Medicinal Chemistry 420
(2 credits)
Alternative and Complementary Medicines

Thursdays 1:30-3:20 Room T639

Gary Elmer, H172j Health Sciences, 543-2055, elmer@u.washington.edu

TA: Jed Lampe
mrda@u.washington.edu

Requirements for Credit

- Research paper
  - Short (4-6 double spaced pages, not including references)
  - Expand on topic presented in class or write on a new topic
  - Literature search
  - Compare with conventional therapy if possible
  - Due date will depend on a “lottery”

A take-home final exam.

- available approximately one week before final exams
- due by 5pm on December 14.
- exam will be based on lecture material presented in class.

Attendance at the lectures.

- Let Dr. Elmer or Mr. Lampe know if you will miss
- Occasional attendance checks will be taken.

- There will be no midterm exams or quizzes.

Grades are on a credit/no credit format

General References on Herbal Products
(comprehensive monographs)

- The Review of Natural Products. Facts and Comparisons Publishing Group, St. Louis MO. 2000. Looseleaf format updated regularly in typical F&C fashion. Available at the UW Bookstore (Health Sciences) for $99 including updates.
- Natural Medicines Comprehensive Database Excellent database available online ($92/yr) or in print version ($92/yr). Online version updated “daily”. http://www.naturaldatabase.com/


General References on Herbal Products


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


– “Friends of the Medicinal Herb Garden Newsletter” newsletter concerning the UW Medicinal Herb Garden
Useful Internet Web sites

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

Herbal Products

- sales of $12 billion $ in USA for dietary supplements (1999)
- sales of about 4 billion $ in USA for botanicals (1999)
- Mass market herbal sales increased 56% from 1996-1997 in USA BUT dropped 15% in 2000
- 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 alopathic 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)

Trends

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, scullcap, 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)
Types of Herbal and Alternative Medicines

- “Crude” dried herbs *
- “European” Phytopharmaceuticals
  - extracts
  - standardized extracts *
- Traditional Chinese Medicines*
- Ayurvedic Medicines
- Homeopathic Medicines*
- Functional Foods/Neutraceuticals *
- Biotherapeutic Agents/Probiotics **
Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan 7, 2001

<table>
<thead>
<tr>
<th>Product</th>
<th>M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ginkgo</td>
<td>99.1</td>
</tr>
<tr>
<td>ginseng</td>
<td>62.5</td>
</tr>
<tr>
<td>garlic</td>
<td>61.2</td>
</tr>
<tr>
<td>echinacea</td>
<td>58.4</td>
</tr>
<tr>
<td>st. John’s wort</td>
<td>56.0</td>
</tr>
<tr>
<td>saw palmetto</td>
<td>43.8</td>
</tr>
<tr>
<td>soy</td>
<td>41.0</td>
</tr>
<tr>
<td>valerian</td>
<td>16.8</td>
</tr>
<tr>
<td>kava</td>
<td>14.7</td>
</tr>
<tr>
<td>evening primrose</td>
<td>8.9</td>
</tr>
<tr>
<td>milk thistle</td>
<td>8.9</td>
</tr>
<tr>
<td>grapeseed</td>
<td>7.9</td>
</tr>
<tr>
<td>bilberry</td>
<td>6.2</td>
</tr>
<tr>
<td>black cohosh</td>
<td>6.2</td>
</tr>
</tbody>
</table>

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: 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
- Ginseng: adaptogen, tonic
- Grape seed: vision, antioxidant
- Evening primrose: dysmenorrhea
- Bilberry: vision, antioxidant
- Garlic: hyperlipidemias, hypertension
- Yohimbe: erectile dysfunction, aphrodisiac

Herbal Products Deemed Unsafe

- Aconite (Bushi)
- 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 meaningful 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
- Consumers must rely on often non-critical books and literature* not meaningful package insert
- Innovator companies have no protection
  - Example: Saccharomyces boulardii*
- Limited "official" monographs for herbals in USA (USP)

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Problems with Existing Regulations

- No GMPs for herbals (proposal by FDA)
- Huge problems in quality control
  - Example: Ginseng*
  - Other examples
- Unethical and criminal elements in industry
  - Example: Adulteration

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Ginseng Tests

6 major ginsenosides
adapted from Consumer Reports, Nov 1995

<table>
<thead>
<tr>
<th>Product</th>
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<tbody>
<tr>
<td>Walgreen’s Gin-Zing</td>
<td>7.6</td>
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<tr>
<td>Herbal Choice</td>
<td>6.8</td>
</tr>
<tr>
<td>American Ginseng</td>
<td>5.5</td>
</tr>
<tr>
<td>Natural Brand Korean</td>
<td>3.9</td>
</tr>
<tr>
<td>Ginsana (extract)</td>
<td>2.8</td>
</tr>
<tr>
<td>KRG Korean Red</td>
<td>2.2</td>
</tr>
<tr>
<td>Solgar Korean</td>
<td>2.0</td>
</tr>
<tr>
<td>Naturally Korean</td>
<td>0.2</td>
</tr>
<tr>
<td>Rite Aid Imperial</td>
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Ginseng Tests

