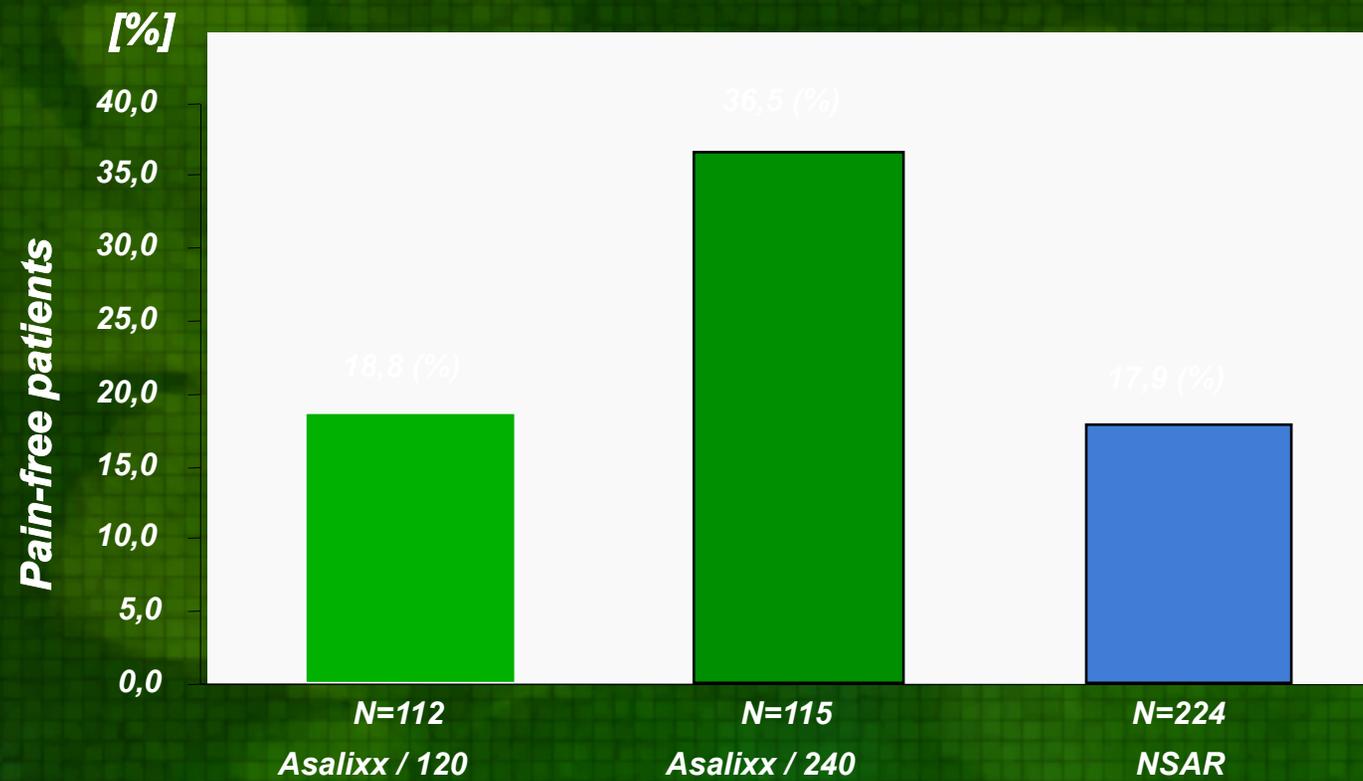
Asalixx[®]

Low Back Pain

Chrubasik, Künzel et al. (Phytomedicine, 2001):

- ***chronic low back pain***
- ***treatment: 4 weeks, 3 groups, open; standard treatment and NSAR vs. standard treatment and Asalixx (BNO 1455)***
- ***BNO 1455 2x1 sct/d, corresponding to 120 mg salicin/d, or 2x2 sct/d, corresponding to 240 mg salicin/d***
- ***n = 112 (BNO 1455 / 2x1); n = 115 (BNO 1455 / 2x2); n = 224 (NSAIDs)***

Asalixx[®]



