Herbal Medicines
and the Clinical Laboratory

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APMG

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Mending a Broken Heart with Alternative Therapies

Secrets of Stress Repair

Healing Cancer With Biophysics

Science Discovers the Healing Touch

Chelation Beats Viagra

Anti-Aging Formula for MALE MENOPAUSE

Pharmaceuticals: Your Money and Your Life
How Popular?

- Survey of 369 patient-escort pairs and reported that 174 patients (47.2%) used herbs
- Most common herbal products:
  - Ginseng (20%)
  - Echinacea (19%)
  - Ginkgo biloba (15%)
  - St John's wort (14%)
<table>
<thead>
<tr>
<th>Herbal Medicine</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>Tonic capable of invigorating users physically, mentally, and sexually; also used for dealing with stress; used in China for more than 5,000 y</td>
</tr>
<tr>
<td>Siberian ginseng</td>
<td>Similar to ginseng</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Treatment of mood disorders, particularly depression</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Mainly to sharpen mental focus in otherwise healthy adults and also in people with dementia; improvement of blood flow in the brain and peripheral circulation; treatment of diabetes mellitus-related circulatory disorders, impotence, and vertigo</td>
</tr>
<tr>
<td>Kava</td>
<td>Relief of anxiety and stress; sedative</td>
</tr>
<tr>
<td>Valerian</td>
<td>Treatment of insomnia</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immune stimulant that helps increase resistance to colds, influenza, and other infections; wound healing</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Treatment of benign prostatic hypertrophy</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Relief from migraine headache and arthritis</td>
</tr>
<tr>
<td>Garlic</td>
<td>To lower cholesterol levels and blood pressure; prevention of heart attack and stroke</td>
</tr>
<tr>
<td>Ginger</td>
<td>Prevention of motion sickness, morning sickness, and nausea</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Treatment of urinary tract infection; decrease kidney stone formation</td>
</tr>
<tr>
<td>Aloe</td>
<td>To heal wounds, burns, skin ulcers; also used as a laxative</td>
</tr>
<tr>
<td>Senna</td>
<td>Laxative</td>
</tr>
<tr>
<td>Dong quai</td>
<td>To alleviate problems associated with menstruation and menopause</td>
</tr>
<tr>
<td>Cat’s claw</td>
<td>Immunostimulant with antiviral activity; also used by people with AIDS; prevention of colds and influenza; treatment of chronic fatigue syndrome</td>
</tr>
<tr>
<td>Hawthorn</td>
<td>For heart failure, hypertension, and angina pectoris</td>
</tr>
<tr>
<td>Pokeweed</td>
<td>Antiviral and antineoplastic; eating uncooked berry or root may cause serious poisoning</td>
</tr>
</tbody>
</table>
Not a Drug but a Dietary Supplement

- FDA mandates that only medicines have to be proven to be safe before being released into the market.
- Not a drug as long as they are not marketed for the prevention of any diseases.
- Classified as "dietary supplements" and are marketed pursuant to the Dietary Supplement Health and Education act of 1994.
Types of Abnormal Lab Results

- Direct interference of a component of the herbal medicine with the assay
- Unexpected concentration of a therapeutic drug due to drug-herb interactions
- Toxic effects of the herbal product
### Table 2
Interference of Herbal Products in Therapeutic Drug Monitoring of Digoxin

<table>
<thead>
<tr>
<th>Herbal Product</th>
<th>Level of Interference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan Su</td>
<td>High</td>
<td>Chan Su has active components such as bufalin, which cross-react with digoxin assays; only Bayer assay has no interference; monitoring free digoxin also eliminates interference</td>
</tr>
<tr>
<td>Dan Shen</td>
<td>Moderate</td>
<td>Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin eliminates interference</td>
</tr>
<tr>
<td>Uzara root (diuretic)</td>
<td>Moderate</td>
<td>Additive effect with digoxin; also interferes with digoxin assay</td>
</tr>
<tr>
<td>Siberian ginseng</td>
<td>Moderate</td>
<td>Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference</td>
</tr>
<tr>
<td>Asian ginseng</td>
<td>Moderate</td>
<td>Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference</td>
</tr>
</tbody>
</table>

