Love Potions, Witches Brews and the Medicine Bag
- An Update on Herbal Medicine

David J. Mokler, Ph.D.
Professor of Pharmacology
University of New England
College of Osteopathic Medicine

Disclosure

The presenter DOES NOT have an interest in selling a technology, program, product, and/or service to CME/CE professionals
Drugs from Nature
What herbs are being used today?

2007 National Health Interview Survey

- 17.7% of US adults had used natural products in the past year

Rate of use among adults using natural products
Herbal Drug Use Today

**Arch Intern Med. 2005;165:281-286**

**Recent Trends in Use of Herbal and Other Natural Products**

Judith P. Kelly, MS; David W. Kaufman, ScD; Katherine Kelley, RPh; Lyon Rosenberg, ScD; Theresa E. Anderson, RN; Alton A. Mitchell, MD

Use of herbal products according to year of interview and age of subject
Weekly Prevalence of Use of Most Commonly Reported Herbal and Other Natural Dietary Supplements in 1998-1999 and 2002 According to Age Among Men*

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>18-44</th>
<th>45-64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panax ginseng</td>
<td>4.1</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>3.6</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>2.1</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>1.4</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Lutein</td>
<td>1.3</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>L-Cysteine</td>
<td>1.4</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Benfotamate</td>
<td>1.4</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Garlic</td>
<td>1.3</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Data are given as percentages and are weighted according to household size.

Weekly Prevalence of Use of Most Commonly Reported Herbal and Other Natural Supplements in 1998-1999 and 2002 According to Age Among Women*

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>18-44</th>
<th>45-64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Johns wort</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>1.5</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Garlic</td>
<td>1.2</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Ephedras</td>
<td>1.2</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Royal jelly</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Lutein</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>L-Cysteine</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Data are given as percentages and are weighted according to household size.
Reasons for Use of Products Containing Herbal and Other Natural Supplements Among Subjects Interviewed in 2002

<table>
<thead>
<tr>
<th>Reason for Use</th>
<th>Men (n = 776)</th>
<th>No. (%)</th>
<th>Women (n = 908)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin</td>
<td>38 (20.5)</td>
<td></td>
<td>67 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Supplement diet</td>
<td>22 (11.9)</td>
<td></td>
<td>32 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>13 (7.0)</td>
<td>23 (7.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive, not otherwise specified</td>
<td>12 (6.4)</td>
<td>15 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician recommended</td>
<td>11 (5.9)</td>
<td></td>
<td>13 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>11 (5.9)</td>
<td>13 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>9 (4.9)</td>
<td>12 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>9 (4.9)</td>
<td>10 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>7 (3.8)</td>
<td>9 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral supplement</td>
<td>5 (2.2)</td>
<td></td>
<td>9 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Preventive uses</td>
<td>4 (2.2)</td>
<td></td>
<td>5 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td>4 (2.2)</td>
<td>6 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ health</td>
<td>4 (2.2)</td>
<td>8 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodybuilding</td>
<td>4 (2.2)</td>
<td>7 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (2.2)</td>
<td>6 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>3 (1.6)</td>
<td>6 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aging</td>
<td>3 (1.6)</td>
<td>6 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (1.6)</td>
<td>6 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental anxiety</td>
<td>3 (1.6)</td>
<td>5 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>3 (1.6)</td>
<td>5 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antioxidant</td>
<td>3 (1.6)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“It is good for you”</td>
<td>3 (1.6)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skins</td>
<td>3 (1.6)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“I need it”</td>
<td>3 (1.6)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>47 (26.4)</td>
<td>89 (27.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ARCHIVES OF
INTERNAL MEDICINE

Copyright restrictions may apply.

GENERAL CONSIDERATIONS

- **Herbs are drugs**
- **Side effects**
- **Drug-drug interactions**
- **Un-regulated**
- **Variability in preparations**
- **Testing of brands**
  - [http://www.consumerlab.com/](http://www.consumerlab.com/)
Definition of dietary supplement:

- A product intended to supplement the diet that contains a vitamin, mineral, an herb or other botanical, an amino acid, ...a dietary substance for use by man to supplement the diet by increasing the total dietary intake; (or a concentrate, metabolite, constituent, extract or combination of any ingredient described above)

Regulation

DSHEA Act of 1994
DSHEA Act of 1994

- Supplements are not ‘food additives’
- Statements of nutritional support allowed
  
  “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease.”
- The burden of proof that a product is unsafe or adulterated lies with the FDA
  
  Examples – tryptophan, ephedra (Ma Huang)

Supplement Labeling

- What must it tell you?
- What can it tell you?
- What it doesn’t tell you?
What **must** it tell you?