Chrubasik et. al., Phytomedicine 2001

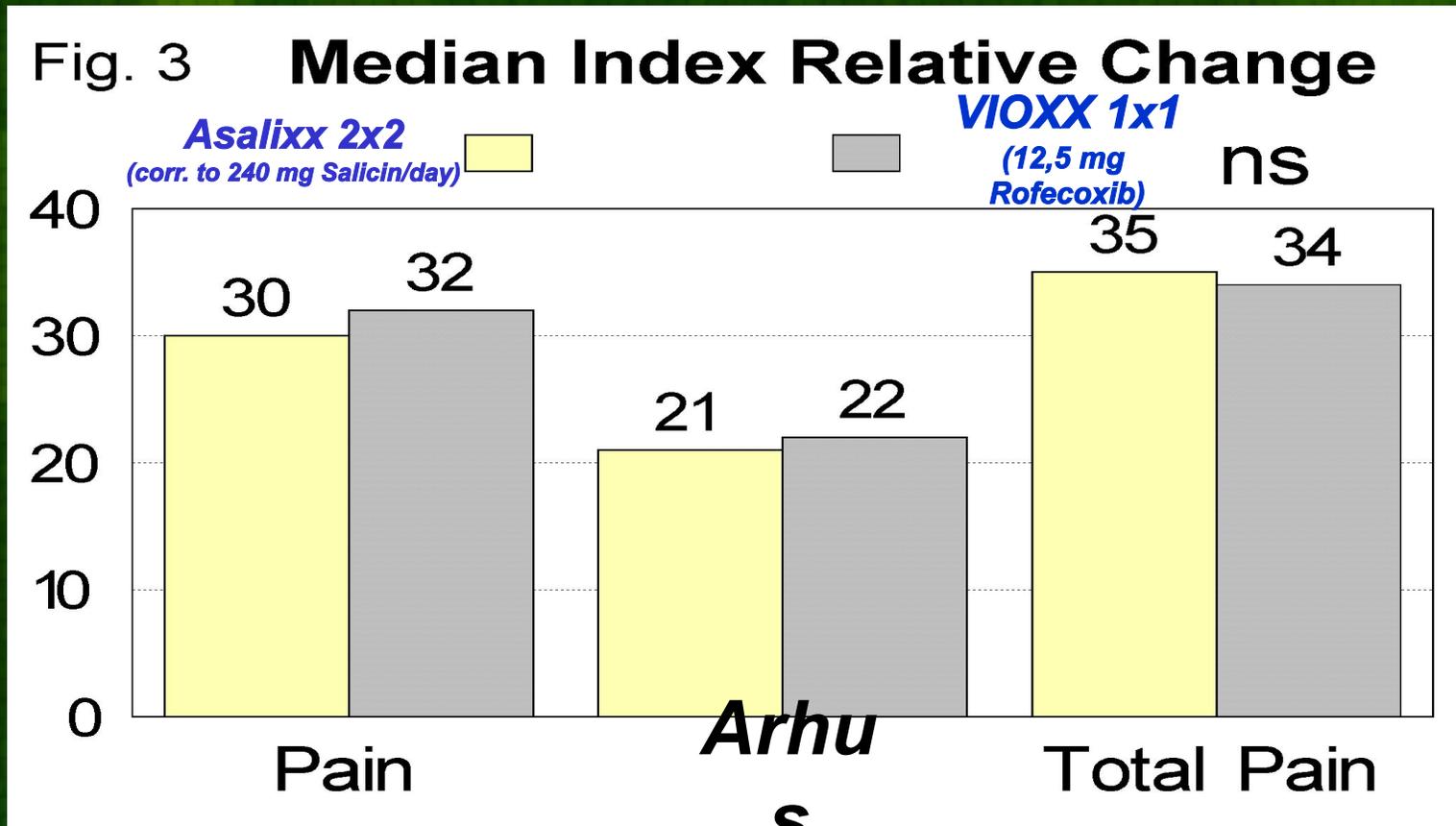
Asalixx[®]

Chronic Low Back Pain

Chrubasik et al., 2001

- **chronic low back pain**
- **treatment duration: 4 weeks**
- **1x1 VIOXX (Rofecoxib, 12.5 mg) vs. 2x2 Asalixx (corr. to 240 mg Salicin daily)**
- **randomized, open label**
- **outcome measures: Arhus Low Back Pain Index, total score and score of the pain component; total pain score;**
- **n = 114 + 114**
- **comparable effectiveness and favorable side effects profile**

Asalixx[®]

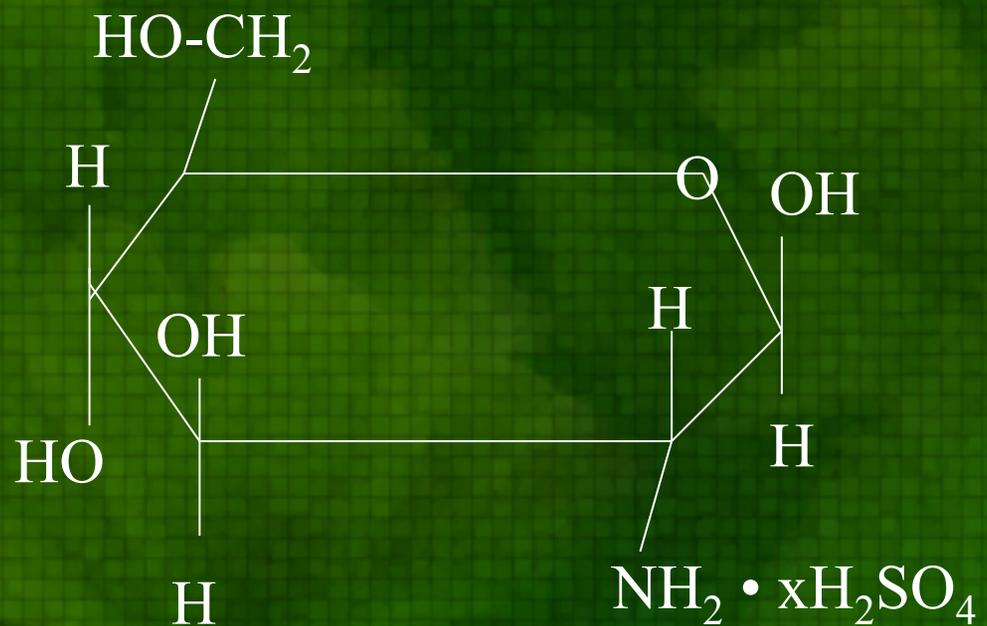


Chrubasik et al. 2001

Nutritional Supplement Considerations

- Glucosamine sulfate***
- Chondroitin sulfate***
- MSM – 500 mg tid***
- SAMe***
- Niacinamide***
- Green-lipped mussel extract***
- Celadrin – cetylated fatty acid esters***

