Herbal Supplements and the Surgical Patient

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Group Health

Objectives

- Review demographic and economic issues related to alternative supplement use
- Describe potential risks of herbal supplements for surgical patients
- Discuss impact of drug-herb interactions on post-anesthesia recovery

“Plantaceuticals”

Atropine (Atropa belladonna)
Digoxin (Digitalis purpurea)
Colchicine (Colchicum autumnale)
Quinine (Cinchona officinalis)
Codeine (Papaver somniferum)
Vincristine (Catharansus roseus)
Taxol (Taxus brevifolia)
Physostigmine (Physostigma venenosum)
Salicylin (Salix purpurea)

Adapted from Archives of Internal Medicine 1998
Herbal History Lesson

2697 BC - China
400 BC - Hippocrates
1500’s - botanical gardens for medical schools
1700’s - herbal use for home health care
1800’s - scientists learn to extract and modify active ingredients from plants
1900’s - pharmaceutical use increases; herbal remedy use decreases
1960’s - renewed interest in “natural health”; nutraceuticals become popular
1992 - NIH establishes the Office of Alternative Medicine
- now known as the National Center for Complementary and Alternative Medicine

Worldwide Use of Alternative Medicine

- Used by >80% of the population in Asia and Africa
- Most popular = herbals
- Very lucrative in the global market

Countries That Regulate CAM

- Germany
- France
- Sweden
- Denmark
- Switzerland
- The Netherlands
- Portugal
- Japan
- China
Herbal supplements constitute the largest growing component of retail pharmacy. Usage has increased >400% over the past 10-15 years. In 2007, dietary supplement expenditures exceeded $15 billion.

Alternative Medicine Use: Adults
- Adult use = 38.3%
  - Female > male
- More prevalent among ages 30-69 years
- More common in the western states
- More common in former smokers
- ↑ health conditions/doctor visits = ↑ use
- Unable to afford health care

Alternative Medicine Use: Kids
- Use by nearly 12% of children
  - Female = male
- More prevalent in 12-17 years of age
- ↑ health conditions/doctor visits = ↑ use
- Unable to afford health care
Rationale for Herbal Medicine Use

"...herbal medicine prescribed by knowledgeable practitioners is safer than conventional medicine...the medicines are more dilute...the side effects tend to be less severe. Pharmaceuticals kill more than 100,000 Americans a year, according to JAMA. No one has shown yet that herbs kill more than even 100 Americans a year, much less 100,000..."

www.motherearthnews.com

What Do Patients Say?

Complementary Therapies in Clinical Practice 2011

Health Care Burden

CDC National Health Interview Survey 2011
Dietary Supplement and Health Education Act (DSHEA)

- Manufacturer can claim that an herbal product affects the body
- Manufacturer cannot claim effectiveness
- Label must state that FDA has not evaluated the herbal agent
- Manufacturer is responsible for assuring truthfulness of label contents

Drugs vs. Supplements: Regulations

<table>
<thead>
<tr>
<th></th>
<th>Rx Drugs</th>
<th>Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proof of Safety</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Proof of Effectiveness</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Post-marketing Surveillance</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Good Manufacturing Practices (GMPs)</td>
<td>Pharmaceutical GMPs</td>
<td>Food GMPs</td>
</tr>
<tr>
<td>Disease Treatment Claims</td>
<td>Allowed</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

Bestseller List

- Cranberry
- Soy
- Saw palmetto
- Garlic
- Echinacea
- Gingko biloba
- Milk thistle
- St. John's wort
- Ginseng
- Black cohosh
- Green tea
- Evening primrose
- Valerian
- Horny goatweed
- Bilberry
- Elderberry
- Grape seed
- Ginger
- Aloe vera
- Horse chestnut
Potential Risks: Ingredients

- Variation in formulations
  - active ingredients
  - excipients
- Contaminants
  - chemicals
  - microbes
  - toxins
- Adulteration
  - medications or other herbs

