Medicinal Chemistry 420
(2 credits)
Alternative and Complementary Medicines

Thursdays 1:30-3:20  Room T747
http://courses.washington.edu/medch420/
Gary Elmer, H172j Health Sciences, 543-2055, elmer@u.washington.edu

Lecture Topics

• Sept 29  Introduction  Herbal Products 1  Gary Elmer
• Oct 6  Tour of the Medicinal Herb Garden (A-K)  Doug Ewing
         Herbal Products 2 (L-Z)  Gary Elmer
• Oct 13  Tour of the Medicinal Herb Garden (L-Z)  Doug Ewing
          Herbal Products 2 (A-K)  Gary Elmer
• Oct 20  Herbal Products 3  Gary Elmer
• Oct 27  Herbal Products 4  Gary Elmer
• Nov 3  Herbal Products 5  Gary Elmer
         Other Dietary Supplements
• Nov 10  Herbal-Drug Interactions  Gary Elmer
         Other Dietary Supplements
• Nov 17  Probiotics  Gary Elmer
         Homeopathic Products
• Nov 24  Holiday
• Dec 1  Toxic Herbal Products  Sid Nelson
• Dec 8  Effective Herbal Counseling  Darleen Wilson
Requirements for Credit

• Research paper
  – Short (4-6 double spaced pages, not including references) and up-to date
  – Write on an herbal or other dietary supplement NOT covered in class. We will cover the “top 20” herbals (see slides for list), probiotics, DHEA, glucosamine, chondroitin, melatonin, CoQ10, and homeopathic products.
  – Do a literature search
  – Follow guidelines for Pharmacy 309 at http://courses.washington.edu/pharm309/).
  – Compare with conventional therapy if possible
  – Due date will be Nov 18.

Weekly Quiz

• Every week there will be a brief (~5 questions) quiz. The time allowed will be 10-15 min.
• quiz will be based on lecture material presented in the previous class.
• You can drop two quizzes with the lowest scores.
• There will be no “make-up” quiz if you are absent.
• At least a 70% on all possible quiz points and a “pass” on the research paper will be needed to get credit for this credit/no credit course.
General References on Herbal Products
(comprehensive monographs)

- The Review of Natural Products. *Facts and Comparisons Publishing Group*, St. Louis MO. 2004. Available at the UW Bookstore. Also available online at UW as “efacts” (http://healthlinks.washington.edu/contentBrowser.jsp?ctype=1)

- Natural Medicines Comprehensive Database
  Excellent database available in print version ($92/yr) or online ($92/yr). Online updated “daily”. Available online at UW at (http://healthlinks.washington.edu/contentBrowser.jsp?ctype=1)

- National Standard Online. Excellent online database with an expert editorial board. $99/year. Available at UW at http://healthlinks.washington.edu/contentBrowser.jsp?ctype=1

Books

- PDR For Herbal Medicines. Medical Economics, Montvale, NJ, 2nd edition, $70. Better than the first edition but ----


References (continued)


Periodicals and Newsletters on Herbal Products

- **“HerbalGram”** published by the American Botanical Council and the Herb Research Foundation; PO Box 201660, Austin TX 78720 www.herbalgram.org A must read.

- **“The Source”** Association of Natural Medicine Pharmacists online newsletter; 8369 Champs de Elysses, Forestville CA 95436. $35/yr www.anmp.org

## Useful Internet Web sites

- **Consumerlab.com.** Consumerlab is evaluating dietary supplements for quality, a worthy goal. To see the complete evaluations, there is a subscription fee of $17.95/yr. The subscription will also provide you access to The Natural Pharmacist, an excellent database of monographs on herbals and other dietary supplements. [www.consumerlab.com](http://www.consumerlab.com)

- **NIH Nat Center for Complementary and Alternative Medicine (NCCAM).** Programs and information of this important NIH program. Link to new IBIDS database on scientific literature on dietary supplements and other databases. Use is free to all. [http://nccam.nih.gov](http://nccam.nih.gov)

- **UW Healthlinks-Alternative Medicine.** Links to many useful sites. [http://healthlinks.washington.edu/clinical/alt_med.html](http://healthlinks.washington.edu/clinical/alt_med.html)


- **Association of Natural Medicine Pharmacists web site.** Natural medicine information for the health professional. Useful site. [http://www.anmp.org/](http://www.anmp.org/)