Glucosamine Sulfate



Glucosamine Sulfate

- $(C_6H_{13}NO_5 \cdot HCl)_2 \cdot Na_2SO_4$*
- Glucosamine is a modified form of glucose (with one nitrogen atom replacing an oxygen atom) called an amino sugar, or aminomonosaccharide*
- Naturally synthesized by the body, glucosamine is used in the biosynthesis of proteoglycans and glycosaminoglycans (the building blocks of cartilage)*
- Supplemental glucosamine is derived from chitin, which is found in the shells of sea animals such as shrimp and lobster*
- Efficacy of glucosamine hydrochloride is still in question*

Glucosamine Sulfate

Overview of Trials for OA

- 13 DBPC trials are reported in the literature – 7 meet quality standards for review.***
- Treatment duration ranges from 4 weeks to 3 years. One trial uses 750 mg/d while the rest use 1500 mg/d.***
- Two 3 yrs trials using a one-a-day dose of 1500 mg show positive WOMAC scores and radiological evidence of slowing of JSN***
- Safety in trials has been excellent***
Arch Intern Med 2003;163:1514-22

Glucosamine Sulfate

3 yr. Trial – OA of the knee

- A randomized, placebo-controlled trial with 212 OA patients- received either 1500 mg of glucosamine sulfate per day or placebo for 3 years***
- Researchers looked for narrowing of the joint space of the knee (signaling disease progression) and assessed the symptoms experienced by all the participants***
- Results: The joints of the placebo group narrowed, while the glucosamine group experienced no changes. Also, the treatment group experienced a 20 to 25% improvement in their osteoarthritis symptoms, compared to the placebo group.***

Lancet 2001;357:251-6

Glucosamine Sulfate

3 yr. Trial – OA of the knee

- ***Similar design to the previous study – 202 patients with OA of the knee were randomized to receive 1500 mg of GS once daily or placebo for 3 years. Symptoms as well as joint space narrowing were measured.***
- ***Placebo group had progressive joint space narrowing (-0.19 mm) after 3 years compared to no change in the GS group (p=0.001). Fewer patients taking GS experienced predefined severe narrowing (>0.5mm) in the GS group compared to placebo. Symptom relief was modestly improved in the GS group compared to placebo.***
- ***Side effects were mild and similar in both groups.***

Arch Intern Med 2002;162:2113-23.

Combination of Glucosamine and MSM

- 118 volunteers (76 women, 42 men), ages 40-70 with symptomatic mild to moderate OA of the knee for at least 6 months prior to the study and whose joints displayed radiological evidence of OA were divided into 4 groups: 1) glucosamine (form and source were not stated in the paper) 500 mg t.i.d. plus placebo (n= 30); 2) MSM 500 mg t.i.d. plus placebo (n = 30); 3) glucosamine 500 mg t.i.d. plus MSM 500 mg t.i.d. (n = 30); or 4) two capsules of placebo t.i.d. (n = 28).***

Combination of Glucosamine and MSM, cont.

- All primary outcome measures were significant at 12 weeks compared to baseline in the glucosamine-only, MSM-only, and glucosamine + MSM groups, while there were no significant changes in the placebo group. The glucosamine + MSM group experienced the most significant improvement, with a decrease in the mean pain index from 1.7 ± 0.47 at baseline to 0.36 ± 0.33 after treatment ($p < 0.001$). Glucosamine-only therapy resulted in a decrease of the mean pain index from 1.74 ± 0.47 at baseline to 0.65 ± 0.71 after treatment ($p < 0.001$), while those in the MSM-only group had a mean pain index of 1.53 ± 0.51 at baseline and 0.74 ± 0.65 after treatment ($p < 0.001$). Compared to the other treatment groups, combination treatment was significantly more effective at reducing pain and swelling ($p < 0.05$).***

Clin Drug Invest 2004;24:353-63.

Glucosamine Sulfate

Negative Effect on Glycemic Control?

- ***PDR for Nonprescription Drugs and Dietary Supplements carries a precaution about the use of GS for patients with diabetes – based on animal studies showing GS administered parenterally can raise plasma glucose levels.***
- ***DBPC trial with 34 type 2 diabetic patients found that 1500 mg of GS combined with 1200 mg of CS per day for 90 days did not result in clinically significant alterations in glucose metabolism (based on Hemoglobin A_{1c} levels).***

Arch Intern Med 2003;163:1587-90

Female Health Conditions

Premenstrual Syndrome, Mastalgia

- ***Primary Considerations***

 - ***Vitex (Chaste tree)***

- ***Nutritional Supplement Considerations***

 - ***Calcium***

 - Vitamin B6***

 - Evening primrose oil***

 - Magnesium***

 - Multiple vitamin-mineral***

 - Potassium gluconate***

 - Vitamin E***



Vitex (Chaste Tree) for PMS

- *170 women (mean age 36 years) with a diagnosis of PMS were randomized to receive either 20 mg of the chaste berry extract ZE 440 or placebo once daily for three menstrual cycles. The primary efficacy variable was the change from baseline to the end of the study (end of the third cycle) on the total score of a measure of PMS symptoms.*
- *At the end of the treatment period, women taking the chaste berry extract had a significantly greater reduction in overall PMS symptom score compared to those taking placebo ($p < 0.001$). Five of the six self-assessment items indicated a significantly greater reduction for the vitex group. The overall responder rate was 52% for the chaste berry group compared to 24% for the placebo group.
BMJ 2001;322:134–7.*

Vitex for Mastalgia

- ***Clinical trials supporting the use of chaste berry for mastalgia (cyclical breast pain) have primarily been completed with a product that combines 32.4 mg of a chaste berry extract with various homeopathic ingredients (Mastodynon®)***

The Breast 1999;8:175–81.