FPIA, fluorescence polarization immunoassay; MEIA, microparticle enzyme immunoassay.
* Bayer Diagnostics, Tarrytown, NY; Roche Diagnostics, Indianapolis, IN; Beckman Coulter, Fullerton, CA.
Chinese Herbals-Chan Su

- Prepared from the dried white secretion of the auricular glands and the skin glands of Chinese toads (Bufo melanostictus Schneider or Bufo bufo gargarzinas Cantor)
  - In Chinese medicines Lu-Shen-Wan and kyushin used for tonsillitis, sore throat, furuncle, and palpitations
  - Stimulation of myocardial contraction and pain relief
  - At high dosages, causes cardiac arrhythmia, breathlessness, seizure, and coma
- Structural similarity between bufadienolides and digoxin accounts for the toxic effects and serum digoxin-like immunoreactivity of Chan Su
  - Falsely elevates the serum digoxin concentration when the FPIA is used
  - Negative interference of Chan Su in serum digoxin measurement has been reported with the microparticle enzyme immunoassay (MEIA)
  - Interfering components in Chan Su are bound very strongly to serum proteins, while digoxin is only 25% protein bound
  - Monitoring the free digoxin concentration eliminates this interference
  - Another way to eliminate this interference is to use the chemiluminescent assay
Digoxin Measurement

- FPIA (Fluorescent Polarization Immunoassay)
- MEIA (Microparticle enzyme immunoassay)
- EMIT (Enzyme Multiplied Immunoassay-Dade-Behring)
- Chemiluminescent assay (Elecsys)
Add Sample and Reagents

Fluorescein labelled drug
Antibody against drug
Drug

Incubation Region

Excitation
Emission
Fluorescence
Detection

Fig 3.9.1 FPIA Equipment Set-up
MEIA

- Solid-phase support consists of very small microparticles in liquid suspension
- Specific reagent antibodies are covalently bound to the microparticles
- Antigen, if present, is then "sandwiched" between bound antibodies and antigen-specific, enzyme-labelled antibodies
- Antigen-antibody complexes are detected and quantitated by analysis of fluorescence from the enzyme-substrate interaction
Enzyme Multiplied Immunoassay
Chinese Herbals-Dan Shen

- Prepared from the root of plant *Salvia miltiorrhiza*
  - Treating various cardiovascular diseases, including angina pectoris
- >20 diterpene quinones known as "tanshinones" have been isolated, structural similarity with digoxin
- Falsely elevated serum digoxin concentrations (FPIA)
- Falsely lowered the digoxin (MEIA)
- No interference with chemiluminescent assay
- Interference of Dan Shen in the FPIA and MEIA eliminated by measuring free digoxin because the digoxin-like immunoreactive components of Dan Shen have much higher serum protein binding than digoxin
- EMI T 2000 digoxin assay and a recently FDA-approved turbidimetric digoxin immunoassay also are free from interference from Dan Shen
Chinese Herbals-Siberian Ginseng