- **American Botanical Council home page.** Links to other sites of interest. [http://www.herbalgram.org](http://www.herbalgram.org)

## Useful Internet Web sites

- **Office of Dietary Supplements, NIH.** Mandated by DSHEA, their mission is to promote research and provide objective information on dietary supplements. [http://ods.od.nih.gov](http://ods.od.nih.gov)

- **American Herbal Products Association.** Trade Association with links to member companies and publications. Also access to HerbMed database providing some references on herbals. Not always up to date, however. Useful general site. [http://www.ahpa.org/](http://www.ahpa.org/)

- **Dr. Duke’s databases.** Database on plants and their chemical constituents with biological activities. Dr. James Duke is a well known authority on ethnobotany. [http://www.ars-grin.gov/duke](http://www.ars-grin.gov/duke)
Free Electronic Newletters

- Natural Medicine News  fbatz@sonic.net
- Dietary Supplement/Food Label News from the FDA  www.fda.gov
- Arbor Clinical Nutrition Updates (Dr. Tony Heilman)  http://arborcom.com

Herbal Products

- sales of $12 – 14 billion $ in USA for dietary supplements
- sales of about 4 billion $ in USA for botanicals
- Mass market herbal sales increased 56% from 1996-1997 in USA BUT has dropped in recent years.
- In 1990 5.8% used “alternative medicines”
- In 1998 25.2% used “alternative medicines”
- Patients with cancer or AIDS take more
- most do not tell their “traditional” provider what they are taking and many take alternative and complementary products together with alopatic drugs

Another Survey on Public Use of Alternative Medicines

- 1,584 S. Carolina adults
- 44% had used CAM within the year
- 25% used alternative medicines within the year
- 62% reported CAM medicines were “extremely or very effective”
- 87.8% would recommend to a friend
- 4% had bad experience
- 63% did not tell MD (15% MD recommended)

Dietary Supplement Education Alliance Survey (Harris Interactive)
July 2001

- N=1022
- 59% take dietary supplements on a regular basis
- 46% take multivitamins
- 23% take herbal and specialty products (15% botanicals, 8% non botanical supplements)
- 95% indicate satisfaction; 75% very satisfied or extremely satisfied
- 25% wrong about expecting immediate results from herbals
- Only 49% consult with health care providers about taking supplements
- Most believe they have sufficient information on using supplements
Distribution of the $4.96 Billion European Market for Over-the-Counter Herbal Medicines in 2003.

The remaining $132 million in sales was divided among Portugal, Hungary, Ireland, Slovakia, Finland, and Norway. Data are from IMS Health. The spending per capita (calculated on the basis of the manufacturers’ prices to wholesalers and recent United Nations projections of 2003 populations) was $25.00 in Germany, $18.80 in France, $9.50 in Italy, $6.50 in Poland, $3.60 in the United Kingdom, $4.10 in Spain, $12.30 in Belgium, $13.00 in Switzerland, $10.90 in Austria, $5.00 in the Netherlands, and $7.40 in the Czech Republic.
Most Common Uses for Herbal Products and Alternative Medicines

• **Musculoskeletal Complaints**
  • arthritis (glucosamine/chondroitin)

• **CNS**
  • fatigue (ginseng and others)
  • insomnia (valerian)
  • anxiety/depression (kava, chamomile, skullcap, St. John’s Wort)

• **Colds/flu/immune** (echinacea, goldenseal, atragalus, pau d’arco)

• **Men** (saw palmetto, pygeum)

• **Women** (black cohosh, soy, evening primrose)

• **Circulation** (ginkgo, garlic)

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Types of Herbal and Alternative Medicines

• “Crude” dried herbs *
• “European” Phytopharmaceuticals
  – extracts
  – standardized extracts *
• Traditional Chinese Medicines*
• Ayurvedic Medicines
• Homeopathic Medicines*
• Functional Foods/Neutraceuticals *
• Probiotics **
• “other” dietary supplements (e.g. melatonin)
Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan 2, 2005
HerbalGram 2005;66:63