Vitex – Proposed Mechanism of Action

- ***While earlier research suggested that chaste berry may increase the release of luteinizing hormone, more recent research has focused on the ability of chaste berry to reduce elevated levels of prolactin late in a woman's menstrual cycle.***
- ***Apparently due to a dopaminergic action of chaste berry leading to a reduction in prolactin, this action may directly relate to the lengthening of the luteal phase and reduction in breast tenderness seen with chaste berry treatment. It may also partially explain the preliminary success found in clinical trials using chaste berry in the treatment of infertility and secondary amenorrhea.***

Vitex (Chaste Berry)

Contraindications

- Clinical trials have reported that adverse events are rare with the use of chaste berry. Among those reported have been urticaria (skin rash with itching), mild gastrointestinal upset, and intermenstrual bleeding.***
- Chaste berry is not recommended for use during pregnancy and its use during lactation is being questioned due to the possible dopaminergic actions mentioned above leading to a suppression of lactation.***
- Due to theoretical interactions, some authors suggest that chaste berry be avoided by women taking oral contraceptives or on hormone therapy. The potential dopaminergic action of chaste berry also suggests that it should not be used concomitantly with dopamine antagonist drugs such as haloperidol or metoclopramide.***

Morning Sickness Associated with Pregnancy

- Primary Considerations***

 - Ginger***

- Other Considerations***

 - Vitamin B6***

 - Acupressure***



Ginger for Nausea and Vomiting of Pregnancy

- ***Six RCTs with a total of 675 women and a prospective observational cohort study (n=187) were evaluated***
- ***The methodological quality of 4 of 5 RCTs was high.***
- ***Four of the 6 RCTs (n=246) showed superiority of ginger over placebo; the other 2 RCTs (n=429) indicated that ginger was as effective as a reference medication (vitamin B6)***
- ***The observational study as well as RCTs showed the absence of significant side effects or AES on pregnancy outcomes.***

Pycnogenol for Pain During Pregnancy

- ***140 women in the 3rd trimester or pregnancy complaining of the appearance or marked exacerbation of pain in the lower back, hip joint, or pelvic (inguinal region), or pain due to varicies or calf cramps were randomized to either 30 mg/day of Pycnogenol (n=80) or no treatment (n=60)***
- ***A significant reduction in pain ($p < 0.01$) was noted in the treatment group compared to placebo and was observed 2 weeks after starting treatment.***
- ***No AEs or abnormal pregnancy outcomes were reported.***

Phytotherapy Res 2006;20:232-4.

Menopause

- *Primary Considerations*

- *Black cohosh*

- *Dietary/supplemental lignans*

- *Soy*

- *Red Clover extract*

Black Cohosh

(Cimicifuga racemosa)

- ***Parts used: rhizome and/or root***
- ***Major constituents***
 - ***Triterpene glycosides (e.g. deoxyactein)***
- ***Mechanisms of action***
 - ***Debate continues regarding the estrogenic actions of the extract – new trials suggest it may act as a selective estrogen receptor modulator with action limited to hypothalamus, bone, and possibly vaginal epithelium***





Black Cohosh Best During Early Menopause?

- ***304 postmenopausal women (45 years or older)***
 - ***Interval of ≥ 12 months since last regular menstruation or an interval of ≥ 6 months since last regular menstruation plus FSH of ≥ 50 IU/L.***
- ***Randomized to receive either Remifemin (20 mg bid) or placebo for 12 weeks. Clinical efficacy was measured using the Menopause Rating Scale (MRS).***
- ***268 women completed the trial and the difference in the decrease in MRS score was significantly greater in the black cohosh group compared to placebo ($p = 0.027$).***

Black Cohosh Best During Early Menopause?, cont.

— Notable were the following findings:

Ÿ When considering women in the early stages of menopause (1 yr. duration) and lower baseline FSH (20 IU/L) compared to women in later stages, the difference in MRS became even greater ($p < 0.001$).

Ÿ The difference in the hot flashes subscore was most significantly changed in the black cohosh group ($p = 0.007$)

— Safety analysis found:

Ÿ 50 women in the black cohosh group reported AEs compared to 47 women in the placebo group. Most were mild with GI upset being most common.

Ÿ No increases in liver enzymes were noted.

Obstet Gynecol 2005;105:1074-83.

Black Cohosh

Better with More Severe Symptoms?

- 122 women (ages 45-60 years) in peri- or early postmenopause with ≥ 3 hot flashes per day. Dose was one capsule of black cohosh per day (42 mg). 12 week trial.***
- The change in the Kupperman Index as well as decrease in hot flashes was not statistically different between the black cohosh and placebo groups.***
- However, when analyzing a subgroup of women with a Kupperman Index score of ≥ 20 (moderate intensity and above) the difference in change of total score reached significance ($p=0.018$). Decrease in hot flash incidence barely reached statistical significance ($p=0.052$). On the MRS, the black cohosh group had a 48% decrease compared to 14% for placebo ($p=0.009$). AEs were mild and similar in both groups.***

Maturitas 2005;51:397-404.