- Statement of identity
- Net contents
- Manufacturer name and address
- Supplement Facts panel
  - Serving size
  - Ingredient listing (name/part/herb or extract)
  - Amount per serving (herbs or “Proprietary blend”)

What **can** it tell you?

- Structure-function claim (w/ FDA disclaimer)
- Expiration date
- Relevant precautions
- “Standardized” or “Full spectrum”
  - Neither of these terms has a definition in the U.S.
What it doesn’t tell you?

- Preparation of the herb
  - Agricultural history of extract
  - Preparation of extract

- Standardization (in U.S.)
  - Contact manufacturer FMI

- Indications

- Dose

Why standardize?

- Assure consistent quality
- Avoid adulteration or substitution
- “Define” the extract for clinical trials and/or patent protection
2007 – FDA ruling

New June 2007 FDA ruling: to require “current good manufacturing practices” (cGMPs) for dietary supplements.
- This rule to take effect in June 2008 for large companies.
- Smaller companies - 2010 to comply.

GMP ensures
- Production in a quality manner without contaminants and with accurate labeling, so product contains what the label states!

2007 – FDA ruling

To try to get accurately labeled herbals advise patients to look for the following symbols on labels
- GMP (Good Manufacturing Practices)
- NSF (National Safety Foundations)
- USP (United States Pharmacopeia)

Note: This does not mandate proof of clinical efficacy or mandatory reporting of side-effects.
Resources

- **Natural Standard**
- **Naturalstandard.com**
- **Consumer Lab**
- **Consumerlab.com**
- **Natural Medicine Comprehensive Database**
- **naturaldatabase.therapeuticresearch.com**

**Natural Standard - Ginko biloba**
Natural Medicine Comprehensive Database

St. John’s Wort

(Hypericum perforatum)
St. John’s Wort

- Blooms on St. John the Baptist’s birthday and is said to bleed red on the day in August he was beheaded

St. John’s Wort - Then

- Used to protect against wounds in battle
- Used to ward off evil spirits
- Used to reveal witches and to make them speak the truth
**St. John’s Wort - Then**

- Medicinally
  - Antiseptic (used in the crusades??)
  - Anti-viral
  - Nerve tonic
  - Anti-depressant
- St Johns Wort is good in tertian and quartan agues (Malaria) and is also used to destroy worms.
- "A tincture of its flowers in spirit of wine is commended against Melancholy and Madness".
  
  Blackwell’s Curious Herbal, 1735

**St. John’s Wort - Today**

- One of most widely used - $48,000,000 in U.S. in 1997
- Standardized to hypericin
- Many studies use an extract of SJW – hypericum extract
- Hypericum may work as re-uptake inhibitor for serotonin and norepinephrine
St. John’s Wort

Clinical Trials

- Systematic review showed 8 trials with almost 1000 patients
- Against placebo or TCA
- Significantly better than placebo (4 trials)
- Equivalent to low dose TCA (4 trials)


St. John’s Wort

Clinical Trials

- Imipramine (75 mg bid) vs STJ (hypericum extract ZE117 bid)
- 324 patients, mild to moderate depression
- Randomized, DB, 6 weeks
- Comparable decrease in depression scores for imipramine and SJW
- Adverse side effects – 39% for SJW and 63% for imipramine

- Woelk et al., BMJ, 2000
St. John’s Wort
Clinical Trials

- Hypericum (900 mg LI 160) vs sertraline (75 mg/d)
- 30 patients, mild to moderate depression
- DB, randomized
- 47% of patients improved on SJW and 40% improved on sertraline
- Small group, small effect size
- Brenner et al., Clin. Ther., 2000