<table>
<thead>
<tr>
<th>Product</th>
<th>M</th>
<th>$</th>
<th>% change</th>
<th>rank in 2003</th>
</tr>
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<tbody>
<tr>
<td>1. garlic</td>
<td>27</td>
<td>-11</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2. echinacea</td>
<td>24</td>
<td>-15</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3. saw palmetto</td>
<td>20</td>
<td>-11</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>4. ginkgo</td>
<td>19</td>
<td>-13</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>5. soy</td>
<td>17</td>
<td>-27</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>6. cranberry</td>
<td>14</td>
<td>+7</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>7. ginseng</td>
<td>12</td>
<td>-10</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>8. black cohosh</td>
<td>12</td>
<td>-22</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>9. St. John’s wort</td>
<td>9</td>
<td>-12</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>10. milk thistle</td>
<td>8</td>
<td>+1</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>11. evening primrose</td>
<td>6</td>
<td>-4</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>12. valerian</td>
<td>4</td>
<td>-9</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>13. green tea</td>
<td>3</td>
<td>+22</td>
<td></td>
<td>17</td>
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<tr>
<td>14. bilberry</td>
<td>2</td>
<td>-18</td>
<td></td>
<td>14</td>
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</table>

Red indicates risk for drug interactions
Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005
HerbalGram 2003;58:71

<table>
<thead>
<tr>
<th>Product</th>
<th>M</th>
<th>$</th>
<th>% change</th>
<th>rank in 2003</th>
</tr>
</thead>
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<tr>
<td>15. grape seed</td>
<td>2</td>
<td>-12</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>16. horny goat weed</td>
<td>2</td>
<td>+12</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>17. yohimbe</td>
<td>2</td>
<td>-22</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>18. horse chestnut</td>
<td>2</td>
<td>+35</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>19. eleuthro</td>
<td>1</td>
<td>-63</td>
<td></td>
<td>13</td>
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<tr>
<td>20. ginger</td>
<td>0.8</td>
<td>-14</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>multi-herbs</td>
<td>52</td>
<td>+29</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>all other</td>
<td>12</td>
<td>-7.5</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>total</td>
<td>257</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Red indicates risk for drug interactions
Note: kava and pycnogenol fell off the top 20 list
Note: total herbal sales are estimated at $4.2 billion
The above figures include sales from food stores, drug stores, and mass market retailers but with Wal-Mart figures not included. It does not include warehouse buying clubs, convenience stores, natural foods stores, multilevel marketers, health professional sales, mail order or internet sales.

Vitamin A (100% Acetate) 5000 IU, Vitamin C 1000 mg, Vitamin E 30 IU, Magnesium (Sulfate) 40 mg, Zinc (Sulfate) 8 mg, Selenium 15 mcg, Manganese 3 mg, Potassium 75 mg, Organic Herbal Extracts: Lonicera, Forsythia, Schizonepeta, Ginger, Chinese Vitex, Isatis Root, Echinacea 350 mg*, Amino Acids: Glutamine, Lysine 50 mg; 1 q 3h
Useful Herbal Products (good evidence in support of uses)

- Echinacea: immune stimulant
- Saw Palmetto: BPH
- Valerium: sedative
- Ginkgo: circulation
- Milk Thistle: liver
- Ginger: nausea
- Chamomile: indigestion
- Fever Few: migraine
- St. John’s Wort: mild/mod depression
- Hawthorn: heart/circulation
- Soy: hormone replacement Rx
- Kava: anxiolytic
- Black cohosh: menstrual, PMS
- Green tea: stimulant (antioxidant)
Possibly Useful Herbal Products
(less evidence or conflicting evidence)

- **pycnogenol** vision, antioxidant uses
- **ginseng** adaptogen, tonic
- **grape seed** vision, antioxidant uses
- **Evening primrose** dysmenorrhea
- **Bilberry** vision, antioxidant uses
- **Garlic** hyperlipidemias, hypertension
- **yohimbe** erectile dysfunction,

Herbal Products Deemed Unsafe

- **Aconite (Bushi)**
- **Aristolochia sp.**
- **Belladonna**
- **Blue Cohosh**
- **Borage**
- **Broom**
- **Calamus**
- **Chaparral**
- **Coltsfoot**
- **Comfrey**
- **Ephedra (Ma Huang)**
- **Germander**
- **Kombucha Tea**
- **Ma Huang** (ephedra)
- **Lobelia**
- **Pennyroyal Oil**
- **Poke Root**
- **Sassafras**
- **Scullcap**
- **Tansy Ragwort**
- **Wormwood**
Complementary and Alternative Medicines “CAM”