Black Cohosh

Negative Trial with Breast Cancer Pts.

- ***85 female patients (18 years or older) with a diagnosis of breast cancer who had completed their primary treatment were enrolled. Patients were divided into two groups: those on tamoxifen and those not on tamoxifen. Of the 85 women entered in the trial, 59 were taking tamoxifen. Women were randomized to receive 20 mg of black cohosh extract or placebo b.i.d with meals for 60 days.***
- ***68 women provided usable hot flash diary data throughout the entirety of the study (24 in the treatment/tamoxifen group, 26 in the placebo/tamoxifen group, 9 in the treatment/no tamoxifen group, and 10 in the placebo/no tamoxifen group).***

Black Cohosh Negative Trial, cont.

- ***Hot flashes declined in both groups with an average reduction in the mean number of hot flashes of about 27% overall. However, the differences in the mean reduction in hot flashes between groups were not significant ($p = 0.86$ via analysis of covariance adjusting for baseline number and tamoxifen use). Similarly, there were no significant differences between the groups in reduction of hot flash intensity or overall hot flash activity score.***
- ***The only menopausal symptom significantly reduced in the black cohosh group was excessive sweating ($p = 0.04$).***

Changes in FSH and LH were insignificant in all groups.

J Clin Oncol 2001;10:2739-45.

Black Cohosh

Treatment of hot flashes in women taking Tamoxifen

- 136 women, ages 35-52 years, who were breast cancer survivors undergoing adjuvant tamoxifen (20 mg/day) treatment. The main inclusion criteria included: perimenopausal status, regular menstrual cycles with normal duration and a diagnosis of ER-positive breast cancer***
- Women were randomized to receive either tamoxifen only (n=46) or tamoxifen plus black cohosh rhizome extract [20 mg/day] (n=90) for 12 months***

Black Cohosh

Treatment of hot flashes in women taking Tamoxifen, cont.

- Among the 90 patients taking both black cohosh and tamoxifen, 46.7% were free of hot flashes at 12 months, while 24.4% still suffered from severe symptoms and 28.9% from moderate symptoms. This difference was significant when compared to the placebo group, which showed no women free of symptoms and 73.9% and 26.1% reporting severe or moderate symptoms, respectively ($p < 0.01$). No serious adverse events were reported in either group.***

Maturitas 2003;44 (Suppl. 1): S59-S65.

Black Cohosh and St. John's Wort

- ***301 women (45-60 years old) experiencing climacteric complaints with a “pronounced psychological component) were randomized to receive a fixed combination of BC/SJW or placebo for 16 weeks. The BC/SJW combo delivered 80/1200 mg for the first 8 weeks and then 40/600 mg for the last 8 wks.***
- ***The mean MRS total score was decreased in the treatment group by 34.8% at week 8 and 50% at week 16 compared to 21.7% and 19.6%, respectively in the placebo group (p<0.001). Superiority of treatment compared to placebo was noted for hot flashes with a decrease of 53.4% at week 16 in the treatment group compared to 25.4% in the placebo group (p<0.001). The HAM-D total score decreased significantly in the BC group compared to placebo (p<0.001). There were no significant differences between groups in adverse events or in treatment tolerability.***

Obstet Gynecol 2006;107:247-55.

HALT!!!!

(The Herbal Alternative for Menopause Study)

- ***Cooperation of the UW, Group Health, and Bastyr University***
- ***Compared the following in 351 women (ages 45-55 years) with 2 or more vasomotor symptoms daily:***
 - ***Black cohosh extract – 160 mg/day***
 - ***Multibotanical/mineral combination: alfalfa, black cohosh, boron, vitex, dong quai, flase unicorn, licorice, oats, pomegranate, Eleuthero***
 - ***Multibotanical plus telephone counseling to increase soy intake***
 - ***Conjugated equine estrogen (0.625 mg) with or without medroxyprogesterone acetate (2.5 mg) – women with a uterus randomized to CEE only***
- ***Treatment period was 12 months with visits at 3, 6, and 12 months***

Maturitas 2005;52:134-46.

HALT!!!!

cont.

- ***After one year, there was no difference in frequency or intensity of vasomotor symptoms was no different between the herb groups and placebo.***
- ***At 3 months, the mean number of night sweats was 12% lower in the BC group and 83% lower in the HRT group compared to placebo.***
- ***At 3 months, the overall Wiklund score was 22% lower and the mean vasomotory symptoms score was 22% lower with black cohosh vs. placebo. HRT was 61% and 73% lower, respectively***

Results from paper by Tori Hudson, ND

Black Cohosh

Secondary Findings Compared to Estrogen

- ***Secondary analysis of data from earlier trial (*Maturitas* 2003;44(Suppl 1):67-77) comparing black cohosh extract (BNO 1055; 40 mg/day), CE (0.6 mg/day), and placebo for 12 weeks.***
- ***BC increased serum levels of bone specific alkaline phosphatase suggesting stimulation of osteoblast activity while CE inhibited osteoclast activity.***
- ***CE showed significant effects on increasing vaginal mucosa superficial cells, while BC caused a very slight increase compared to placebo.***
- ***BC had no effect on 17β -estradiol and led to a slight decrease in SHBG levels***
- ***Liver enzymes remained unchanged in all three groups and actually went down slightly in the BC group.***
Menopause 2006;13:185-96.

Black Cohosh Hepatotoxicity?