St. John’s Wort
Clinical Trials

- SJW vs. placebo
- 300 pts, major depression, 8 weeks
- No differences in depression scores
- Greater number of patients reaching remission – 14.3% vs 4.9%
- Shelton et al., JAMA, 2001
St. John’s Wort
Clinical Trials

Adverse side effects

- Dry mouth
- GI disturbances
- Photosensitivity
- Sedation

Drug-drug interactions

- Serotonin syndrome
  - When combined with other anti-depressants
  - Restlessness, muscle twitches, myoclonus, sweating, hypertension, may lead to coma
St. John’s Wort
Clinical Trials

- Drug-drug interactions
- Induces CYP450-3A4
  - Major liver enzyme
  - Decreases serum concentration of other drugs
    - Cyclosporin
    - Oral contraceptives
    - HIV anti-viral drugs
    - Digoxin

St. John’s Wort
Clinical Trials

- Proposed trials
  - Anxiety and social phobia
  - Minor depression
  - Obsessive-compulsive disorder
St. John’s Wort

- Useful in mild to moderate depression
- Ineffective in major depression
- Well tolerated with few adverse side effects
- Significant drug-drug interactions

Kava Kava
Kava kava

- Piper Wichmanii
- Piper Methysticum

“I drink kava each Friday evening, after a week's worth of teaching high schoolers. Ordinarily on Fridays, the events of the week loop repeatedly yet pointlessly through my mind. Kava's relaxing properties allow me to drop this loop, and concentrate on whatever I like. Nicest of all is the way kava affects my dreams. On kava nights, my dreams involve long, epic voyages through blue-green seas, populated by strange, friendly water animals. Like last night - my travel and conversation partner was a manatee with violet eyes. These are more like the dreams I remember having as a child, and a total departure from my usual stress-induced dreams of grading papers, running out of chalk” - J. Prince (Seattle, WA)
Kava Kava

- **Natural valium??**
- **Mild stimulant**
- **Anti-Anxiety**
- **Anti-Fatigue**

- Active constituents – kavapyrones (4) and other kava alkaloids
- May increase GABA receptor
- May inhibit reuptake of norepinephrine
- May increase dopamine

Kava kava

- **Clinical trials**
- **As effective as oxazepam (38 pts with anxiety)**
- **More effective than placebo (58 patients with anxiety)**
- **More effective than placebo for 8 weeks (101 patients with anxiety)**
- **Anxiety - Level of evidence - A**
Side Effects and Interactions

- Liver toxicity (case reports)
  - Withdrawn in Europe and Canada
- Potentiate benzodiazepines and other sedatives
- May increase activity of anti-coagulants
- May worsen symptoms of Parkinson’s disease
- May inhibit P450 metabolism
- Dependence

Marijuana

Cannabis sativa

Cannabis indica
Cannabis Indica

Given in full dose to man, this drug causes exhilaration and periods of constant laughter arising from the slightest cause, the person seeming convulsed with merriment; in other cases the sensations are disagreeable, and even death may seem imminent to the deranged mind. – Practical Therapeutics, Hare, 1895.

Marijuana

Common name for a tall annual herb (Cannabis sativa) of the family Cannabinaceae

Native to Asia but now widespread because of its formerly large-scale cultivation for the bast fiber (also called hemp) and for the drug it yields
Marijuana - Then

When a patient suffers from sleeplessness which is due in part to pain and in part to nervousness, the following prescription may be given:

Marijuana - Then

Other uses (1895)

- Chronic inflammation
- Gastralgia
- Metorrhagia
- Nervous and spasmotic dysmenorrhea
- Gonorrhea
- Sexual stimulant
Marijuana - Then

The employment of this most valuable remedy is handicapped by its frequent lack of power—a fault which is largely dependent upon its preparation. The drug as prepared by Parke, Davis and Co. has proved efficacious in the author's hands for a number of years. The physician should always employ some preparation known by him to be active by personal trial before condemning the drug as a failure in a given case. – Practical Therapeutics, Hare, 1895.