Formulation Variations: Feverfew

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Label Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>capsule</td>
<td>400</td>
</tr>
<tr>
<td>capsule</td>
<td>125</td>
</tr>
<tr>
<td>capsule</td>
<td>250</td>
</tr>
<tr>
<td>gelcap</td>
<td>143</td>
</tr>
<tr>
<td>tablet</td>
<td>75</td>
</tr>
<tr>
<td>tablet</td>
<td>200</td>
</tr>
<tr>
<td>alcohol extract</td>
<td>60 per 30 drops</td>
</tr>
<tr>
<td>glycerin extract</td>
<td>250/ml</td>
</tr>
</tbody>
</table>

Adapted from American Journal of Health-System Pharmacy 2002

Formulation Variations: Cranberry

- Phenomenal sales growth
- Formulations limited by high acidity and polyphenolic content
  - variable plant expression of phenolics
  - poor absorption of some phenolics in GI tract
  - phenolic modification by CYP 450 enzymes
- Cranberry supplements may contain dozens of other ingredients
Contaminants in Herbal Products

<table>
<thead>
<tr>
<th>Adulterant</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>botanicals</td>
<td>digitalis, rauwolfia, belladonna alkaloids</td>
</tr>
<tr>
<td>microorganisms</td>
<td><em>S. aureus, E. coli, P. aeruginosa</em></td>
</tr>
<tr>
<td>microbial toxins</td>
<td>aflatoxins, endotoxins</td>
</tr>
<tr>
<td>pesticides</td>
<td>chlorine, phosphates, carbamates</td>
</tr>
<tr>
<td>fumigation agents</td>
<td>ethylene oxide, methyl bromide, phosphine</td>
</tr>
<tr>
<td>metals</td>
<td>lead, mercury, arsenic, cadmium</td>
</tr>
<tr>
<td>drugs</td>
<td>anti-inflammatory, steroids, coumarins, colchicine, sildenafil</td>
</tr>
</tbody>
</table>

Adapted from New England Journal Medicine 2002

Herbals Containing Coumarins

- alfalfa
- fenugreek
- red clover
- sweet clover
- sweet woodruff

Chinese Herbals: Heavy Metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Herbal Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>lead</td>
<td>Babaodan, Tieng Dieda Wan, Shanhaidan capsules</td>
</tr>
<tr>
<td>mercury</td>
<td>China Ling Zhi capsules, Ching Fei Yi Huo Wan, Gan Mao Ling, Shi Hu Pian, Su Shi Bai Feng Wan, Tien Wang Pu Xin Wan, Xiang Sha Yang Wei Wan</td>
</tr>
<tr>
<td>arsenic</td>
<td>Chunbaodai tablet, Fargelin for Piles, Wild Ling Chih, Zhu Bei Dinchuanpian</td>
</tr>
<tr>
<td>copper</td>
<td>Hindu Magic Pills</td>
</tr>
</tbody>
</table>

Anaesthesia 2002
Intentional Adulteration

<table>
<thead>
<tr>
<th>Supplement Type</th>
<th>Adulterant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PO herbal medicines</strong></td>
<td>aminopyrine, phenylbutazone</td>
</tr>
<tr>
<td></td>
<td>diazepam, chlorpheniramine</td>
</tr>
<tr>
<td></td>
<td>triamcinolone, phenytoin</td>
</tr>
<tr>
<td></td>
<td>valproate, carbamazepine</td>
</tr>
<tr>
<td></td>
<td>testosterone, sildenafil</td>
</tr>
<tr>
<td><strong>weight loss aids</strong></td>
<td>norpseudoephedrine</td>
</tr>
<tr>
<td><strong>herbal creams</strong></td>
<td>corticosteroids</td>
</tr>
<tr>
<td><strong>prostate health drugs</strong></td>
<td>coumarins, indomethacin</td>
</tr>
<tr>
<td></td>
<td>diethylstilbestrol</td>
</tr>
</tbody>
</table>

Adapted from American Journal of Health-System Pharmacy 2003

Herbals and Adverse Reactions

- Events documented during a 5-year period:
  - Over 2600 events
  - Over 100 deaths
- Problems with reporting:
  - No reporting
  - Event not recognized
  - Event identified but not attributed to herbal use