- In February the Australian Therapeutic Goods Administration (TGA) issued a policy for a new label warning to be required for all herbal products containing black cohosh. TGA cited at least 47 adverse event reports (AERs) of hepatotoxicity that have been collected worldwide that have been allegedly associated with black cohosh-containing products. Even though some of these products have contained multiple herbs, some observers have classed them as black cohosh-related AERs.***
- TGA acknowledged that “Although some reports are confounded by multiple ingredients, by more than one medication or by other medical conditions, there is sufficient evidence of a causal association between Black cohosh and serious hepatitis.” The TGA policy requires the following label statement on black cohosh products: “Warning: Black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional”.***

Black Cohosh Hepatotoxicity?, cont.

- ***NIH held a one-day “Workshop on the Safety of Black Cohosh in Clinical Studies” in November 2004. The consensus of the experts assembled at the NIH conference concluded that there is inadequate evidence that black cohosh preparations are causally associated with hepatotoxicity. However, NIH concluded that liver enzyme levels will be monitored in all women currently enrolled in NIH-funded trials on black cohosh as a precautionary measure***
- ***In June 2005 Schaper & Brümmer, the manufacturers of Remifemin®, introduced into the U.S. market new packaging with the following warning: “Consult your healthcare practitioner prior to use if you have a history of liver disease or are taking prescription drugs.”***

Black Cohosh Hepatotoxicity?, cont.

- According to Dr. Tori Hudson:***
- Experts in botanical toxicology suggest that in women without a history of liver disease, or in women using less than 1 g of crude herb per day, that there is little risk***
- Current studies and one ongoing at Columbia University have not observed hepatotoxicity***
- May want to monitor liver enzymes quarterly after 3 months of continuous use***

Dosage and Safety

- *Usual dosage recommendation is 20 mg b.i.d. – extract standardized to 2.5% triterpene glycosides*
- *Most women notice results after two to four weeks of use*
- *Side effects are rare, but pregnant or lactating women should not use this herb*
- *No know drug interactions*

Hops for Hot Flashes?

.... "one bourbon, one scotch, and one beer"

- Women (ages 45-60 years) who had not experienced menses for at least 12 months and with at least 2 to 5 hot flashes per day were randomized to receive placebo (n=26) or a standardized hop extract (8-prenylnaringenin; 8-PN) at one of two doses of 8-PN per day – 100 mcg (120 mg extract; n=20) or 250 mcg (300 mg extract; n=21) for 12 weeks.***
- All three groups had a significant reduction in Kupperman Index scores at weeks 6 and 12 with only the "low dose" group showing superiority compared to placebo at week 6 ($p = 0.023$) but not week 12.***
- Both treatment groups showed statistically significant reductions in hot flash scores at week 6 but not week 12 compared to placebo.***
Maturitas 2006;54:164-75.

Another Cure for Hot Flashess?



Lignans: A Definition

- *Lignans are one of three main groups of plant compounds classified as phytoestrogens. The other two are isoflavonoids and coumestans. All three groups are characterized by diphenolic rings, making them structurally similar to endogenous estrogen.*
- *The predominant plant lignans of dietary importance are matairesinol, hydroxmatairesinol and secoisolariciresinol.*
- *These are converted in the gut to the mammalian lignans, enterolactone (ENL) and enterodiol (EDL).*

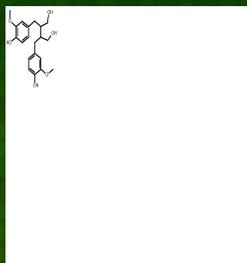
	SECO (mg/100g)	MAT (mg/100g)	7- HMR
Flaxseed	180	1	
Sesame seed	trace	0.2	1.3
Rye, Wheat, Oat, Barley	0.05 – 0.1	0 – 0.1	
Cranberry Strawberry	0.5 – 1	trace	
Tea (different varieties)	0.5 – 1.25	trace	
Soy (different varieties)	0.01 – 0.05	trace	

Lignans: How are they converted?

- *Plant lignans, often ingested as sugar conjugates (e.g. seicosolariciresinol diglucoside), are deconjugated by gastric HCl and anaerobic microbe-derived β -glycosidases and converted, through a series of metabolic reactions, to their respective mammalian derivatives (ENL, EDL).*
- *The requirement of healthy gut flora in this conversion process has been demonstrated in studies and it has been shown that the administration of antibiotics or induced germ-free environments inhibit production of ENL and EDL.*

Dietary and Supplement Lignan Conversion

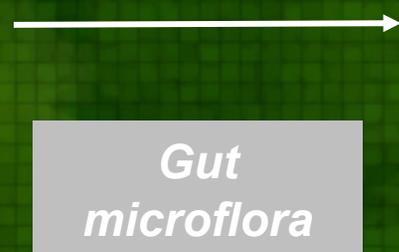
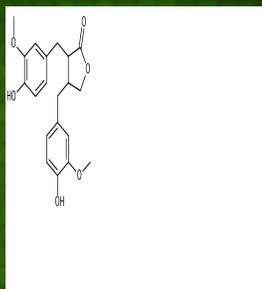
Secoiso-lariciresinol