Marijuana - Today

- Cannabinoid receptors
- Throughout the brain and spinal cord
- Endogenous cannabinoid
Marijuana - Today

- Nausea and vomiting (FDA approved as THC extract - Marinol)
- Glaucoma
- Wasting syndromes
- Pain - level of evidence - B
- Symptoms of MS - level of evidence B

Marijuana - Today

- Side effects and Toxicity

  - Psychoactive
  - Hypotension
  - Dependence
Chondroitin Sulfate in Osteoarthritis

- Bourgeois P, et al.
  - 127 pts, 1,200 mg, effective at 3 months
- Bucsi L, et al.
  - 80 pts, 800 mg, effective over 6 months
- Conrozier T.
  - 104 pts, 800 mg, effective after 1 year
- Morreale P, et al.
  - 146 pts, 1,200 mg, effective for 6 months
- Uebelhart D, et al.
  - 42 pts, 800 mg, effective over 1 year
  - 119 pts, 1,200 mg, effective over 3 years
How Chondroitin Sulfate Eases Osteoarthritis

- Increasing levels of chondroitin sulfate available to articular cartilage.
- Increasing levels of other important proteoglycans available to the articular cartilage.
- Decreasing activity of elastase, thus decreasing the degradation of collagen.
- Decreasing inflammation

Level of evidence - B

Chondroitin Sulfate’s Atherosclerotic Promise

- Decreasing plasma levels of cholesterol and other lipids.
- Decreasing atherosclerotic plaque formation.
- Decreasing inflammation

Level of evidence - D
Panax Ginseng

▲ **Asian ginseng** (Panax ginseng C.A., Meyer)
  ▲ *Panax, Chinese, or Korean ginseng.*

▲ **American ginseng** (Panax quinquefolius L.)

▲ **Siberian ginseng, also called eleuthero** (Eleutherococcus senticosus Rupr ex Maxim),
Panax Ginseng

- Enhances immune system - Level of evidence B
  - Antiviral activity
  - Decreased colds and flu
  - Decreased recurrence of herpes simplex with eleuthero
- Enhances mental activity - Level of evidence B
  - Variable results – some positive
- Enhances general well-being
  - 200 mg per day for 8 weeks
  - Energy, mood and vigor

Panax Ginseng

- Doses
  - 200 mg daily of extract containing ginsenosides
  - 300-400 mg of Siberian ginseng (eleuthero)
- Side effects - rare
  - Estrogen-like effects
  - Mania with anti-depressants
  - Reduced efficacy of coumadin
  - May interfere with tests for digoxin
  - May reduce insulin requirements
Typically extract of leaves of Ginko biloba tree
- Oldest surviving species of tree
- Extinct in Europe but survived in Asia
- Some trees cultivated for over 1,000 years
- Original Chinese medicine used seeds

Huperzine A is extract from leaves of Chinese toothed club moss (Huperzia serrata or synthetically manufactured.)
Ginko Biloba

- Alzheimer’s Disease
  - German Commission E
  - As effective as any approved medication for Alzheimer’s disease
  - Mildly effective in elderly with memory loss
  - Weak in younger patients

- Intermittent claudication

Ginko Biloba

- Preliminary double-blind trials
  - PMS
  - altitude sickness
  - Glaucoma
  - macular degeneration
  - Vertigo
  - sudden hearing loss

- Increases blood flow
Ginko Biloba

**Dosage**
- 40-80 mg 3 times a day of 50:1 extract standardized to contain 24% ginkgo-flavone glycosides

**Side effects**
- Relatively safe
  - Not established in young children, pregnant women or in kidney or liver disease
- Anti-coagulant
  - Interactions with anti-coagulants
- Lowers seizure threshold
- Reduces efficacy of calcium channel blockers
- May increase efficacy of anti-psychotic drugs
Garlic - *Allium sativum* L.

- **Cardiovascular disease**
  - Hyperlipidemia - Level of evidence A
  - Hypertension - Level of evidence A
  - Atherosclerosis - Level of evidence C
    - Decreases formation of atherosclerotic plaques
    - Decreases risk of 2nd heart attack
- **Common cold - Evidence C**
- **Cancer (prevention) - Evidence C**
  - Stomach and colon
- **Mosquito repellant - Level of evidence C**
Chinese herbal medicine
A different approach

- 22,000 herbs
- 3000 years
- combinations of herbs individually prepared after patient history
- specialty medicine

References

- Boullata, J.I. and Nace, A.M. Safety issues with herbal medicine. Pharmacotherapy 2000; 20 (3)
Questions?