6 major ginsenosides
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<tr>
<td>Nature Resource Korean</td>
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<tr>
<td>KRG Korean Red</td>
<td>2.1</td>
</tr>
<tr>
<td>Naturally Korean</td>
<td>0.3</td>
</tr>
<tr>
<td>Rite Aid Imperial</td>
<td>0.1</td>
</tr>
<tr>
<td>Herbal Harvest</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nature’s Herbs</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
### Content of Ginkgo Products (24/6)

- **Product** - **Flavone glycosides (%)** | **Terpene lactones (%)** | **$/tab**
- American Fare - 23.2 | 7.6 | .11
- Health Finest - 28.4 | 10.9 | .22
- Lichtwer Pharma Ginkai - 26.0 | 9.9 | .30
- Natural Brand - 24.3 | 8.8 | .21
- Nature Made - 29.1 | 6.4 | .40
- Nature's Resource - 25.8 | 9.2 | .18
- Nature's Way Ginkgold - 22.9 | 6.9 | .35
- Pharmaton BioGinko - 25.4 | 7.7 | .28
- Pharmaton Ginkoba - 23.7 | 8.2 | .31
- Rite Aid - 25.6 | 9.3 | .25
- Sundown - 22.2 | 9.8 | .23
- Your Life - 27.9 | 9.9 | .22

### Hypericin Content of St. John’s Wort

- **Product** - **% label claim** | **$/tab**
- Nature’s Resource - 140.0 | .15
- Nature’s Herbs - 131.4 | .17
- Safeway Select - 90.0 | .20
- Trader Joe’s - 82.2 | .09
- Kira - 87.8 | .30
- Enzymatic Therapy - 78.9 | .22
- Jarrow Formulas - 76.7 | .17
- Futurebiotics - 50.5 | .25
- Pure Source - 22.2 | .12
- Sundown Herbals - 20.0 | .11

### Phenolics Content of Echinacea

- **Product** - **Phenolics (%)** | **$/tab**
- American Fare - 4.5 | .12
- One-A-Day - 4.0 | .30
- Sunsource Echinex - 3.9 | .40
- Your Life - 3.2 | .18
- Nature’s Herbs - 2.5 | .10
- Celestial Seasonings - 2.3 | .27
- Rite Aid - 1.6 | .05
- Nature’s Way - 1.5 | .11
- Nature’s Fingerprint - 1.2 | .26
- Nature’s Made - 1.1 | .17
- Nature’s Resource - 1.1 | .07
- Sundown Herbals - 0.8 | .05

### Avoid

- Sundown Herbs - low tests for sjw, echinacea, ginkgo
- Nature’s Resource - low for echinacea, ginseng, high for sjw, variable ginkgo
- Nature’s Herbs - low for ginseng, echinacea, high for sjw
- Nature Made - low for echinacea, variable for ginkgo
- Rite Aid - low for echinacea, ginseng
- Nature’s Way - low for echinacea, but correct on ginkgo; ? recommendation

### New England journal of Medicine Bad Press

- “Contamination of Botanical Dietary Supplements by Digitalis lanata” Slifman et al. NEJM 339:806-811,1998 (dig. found in plantain containing products)
- “Butyrolactone-Induced Central Nervous System Depression after Ingestion of RenewTrient, a Dietary Supplement” LoVecchio et al. NEJM 339:847-848, 1998. (CNS depression)

### 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
Solutions

- New compendial monographs on herbals underway
  - Comission E Monographs English Translation-now available*
  - USP 12 completed and more under development (USP24-NF14)
  - Micromedex and other objective “use monographs”
  - WHO Monographs on Selected Medicinal Plants
- GMPs for Dietary Supplements are imminent

New USP Herbal Monographs - 9th supplement to the USP 24 - NF 19
- Chamomile
- feverfew
- powdered feverfew
- ginkgo
- oriental ginseng
- powdered oriental ginseng
- St. John’s wort
- powdered St. John’s wort
- saw palmetto
  - Others being developed: cranberry, echinacea, ephedra, American ginseng, Siberian ginseng, hawthorn, kava, licorice, milk thistle, nettle root, ginger, valerian, comfrey

- 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 St. John’s Wort vs SSRI vs placebo study
  - Saw Palmetto for PBH
  - pressure is on for FDA to “adapt” to CAM

Product Selection Issues

- Select “name brands” recognized for quality
  - ask companies for quality control data
- select “standardized” products that give potency per unit of the product
- 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

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

Some “Name Brand” Botanicals

Warner Lambert
Quanterra Mental® (ginkgo)
Quanterra Prostate® (saw palmetto)

Whitehall-Robins Healthcare
Centrum® botanicals line

Pharmaton (Boehringer Ingelheims)
Ginsana ® (ginseng)
Ginkoba ® (ginkgo)
Venastat ® (horse chestnut)
Movana ® (St. John’s wort)

SK-Beecham
Allana ® (valerian and hops)

Phyto-Phamica
Nature’s Way