- Ingestion of Siberian ginseng was associated with elevated digoxin concentrations
- Produces only modest interference in the digoxin FPIA and MEIA
- Asian ginseng also showed modest positive (FPIA) and modest negative (MEIA) interference
<table>
<thead>
<tr>
<th>Herbal Product</th>
<th>Interacting Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>Warfarin</td>
<td>Ginseng may decrease effectiveness of warfarin</td>
</tr>
<tr>
<td></td>
<td>Phenelzine</td>
<td>Toxic symptoms, eg, headache, insomnia, and irritability</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Paroxetine hydrochloride</td>
<td>Lethargy, incoherence, nausea</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Decreased AUC; peak and trough concentration of digoxin; may reduce effectiveness of digoxin</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Lower cyclophosphamide concentration due to increased clearance may cause transplant rejection</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Lower concentration, thus decreases the efficacy of theophylline</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Lower concentration may cause treatment failure in patients with HIV</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Aspirin</td>
<td>Bleeding; ginkgo can inhibit PAF</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Thiazide</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Kava</td>
<td>Alprazolam</td>
<td>Additive effects with CNS depressants, alcohol</td>
</tr>
<tr>
<td>Garlic</td>
<td>Warfarin</td>
<td>Increased effectiveness of warfarin; bleeding</td>
</tr>
<tr>
<td>Ginger</td>
<td>Warfarin</td>
<td>Increased effectiveness of warfarin; bleeding</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Warfarin</td>
<td>Increased effectiveness of warfarin; bleeding</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Warfarin</td>
<td>Dong quai contains coumarin; dong quai increases INR for warfarin, causes bleeding</td>
</tr>
<tr>
<td>Dan Shen</td>
<td>Warfarin</td>
<td>Increased effectiveness of warfarin owing to reduced elimination of warfarin</td>
</tr>
<tr>
<td>Soy milk</td>
<td>Warfarin</td>
<td>Causes decline in INR</td>
</tr>
<tr>
<td>Comfrey</td>
<td>Phenobarbital</td>
<td>Increased metabolism of comfrey producing a lethal metabolite from pyrrolizidine; severe hepatotoxic effects</td>
</tr>
<tr>
<td>Borage oil</td>
<td>Phenobarbital</td>
<td>May lower seizure threshold, requiring dosage increase</td>
</tr>
<tr>
<td>Evening primrose oil</td>
<td>Phenobarbital</td>
<td>May lower seizure threshold, requiring dosage increase</td>
</tr>
<tr>
<td>Licorice</td>
<td>Spironolactone</td>
<td>May offset the effect of spironolactone</td>
</tr>
<tr>
<td>Shankhpushpi</td>
<td>Phenytoin</td>
<td>Lower phenytoin level and loss of seizure control</td>
</tr>
</tbody>
</table>
Unexpected Concentrations

- Dong quai used for treatment of menstrual cramps, irregular menses, and menopausal symptoms
  - Elevate INR and increase bleeding time in patients taking warfarin
- Licorice
  - Anti-inflammatory herb and also as a remedy for gastric and peptic ulcers
  - Carbenoxolone, one of the components of licorice, can elevate blood pressure and cause hypokalemia
  - May offset the ability of spironolactones
Unexpected Consequences

- St John's wort is prepared from *Hypericum*
  - Many chemicals have been isolated from St John's wort, including hypericin, pseudohypericin, quercetin, isoquercitrin, rutin, amentoflavone, hyperforin, other flavonoids, and xanthones
- Activates cytochrome P-450 mixed-function oxidase liver enzymes (CYP3A4)
- Decrease concentrations of digoxin, cyclosporine, indinavir, theophylline
Unexpected Consequences

- Of 2,069 samples of traditional Chinese medicines obtained from 8 hospitals in Taiwan, 23.7% contained pharmaceuticals
  - Caffeine
  - Acetaminophen
  - Indomethacin
  - Hydrochlorothiazide
  - Prednisolone
  - NSAIDs
  - Heavy metals
Unexpected Consequences

- **Kava-Kava**
  - Abnormal Liver Function Test results
  - Additive effects with central nervous system depressants
  - Severe hepatitis
- **Chaparral**
  - Abnormal Liver Function Test results
  - Antioxidant and an anticancer herbal product
  - Chaparral-associated hepatitis
- **Mistletoe**
  - Liver Damage
  - Digestive aid, heart tonic, and sedative. Mistletoe berries are poisonous.
  - Hepatitis probably due to mistletoe
- **Germander**
  - Elevated Liver Enzyme Levels
  - Remedy for weight loss and as a general tonic
  - Germander-induced hepatotoxicity Acute cholestatic hepatitis
Unexpected Consequences

- Kelp
  - Abnormal Thyroid Profile
- Ginseng
  - Hypoglycemic properties
- Fenugreek, ginger, nettle, sage, and devil's claw
  - Hypoglycemic
Unexpected Consequences

- **Licorice and Hypokalemia**
  - Fifty-nine licorice-induced hypokalemic myopathy cases
  - Renin activity and aldosterone concentrations in serum usually decrease.