Results of Herb-Drug Interactions

[Graph showing percentage of adverse effects due to herb-drug interactions]

Drugs Aging 2009
Some Specific Interactions

<table>
<thead>
<tr>
<th>Herb</th>
<th>Medication</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>garlic</td>
<td>warfarin, chlorpropamide</td>
<td>bleeding, ↑ INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>ginkgo</td>
<td>warfarin, aspirin, thiazides, trazodone</td>
<td>bleeding, ↑ blood pressure, ↑ sedation</td>
</tr>
<tr>
<td>ginseng</td>
<td>warfarin, phenelzine</td>
<td>↑ INR, bleeding, insomnia, tremors, mania</td>
</tr>
<tr>
<td>kava</td>
<td>alprazolam</td>
<td>sedation</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>sertraline, paroxetine, nefazodone, warfarin, oral contraceptives, theophylline, digoxin, cyclosporine</td>
<td>symptoms of ↑ serotonin, ↓ INR, altered menstrual bleeding, ↓ plasma concentrations</td>
</tr>
</tbody>
</table>

Adapted from American Journal of Medicine 2004

Permissum Patiens Caveo

- Patients taking prescription or OTC drugs
- Women who are pregnant or breastfeeding
- Patients <18 or >65 years of age
- Patients who plan to have surgery

“Many herbal supplements can affect the success of surgery… may decrease the effectiveness of anesthetics or cause dangerous complications, such as bleeding or high blood pressure…”

www.mayoclinic.com

Shall We Inform the Surgeon?

- Studies reveal that 70% of surgical patients hide herbal usage from physicians
- Reasons for lack of disclosure by patients
  - Fear of ridicule
  - Assumption that herbs are unrelated to care
  - Perception that herbs are not medicines
  - Belief that practitioners are not knowledgeable about alternative medicine
A Real Patient...

- **AM Cleanse**: 1 tab PO daily
- **Womens DHEA**: 1 tab PO daily
- **Cell-u-less**: 2 tabs PO TID
- **Thermobond**: 2 tabs PO TID
- **Joint Support**: 2 tabs PO TID
- **Carboguard**: 1 tab PO TID
- **Mentabalance**: 1 tab PO TID
- **Aminogen**: 1 tab PO TID
- **Megaginseng**: 1 tab PO BID
- **St. Johns wort**: 1 tab PO BID
- **Ultimate gingko**: 1 tab PO BID
- **Ocular Defense**: 1 tab PO BID
- **Extreme C**: 1 tab PO BID
- **Tripleberry complex**: 1 tab PO BID
- **Cardio Toconox**: 1 tab PO QHS

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**Surgical Oncology Patients**

[Graph showing types of complementary or alternative medicine used by patients]

Canadian Journal of Surgery 2009

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**Cardiovascular Surgery Patients**

[Graph showing percentage of patients using different supplements]

Heart, Lung, and Circulation 2011
Usage Reported at Pre-Op Visit

Number of products taken by surgical patients

Type of natural products taken by surgical patients

BMC Complementary and Alternative Medicine 2009

Plastic Surgery Patients

<table>
<thead>
<tr>
<th>Age range, y</th>
<th>No of patients</th>
<th>Percent taking herbal remedies</th>
<th>Percent taking vitamin supplements</th>
<th>Percent taking dietary supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>5</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-34</td>
<td>8</td>
<td>25</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>35-44</td>
<td>10</td>
<td>20</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>45-54</td>
<td>12</td>
<td>17</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>55-64</td>
<td>23</td>
<td>26</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>65+</td>
<td>37</td>
<td>3</td>
<td>16</td>
<td>24</td>
</tr>
</tbody>
</table>

www.epilepsy.com 2011

Potential Surgical Risks

Adapted from JAMA 2001

Ginseng
- Hypoglycemia
- Inhibits platelet aggregation (may be irreversible)
- Inhibits PT/PTT in animals
- Increases anticoagulation effect of warfarin