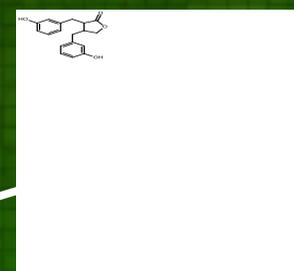
Enterodiol



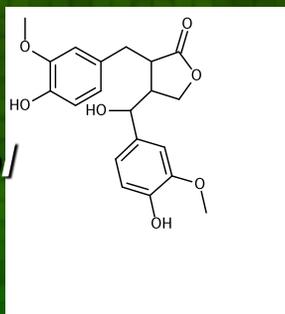
Matairesinol



Enterolactone



Hydroxymatairesinol



Serum Enterolactone and Premenopausal Breast Cancer Risk

- ***Plasma enterolactone and genistein were measured in 220 premenopausal women with breast cancer and 237 age-matched controls from a population-based study in Germany***
- ***Median plasma enterolactone concentrations in cases and controls were 6.3 and 9.7 nmol/l, respectively, and median genistein concentrations were 4.5 and 3.7 nmol/l, respectively. Adjusted odds ratios were 0.42 (0.20-0.90) and 0.38 (0.17-0.85) ($p=0.007$) for women in the third and fourth quartile of plasma enterolactone. No significant association was noted for genistein.***

European J Cancer Prevent 2006;15:225-32.

Calendula Ointment for Radiation-Induced Dermatitis in Breast Cancer Patients

- ***254 women (mean age 55.8 years) with breast cancer receiving postoperative radiation therapy were randomized to receive either topical calendula cream or trolamine (a soap substitute used in burn patients) – medications were applied to the affected area(s) twice per day (more if needed) for 8 months.***
- ***Grade 2 or 3 skin toxicity was experienced in 41% of the women in the calendula group compared to 63% in the trolamine group ($p < 0.001$). The VAS for pain was significantly less in the calendula group ($p = 0.03$).***
- ***No allergic reactions were reported in the women using calendula.***

J Clin Oncol 2004;22:1447-53.

Propolis Douche for Chronic Vaginitis

- ***In an open-label study, 54 women (18 years and older and premenopausal) with recurrent vaginal infection who had undergone at least one cycle of antibiotic treatment in the previous 6 months were treated with a vaginal douche containing a 5% aqueous solution of propolis. Using an applicator, women were instructed to apply 30 ml of the solution on 7 consecutive days.***
- ***At baseline, BV was present in 27 women (BS 3, n =12; BS 2, n = 15) and 22 had VVS (CS 4. n = 7; CS 3, n = 10; CS 2, n = 5). In two women in the BV group, Gardnerella was the predominant organism. At the 14-day follow-up examination, vaginal smears were improved in 41 patients (75.9%). In those with BV, 20 of 27 (74.1%) of women had a lower BS (mean 1.5 ± 0.6 vs. 2.4 ± 0.5 at baseline), and diagnosed cases decreased from 27 to 11 ($p < 0.001$ for both measures).***

Propolis Douche for Chronic Vaginitis, cont.

- ***Of the 22 VVC patients, 21 had improved smears. However, 9 women (40.9%) still had candidiasis (CS 3, n =2; CS 2, n =7; CS 1, n = 3; CS 0, n = 10). The mean CS fell from 3.1 ± 0.7 to 1.0 ± 1.1 ($p < 0.001$).***
- ***Overall, 47 women (87%) reported relief of at least one complaint. In the BV group, three women (11.1%) were free of any symptoms and 16 (59.3%). Of the 22 patients with VVC, one was symptom-free and 11 had 1–3 complaints of minimal grading. In 36 patients (66.7%), the subjective relief reported corresponded with improved smears. At the 6-month telephone contact, 33 of the 47 women reporting improved well-being at 14 days were satisfied with their condition and had not felt any need for further treatment. In 14 women, vaginal infections had recurred within the 6 months.***

International J Gynecol Obstet 2005;98:127-32.

Male Health Conditions

Benign Prostatic Hyperplasia

– Primary Considerations

• Saw palmetto

• Beta-sitosterol (mixed sterols) – 20 mg tid

– Other Considerations

• Rye pollen extract (chronic nonbacterial prostatitis)

• Pygeum – 100 mg/day

• Nettle – 120 bid

• Pumpkin seed oil

Saw Palmetto

(Serenoa repens, Sabal serrulata)

— ***Part used: The berries***

— ***Major constituents***

• ***The lipid-soluble components of the berry – the purified liposterolic extract contains 80-95% fatty acids and sterols (including beta-sitosterol). Other constituents include esters, long-chain alcohols, and polysaccharides.***





Saw Palmetto

Possible Mechanisms of Action

- ***Inhibition of 5-alpha-reductase and 3-ketosteroid reductase (?)***
- ***Inhibits binding of dihydrotestosterone to prostate cells (about 60% less than finasteride)***
- ***Inhibits production of basic fibroblast growth factor and epidermal growth factor***

Saw Palmetto

Mechanism of Action

- ***Di Silverio F, et al. Prostate 1998;37:77-83.***
 - ***25 men (mean 68 years) with BPH treated with 320 mg/day or nothing for 3 months.***
 - ***Those treated with saw palmetto had significant reductions in DHT and epidermal growth factor and rise in testosterone. The lower DHT levels were particularly noted in the periurethral zone.***
- ***In vitro study indicates that saw palmetto and not nettle, beta-sitosterol, or pumpkin, demonstrated alpha1-adrenoreceptor-inhibitory properties in vitro (Prostate 1999;38:208-15).***