- **Lead Poisoning Due to Herbs**
  - Herbal medicines contaminated with
  - Patient was taking an herb purchased in India
  - Chinese herbal medicine Cordyceps
    - Lead content in the Chinese medicine was found to be as high as 20,000 ppm
<table>
<thead>
<tr>
<th>Herb</th>
<th>Toxic Effect or System Affected</th>
<th>Intended Use (Should Anyone Use?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfrey</td>
<td>Hepatotoxic</td>
<td>Repairing of bone and muscle; prevention of kidney stones</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Cardiovascular</td>
<td>Herbal weight loss</td>
</tr>
<tr>
<td>Chan Su</td>
<td>Cardiovascular</td>
<td>Tonic for heart</td>
</tr>
<tr>
<td>Borage oil</td>
<td>Hepatotoxic; hepatocarcinogenic</td>
<td>Source of essential fatty acids; rheumatoid arthritis; hypertension</td>
</tr>
<tr>
<td>Calamus</td>
<td>Carcinogenic</td>
<td>Psychoactive, not promoted in the United States</td>
</tr>
<tr>
<td>Chaparral</td>
<td>Hepatotoxic; nephrotoxic; carcinogenic</td>
<td>General cleansing tonic; blood thinner; arthritis remedy; weight loss product</td>
</tr>
<tr>
<td>Licorice</td>
<td>Pseudoaldosteronism (sodium and water retention, hypertension, heart failure)</td>
<td>Treatment of peptic ulcer; flavoring agent</td>
</tr>
</tbody>
</table>
Toxic Effects

- Ginseng
  - In 1979, the term *ginseng abuse syndrome* was coined as a result of a study of 133 people who took ginseng for 1 month.
  - Central nervous system stimulation ranging from depersonalization and confusion to symptoms of hypertension, nervousness, sleeplessness, skin eruption, and morning diarrhea.
Toxic Effects

- Ginkgo Biloba
  - Sharpen mental focus and to improve diabetes mellitus-related circulatory disorders
  - May cause gastric disturbances, headache, and dizziness
  - Bleeding with one case of spontaneous intracerebral hemorrhage and postoperative bleeding after laparoscopic cholecystectomy
Toxic Effects

- **Echinacea**
  - Hepatitis, asthma, rash, myalgia, and nausea

- **Garlic**
  - Chopped garlic-and-oil mixes left at room temperature can result in fatal botulism food poisoning according to the FDA.

- **Ma Huang (Ephedra-Containing Herbal Diet Pills)**
  - Herbal weight-loss products that often are referred to as herbal fen-phen
  - May contain St John's wort and are sold as "herbal Prozac."
  - "Herbal ecstasy" another ephedrine-containing product, can induce a euphoric state
  - Contraindicated use of ephedra by patients with high blood pressure, glaucoma, or thyrotoxicosis
Surgical Procedures

- American Society of Anesthesiologists
  - Patients should discontinue their herbal medicines at least 2 weeks before surgery
- Other recommendations
  - Garlic and ginseng should be discontinued at least 7 days before surgery
  - Ginkgo biloba should be discontinued 3 days before surgery because it inhibits platelet aggregation, causing bleeding
  - Kava should be discontinued at least 24 hours before surgery because kava can increase the sedative effect of anesthetics
  - Ma huang (ephedra) should be discontinued 24 hours before surgery because ma huang increases the blood pressure and the heart rate
  - St John's wort should be discontinued 5 days before surgery
Health nuts are going to feel stupid someday, lying in hospitals dying of nothing.

Redd Foxx (1922 - 1991)
References