- Fall under “Dietary Supplement” regulatory status (except homeopathic products)
- Dietary Supplements
  - vitamins, minerals, hormones
  - whole plant material, extracts of plants,
  - amino acids
  - miscellaneous “natural” products
    (e.g. glucosamine sulfate, melatonin)

Regulatory Issues

- Federal Food and Cosmetic Act of 1938 - safe
- Kefauver-Harris Act of 1962 - efficacy
- Vitamin and Mineral Amendments of 1972 - high dose OK
- Nutrition Labeling and Education Act of 1990 - food labels
- Dietary Health and Education Act of 1994 (DSHEA) -
Dietary Health and Education Act of 1994 (DSHEA)

- dietary supplements are not considered foods, food supplements or drugs
- no “therapeutic claims” unless approved by FDA
- no “health claims” unless approved by FDA
- limited “structure/function” claims allowed if there is some evidence to support them
  - examples of structure/function claims
- FDA must show product is unsafe
- Label must have a disclaimer “This statement has not been evaluated by the FDA”
- “third party” literature regs.
- Advertising regulated by FTC; all else by FDA

New DSHEA Labeling Requirements

- implied claims banned also
- health maintenance claims OK
- definition of “disease” narrowed so that “life stage” symptoms (acne, hot flashes, wrinkles etc) are not considered diseases
- “science-based” regulatory program for dietary supplements will be in place at the FDA by 2010
- voluntary adverse event reporting started (thro MedWatch and Special Nutritionals Adverse Event Monitoring System)
Problems with Existing Regulations

• requirements to make therapeutic claims are unrealistic
  – herbals are not patentable
  – no consideration for long safe use
  – less consideration for non USA studies
• dietary supplement label is inappropriate
• meaningful package insert lacking
• innovator companies have no protection
  – example: Saccharomyces boulardii*
• limited “official” monographs for herbals in USA (USP)

Problems with Existing Regulations

• No GMPs for herbals (proposal by FDA)
• Huge problems in quality control
• Unethical and criminal elements in industry
  – example: adulteration
Hypericin and Hyperforin in Eight Brands of St. John’s Wort

<table>
<thead>
<tr>
<th>Product</th>
<th>Hypericin (%)</th>
<th>Hyperforin (%)</th>
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</thead>
<tbody>
<tr>
<td>Hyperifin</td>
<td>0.29</td>
<td>1.89</td>
</tr>
<tr>
<td>PNC</td>
<td>0.12</td>
<td>0.20</td>
</tr>
<tr>
<td>Brite-Life</td>
<td>0.22</td>
<td>1.16</td>
</tr>
<tr>
<td>ShopKo</td>
<td>0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>Shurfine</td>
<td>0.17</td>
<td>0.29</td>
</tr>
<tr>
<td>YourLife</td>
<td>0.28</td>
<td>0.19</td>
</tr>
<tr>
<td>Nature’s Balance</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Natrol</td>
<td>0.25</td>
<td>0.48</td>
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</table>

Variation in the Amounts of Active Ginsenosides (Panax Species) and Eleutherosides (Eleutherococcus senticosus) in Ginseng Products in Relation to the Amounts Indicated on Their Labels.
Adapted from Harkey et al. (Am J Clin Nutr 2001;73:1101-6), with the permission of the publisher.
Estimated Daily Lead, Mercury, and Arsenic Ingestion for Heavy Metal-Containing HMPs Recommended for Adults and Children

Internet Marketing of Herbal Products Study
Morris and Avorn JAMA 2003;290:1505-1509

Methods: Searched using 5 search engines the first page hits for 8 popular herbals

Findings: 273 of 338 (81%) made 1 or more health claim
only 12% provided references to back claim
only 39% of kava sites mentioned hepatotoxicity
Examples of Internet Health Claims (JAMA 2003;290:1505-1509)

Ginkgo Biloba  “Its effects in improving circulation also contribute to its use for impotency and peripheral vascular insufficiency …. Ginkgo treats depression, headaches, memory loss and ringing in the ears (tinnitus). It is also recommended for Alzheimer’s, asthma, eczema, heart and kidney disorders.”

St John's Wort  “St John's wort is effective in the treatment of mild to moderate depression … recent studies have shown that it could have a potent anti-viral effect against enveloped viruses.”