Ephedra
- Myocardial infarction, cerebrovascular accident
- Depletes endogenous catecholamine stores, which can cause intraoperative hemodynamic instability
- Life-threatening interaction with MAO inhibitors

Garlic
- Inhibits platelet aggregation (may be irreversible)
- Increases fibrinolysis
- Increases risk of bleeding
- Equivalent blood pressure lowering

Ginkgo biloba
- Inhibits platelet-activating factor, leading to increased bleeding risk
### Potential Surgical Risks

<table>
<thead>
<tr>
<th>Herb</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kava</td>
<td>Sedation, anxiolyis, increases sedative effect of anesthetics, potential for addiction, tolerance, withdrawal</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Many drug–drug interactions via induction of CYP 450 enzymes</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Activates cell-mediated immunity, allergic reactions, immunosuppression</td>
</tr>
<tr>
<td>Valerian</td>
<td>Increases sedative effect of anesthesia, withdrawal, may increase anesthesia requirements</td>
</tr>
</tbody>
</table>

Adapted from JAMA 2001

### Toxicities Associated With Herbals

<table>
<thead>
<tr>
<th>Hepatic</th>
<th>Renal</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>chaparral</td>
<td>horse-chestnut saponin</td>
<td>aconite root tuber</td>
</tr>
<tr>
<td>germander</td>
<td>Chinese yew</td>
<td>leigongteng</td>
</tr>
<tr>
<td>impila root</td>
<td>impila root</td>
<td>licorice root</td>
</tr>
<tr>
<td>kava</td>
<td>jering fruit</td>
<td>mahuang</td>
</tr>
<tr>
<td>kombucha</td>
<td>penmyroyal oil</td>
<td>pokeweed</td>
</tr>
<tr>
<td>mahuang</td>
<td>star fruit</td>
<td>Scotch broom</td>
</tr>
<tr>
<td>penmyroyal oil</td>
<td>aristolochic acid</td>
<td>squirting cucumber</td>
</tr>
<tr>
<td>skullcap</td>
<td></td>
<td>oleander</td>
</tr>
<tr>
<td>soy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phytoestrogens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from New England Journal of Medicine 2002

### Ma Huang and Hepatotoxicity

American Journal of Gastroenterology 1996
**Chinese Herbs Nephropathy (CHNP)**

- Chinese herbs used for weight loss and nutrition
- CHNP discovered in 1992
- Clinical presentation: subacute renal failure
- Pathology: acellular fibrosis, no glomerular lesions

**CHNP and Patients in Taiwan**

<table>
<thead>
<tr>
<th>BUN (initial)</th>
<th>BUN (biopsy)</th>
<th>Serum Cr (initial)</th>
<th>Serum Cr (biopsy)</th>
<th>CrCl (biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>79</td>
<td>1.2</td>
<td>8.4</td>
<td>9.8</td>
</tr>
<tr>
<td>21</td>
<td>91</td>
<td>1.4</td>
<td>8.9</td>
<td>6.5</td>
</tr>
<tr>
<td>NA</td>
<td>82</td>
<td>NA</td>
<td>10.4</td>
<td>5.6</td>
</tr>
<tr>
<td>27</td>
<td>47</td>
<td>1.9</td>
<td>3.7</td>
<td>15.8</td>
</tr>
<tr>
<td>30</td>
<td>33</td>
<td>2.3</td>
<td>2.4</td>
<td>20.9</td>
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<tr>
<td>21</td>
<td>97</td>
<td>0.9</td>
<td>10.8</td>
<td>5.6</td>
</tr>
<tr>
<td>43</td>
<td>40</td>
<td>3.1</td>
<td>3.8</td>
<td>18.8</td>
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<tr>
<td>23</td>
<td>24</td>
<td>1.6</td>
<td>1.9</td>
<td>48.8</td>
</tr>
<tr>
<td>21</td>
<td>53</td>
<td>1.4</td>
<td>3.5</td>
<td>21.7</td>
</tr>
</tbody>
</table>

Adapted from American Journal of Kidney Disease 2000

**Nephrotoxicity**

American Journal of Kidney Diseases 2000
Latest Warning: *Aristolochia macrophylla*