Saw Palmetto

- *Common/Potential Clinical Uses*
 - *Benign prostatic hyperplasia*

Saw Palmetto

BPH

— ***A meta-analysis of 18 randomized, clinical trials involving extracts of *Serenoa repens* (saw palmetto) [monopreparations and combination products] to treat patients with BPH. Overall, the authors concluded saw palmetto extracts were superior to placebo and comparable with finasteride in relieving lower urinary tract symptoms. Overall the studies showed that saw palmetto increased peak urinary flow by 24% and mean urine flow by 28%, reduced nocturia by 25%, and residual urine volume by 43% compared to placebo. Study volunteers were significantly less likely to report erectile dysfunction when taking saw palmetto compared to finasteride (1.1% vs. 4.9%, $p < 0.001$). JAMA 1998,280:1604-9.***

Saw Palmetto Comparison with Finasteride

- A six month, double-blind trial compared saw palmetto extract (Permixon®) with finasteride in 1,098 men with moderate BPH. Patients were randomized to receive either 160 mg of saw palmetto b.i.d. or finsteride at a dose of 5 mg once daily.***
- Both treatments were assessed as decreasing symptoms of BPH and improving peak and mean urinary flow equally. The saw palmetto group had an overall decrease on the IPSS of 37% compared to 39% for the finasteride group. The finasteride group had a much larger decrease in prostate volume (18%) compared to the saw palmetto group (6%) and also led to a 41% decrease in PSA levels compare to no change in the saw palmetto group. Loss of libido and impotence were reported more commonly in the finasteride group (3.0% and 2.8%) compared to the saw palmetto group (2.2% and 1.5%).***

Saw Palmetto Comparison with Tamsulosin

- ***594 men with symptomatic BPH were randomized to receive either 320 mg/day of a liposterolic extract of saw palmetto (Permixon) or 0.4 mg/day of tamsulosin hydrochloride (Flomax).***
- ***At 12 months, the I-PSS decreased by 4.4 in both groups with a mean percentage change from baseline of 27.5% for the tamsulosin group and 26.7% for the saw palmetto group. The adjusted mean scores for Qmax were similar in both treatment groups (1.89 m/s for tamsulosin and 1.79 ml/s for saw palmetto). Neither group showed a significant change in PSA levels and the tamsulosin group had a significantly greater incidence in “ejaculation disorders” (4.2% vs. 0.6%, $p = 0.001$).***

Eur Urol 2002;41:497–506.

Saw Palmetto/Nettle Root Comparison with Tamsulosin

- 140 male outpatients (50 years of age and older) with lower urinary tract symptoms (LUTS) associated with BPH were randomized to receive one capsule of PRO 160/120 b.i.d. or one capsule of tamsulosin (0.4 mg) plus one placebo capsule for 60 weeks.***
- At week 60, the I-PSS total score was reduced by a median of 9 points in both groups. The time course of LUTS amelioration was similar in both groups. In total, 32.4% of the patients in the PRO 160/12 group and 27.9% in the tamsulosin group were rated as responders (e.g. I-PSS \leq 7 points).***

Arzneim-Forsch Drug Res 2006;56:222–9.

Saw Palmetto - Progression of Lower Urinary Tract Symptoms

- 189 men (> 50 years old) presenting with mild lower urinary tract symptoms (LUTS) suggestive of bladder outlet obstruction (BOO) and an International Prostate Symptom Score (IPSS) of < 8 received 320 mg of saw palmetto extract daily for 2 years and were compared to a group receiving no treatment.***
- Saw palmetto significantly reduced the incidence of clinical progression and the effect was noticed as early as 6 months. At the end of 24 months, the incidence of progression was significantly less in the saw palmetto group (16%) compared to the watchful waiting group (24%) (p = 0.03).***
World J Urol 2005;25:255-6.

Saw Palmetto

Recommended Use/Safety Issues

- Liposterolic extract – 320 mg/day, usually divided into two daily doses. Symptom relief may be noticed as early as two weeks but an initial evaluation of at least six months is recommended. Saw palmetto is designed for long-term, continuous use.***
- Side effects are rare and are usually limited to mild GI upset. A review of clinical trials concluded about 1.1% of patients taking saw palmetto experienced erectile dysfunction (compared to 4.9% for finasteride).***
- No known contraindications or drug interactions.***

Saw Palmetto PSA Inhibition?

- *A recent in vitro study found that saw palmetto extract did not inhibit the release of PSA from prostatic epithelial or fibroblast cells following the addition of testosterone (Prostate 1999;40:232-41).*
- *Several clinical studies have shown no effect on PSA, including three 6 months or longer:*
 - *1 year (Phytother Res 1997;11:558-63).*
 - *6 months (Urology 1998;51:1003-7).*
 - *6 months (Prostate 1996;29:231-40).*

Resources

- **American Botanical Council**
(www.herbalgram.org)
- **American Herbal Products Association**
(www.ahpa.org/herbmed/search)
- **USP – Dietary Supplement Verification Program**
(www.usp-dsvp.org)
- **Monographs/Textbooks**
 - **ESCOP** (www.escop.com) - also available from ABC
 - **American Herbal Pharmacopoeia** (www.herbal-ahp.org)
 - **ABC Clinical Guide to Herbs; Commission E**
Monographs/Herbal Medicine (Expanded Commission E)
 - **The Handbook of Clinically Tested Herbal Remedies**
 - **WHO Monographs**



The American Botanical Council

T H E A B C
CLINICAL
G U I D E T O
HERBS



Mark Blumenthal