Echinacea  “Because it has natural antibiotic actions, Echinacea is considered an excellent herb for infections of all kinds. In addition, it works to boost lymphatic cleansing of the blood, enhances the immune system and has cortisone like properties which contribute to its anti-inflammatory action. It is recommended for stubborn viral infections, yeast infections and for arthritic conditions.”

Saw Palmetto  “The lipophilic extract of the saw palmetto (ser repens) berries is the most widely used herbal preventive and therapeutic agent for benign prostatic hyperplasia (BPH).”

Solutions: Presidents Commission on Dietary Supplement Labels recommendations and suggestions to FDA ('97)

• * set up system to review botanicals for OTC status

• urge to study regulatory systems in other countries

• call for surveillance of adverse effects

• set up system for “traditional use claims” or the like for products that may not meet OTC data requirements

• call for use of outside experts in product reviews
FDA Warnings

• FDA posts warnings of contaminated or harmful supplements
  • tiratricol or TRIAC (triiodothyroacetic acid)
  • aristolochic acid (renal toxicity)
  • ephedra alkaloids
  • Comfrey
  • Kava and hepatotoxicity
• FDA recall of PC-SPES (contamination with warfarin and maybe DES)
• To get email postings see www.fda.gov

Solutions

• New compendial monographs on herbals underway
  – Comission E Monographs English Translation-now available*
  – USP monographs (USP24-NF14) and label logo
  – Micromedex and other objective “use monographs”
  – WHO Monographs on Selected Medicinal Plants

• GMPs for Dietary Supplements are imminent
USP-NF

- United States Pharmacopoeia/National Formulary
- Non profit corporation that sets standards for drugs and biologics
- Is in the process of creating standards for dietary supplements
  - Limits on heavy metals, pesticides
  - Limits on microbial contamination
  - Quality control specs for marker compounds

USP Dietary Supplement Verification Program

- Manufacturer must agree to meet standards set by USP and their monographs
- Must agree to inspections and random analyses of products
- USP analyzes the product and inspects the manufacturing facility
- Pharmavite is the first manufacturer to seek USP verification (Nature Made, Nature’s Resource) for their line of herbals and dietary supplements. The “USP” will appear on the labels.
Consumerlab.com

• A private company testing and certifying dietary supplements

• Membership is $24/yr and includes access to The Natural Pharmacist database

• Manufacturers whose products “pass” are listed on consumerlab’s website (www.consumerlab.com)

• Manufacturers who do not pass are also listed

• A manufacturer whose product “passes” can (for a fee) include the consumerlab seal on their label

– better books, journals, and literature now available

– better education on subject in pharmacy schools and other health professions training

– more frequent and better CE programs

– more research activity in USA
  • NIH funded studies

– pressure is on for FDA to “adapt” to CAM
Product Selection Issues

- Select “name brands” recognized for quality
- select “standardized” products that give potency per unit of the product of an important marker compound
- select products used in the positive clinical trials
- select “standardized extracts” where appropriate
- select products that have batch numbers, expiry dates, and have the new label elements
- avoid complex herbal mixtures

Some “Name Brand” Botanicals

Warner Lambert
  Quanterra Mental® (ginkgo)
  Quanterra Prostate® (saw palmetto)
Whitehall-Robins Healthcare
  Centrum® botanicals line
Pharmaton (Boehringer Ingelheim)
  Ginsana ® (ginseng)
  Ginkoba ® (ginkgo)
  Venastat ® (horse chestnut)
  Movana ® (St. John’s wort)
SK-Beecham
  Alluna ® (valerian and hops)
Pharmavite
  Nature Made ®
  Nature’s Resource ®
Phyto-Phamica
  Nature’s Way
What can we do?

• Dialog with NDs and other prescribers

• ask patients about herbals they may be taking

• offer the best products

• press for regulatory reform

• stay informed

Choosing Herbals - Advice for patients

• Be sure you have an accurate diagnosis.
• Select a “name brand”, quality product;
• If the advertising says “cure” “breakthrough” “detoxify” etc – forget it!
• Tell your doctor and pharmacist what you are taking to avoid interactions with Rx or other OTC medications.
• Use one supplement (single ingredient) at a time.
• Keep the container with labels in case of future adverse reactions.