- Aka birthwort
- Widely used in Taiwan
- Primary contributor to upper urinary tract cancer
- Plant toxin is aristolochic acid
- 83% of patients had renal DNA changes related to the plant toxin (n=151)

HealthDay News 2012

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**Cardiotoxicity: “Herbal Cleansing”**

- Female with no prior medical history
- Symptoms of nausea, vomiting, weakness
- Hyperkalemia
- Serum digoxin concentration of 1.7 ng/ml

Annals of Emergency Medicine 2003

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**Digitalis and Oleander**

www.nlm.gov  
www.phoenix.about.com
Digitalis and Oleander

Critical Care Clinics 1997

Potential Anti-Clotting Mechanisms

Decreased Platelet Aggregation
- Evening primrose -2
- Horsetail rush – 3,5
- Dong quai - 3
- Grape seed extract
- Ginger - 2
- Garlic – 1,2,3
- Gingko - 4

Inhibition of Clotting
- Chamomile - unknown
- Dandelion root - unknown
- Horse chestnut - unknown
- Chinese peony - 6
- Bladderwrack - 7

Adapted from Aesthetic Surgery Journal 2012

Surgical Complications and Kava

• Sedation through GABA receptor activation
• Hypotension via Na⁺ and Ca²⁺ channel inhibition
• Hepatotoxicity
• Platelet inhibition

Journal of Clinical Anesthesia 2004
**Anesthetics and St. John’s Wort.**

- Active ingredient is hypericin
  - has affinity for adenosine and GABA receptors
- Other components: naphthoquinones, flavanoids, hyperphorin
  - hyperphorin induces CYP 3A4 and 1A2 enzymes
- Sedation may be caused by interaction with:
  - anesthetics
  - neurotransmitter sites
  - hepatic enzyme sites

**Delayed Emergence From Anesthesia**

<table>
<thead>
<tr>
<th>Time after anesthesia</th>
<th>Patient condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes</td>
<td>No response to painful stimuli</td>
</tr>
<tr>
<td>45 minutes</td>
<td>Flex and moan to pain</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Spontaneous eye opening</td>
</tr>
<tr>
<td></td>
<td>Oriented to time and place</td>
</tr>
</tbody>
</table>

*Anesthesiology 2002*

**Herbals: Arachidonic Acid Pathway**

![Diagram of Arachidonic Acid Pathway](image)

*Journal of the American Academy of Orthopedic Surgeons 2011*
Postsurgical Inflammation

- Licorice
- Goldenseal
- Echinacea

The Pharmacist’s Role

- Ask the right questions
- Communicate with the healthcare team
- Advise discontinuation of herbals at least two weeks before surgery.
- Know the potential adverse effects
- Monitor for drug-herb interactions

What to Ask Before Surgery

1. Are you currently taking any of the following: an herbal product, herbal supplement, tea, herbal food, or other "natural remedies"?
2. Have you taken any herbal or homeopathic supplements in the past?
3. In the past four weeks, what types of tea have you consumed?
4. In the past four weeks, what types of vegetables and plant products have you eaten?
5. Are you taking any dietary supplements or vitamins?
   a. How long have you been taking it?
   b. Who prescribed it for you or recommended it to you?
6. In the past four weeks, have you taken any pills, medications, or supplements that were prescribed on the internet?
7. What other medications are you taking?
Educate the Patient!

- Variability between formulations
- Unknown contaminants, adulteration
- Interference with prescription drugs
- Caution regarding Internet information
- Disclosure of herbal use to health care team.

Steps For Supplement Selection

- Safety assessment
  - Rating: likely safe to unsafe
- Effectiveness assessment
  - Rating: effective to likely ineffective
- Product quality assessment

Safety and Effectiveness

Natural Medicines Comprehensive Database
Product Quality Assessment

- Look for the USP-verified symbol
- Indicates rigorous testing and verification
- Ensures good manufacturing practices
- Verifies that no contaminants are present
- USP standards are enforceable by the FDA