Learning Objectives

- What is CAM?
- How does CAM differ from allopathic medicine?
- Who uses CAM?
- How are botanical remedies and CAM linked?
- What are the federal regulations concerning botanical CAM in US?
Stats!!!

- 80-85% of the world population is reliant on traditional forms of medicine (especially botanicals) for their primary source of healthcare (WHO, 2001)
- OTC use of herbal products and self-medication in the US and Europe is gaining popularity as more of the public seeks complementary and alternative medical solutions
- Less than 0.5% of the ~265,000 flowering plants on earth have been studied for their chemistry and medicinal applications (Cox and Balick 1994, Scientific American)
Use of TM for primary health care is extensive in some developing countries

Source: WHO Traditional Medicine Strategy, 2002-2005
Percentage of population which has used CAM at least once in selected developed countries

Source: WHO Traditional Medicine Strategy, 2002-2005
What is CAM?

• **Definition**: Group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.

• “complementary” refers to use of CAM **together** with conventional medicine

• “alternative” refers to use of CAM in **place of** conventional medicine
General Categories of CAM

• Natural products
  – This is where plants fit in!!
• Mind-body medicine
• Manipulative and body based practices
• Movement therapies
• Energy therapies
• Traditional healers
  – Plants again??
• Whole medical systems
  – Plants yet again??
Natural products

- Herbal medicine (botanicals)
- Vitamins
- Minerals
- Probiotics
- Other “dietary supplements”
  - Most popular: fish oils, Echinacea (NHIS, 2007)
- Uses: both disease management and health promotion
Mind-body medicine

• Focus on interactions among the brain, mind, body and behavior with the intent of improving health
  – Meditation
  – Yoga
  – Acupuncture
  – Deep breathing exercises
  – Guided imagery
  – Hypnotherapy
  – Progressive relaxation
  – Qi gong
  – Tai chi
Manipulative & Body-based Practices

• Focus on the structures and systems of the body, including bones and joints, soft tissues, circulatory and lymphatic systems
  – Spinal manipulation
    • Chiropractic/osteopathic manipulation
  – Massage therapy
Movement therapies

- Movement based approaches used to promote physical, mental, emotional, and spiritual well-being
  - Feldenkrais method
  - Alexander technique
  - Pilates
  - Trager psychological integration
Energy field therapies

- May be veritable or putative energy fields
  - Electromagnetic fields
    - Magnet therapy
    - Light therapy
  - Biofields
    - Qi gong
    - Reiki
    - Healing touch
Traditional healers

- Techniques specific to their culture and passed down generation to generation
- Based on indigenous beliefs, theories, and experiences – and may incorporate one or more aspects of other CAM fields (e.g. natural products and mind-body medicine)
Whole medical systems

• Complete systems of theory and practice that have evolved over time in different cultures and apart from conventional medicine
  – TCM
  – Ayurvedic medicine
  – Homeopathy
  – Naturopathy
History of CAM

• Man has used these treatments for a long time:
  – Natural products (iceman from Italian Alps)
  – Mind-body (TCM & Ayurvedic medicine >2,000 years ago)
  – Manipulative medicine (used by ancient Greeks, Romans and Egyptians)
## Modern trajectories

- DSHEA and dietary supplements
- Botanical drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Description/Allowed claims/Safety standard</th>
<th>Example</th>
<th>Regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs (New chemical entity)</td>
<td>Single compounds For use in the diagnosis, cure, mitigation, treatment or prevention of disease Risk/benefit analysis</td>
<td>Paclitaxel, morphine, aspirin</td>
<td>IND/NDA process FDA approval</td>
</tr>
<tr>
<td>Botanical drugs</td>
<td>Extracts from a single plant For use in the diagnosis, cure, mitigation, treatment or prevention of disease Risk/benefit analysis</td>
<td>Polyphenone E (topical), Senokot (over the counter)</td>
<td>IND/NDA process FDA approval</td>
</tr>
<tr>
<td>Dietary supplements (nutraceuticals)</td>
<td>Extracts intended to supplement diet Structure/function claims; health claims; nutrient claims Reasonable expectation of safety under the intended use</td>
<td>Garlic extract</td>
<td>Premarket FDA notification or history of use</td>
</tr>
<tr>
<td>GRAS ingredients (used mainly for botanical extracts)</td>
<td>Extracts which affect food characteristics Structure/function claims; health claims; nutrient claims Reasonable certainty of no harm; not subject to Delaney(^a) clause</td>
<td>Phytosterols</td>
<td>Self- affirmation by experts; pre-1958 common use</td>
</tr>
<tr>
<td>Food additives (used mainly for synthetic chemicals)</td>
<td>Purified mixtures which affect food characteristics Structure/function claims; health claims; nutrient claims Reasonable certainty of no harm; subject to Delaney clause</td>
<td>Carrageenan, hop extract</td>
<td>Premarket FDA approval</td>
</tr>
<tr>
<td>Medical and special dietary-use food</td>
<td>Food or food ingredient that provides a health benefit beyond the nutrients it contains; ingredients must be GRAS Structure/function claims; health claims; nutrient claims</td>
<td>Flavocoxid (Limbrel)</td>
<td>Self-affirmation by experts; physician supervised or prescribed</td>
</tr>
<tr>
<td>Cosmeceuticals</td>
<td>Extracts which supplement cosmetic products No claims Safety established by manufacturer</td>
<td>Aloe cream</td>
<td>None</td>
</tr>
</tbody>
</table>

\(^a\)The Delaney clause mandates absence of chemicals found to induce cancer in humans or animals.
Types of drugs derived from plants

- **Herbal drugs, drugs derived from parts of a medicinal plant**
  - These are known as herbal medicinal products, herbal remedies or phytomedicines
    - For example St. John’s wort, *Ginkgo biloba*, chamomile flowers, and senna leaves

- **Natural Products, or compounds isolated from nature**
  - These are pure chemical entities, often used in the form of licensed medicines. They may be produced synthetically but were originally discover from plants
    - For example: Morphine, Digoxin, Taxol, Quinine, and Caffeine

- **Nutraceuticals or dietary supplements**
  - Many foods are known to have beneficial effects on health
    - For example: Garlic, Flavonoid containing plants, carotenoid containing plants
• Herbal medicinal plants (HMP) sometimes are used as conventional pharmaceutical medicines but often are part of Complementary and Alternative Medicine (CAM)

• The use of herbal medicines and nutraceuticals is extensive, increasing and complex

• It is estimated that in both western Europe and the USA consumers expend around 4 billion dollars a year in HMP

• Plant-derived medicines are useful therapeutic options that in many cases have been proven to be clinically effective
**These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat cure or prevent any disease.**
• Pharmacists, nurses and general practitioners need to be competent in advising consumers on the safe, effective and appropriate use of all medicines including herbal medicines

• Health care professionals also need to be aware of the products and health care products that patients are taking

• HMPs purchases are made on a self selection basis from pharmacies, health-food stores, supermarkets, mail order and via the Internet

• With the exception of pharmacies there is no health professional on hand to provide information and advice to the patient on the use of HMP
Patient perceptions on the use of herbal medicinal products

- Appeal of products from “nature”
- Perception that products from “nature” are “safe” or at least “safer” than conventional products
- Philosophical views
- Religious views
- Less expensive
- They do not require prescription
- Give a sense of control to the patient
• Many individuals do not seek professional advise before purchasing or using HMP even when purchased in a pharmacy
• Consumers tend to rely on their own knowledge or they are guided by their friends, relatives or the popular media
• Not all individuals will inform their doctor or pharmacists if they are using HMPs
• Many health care professionals do not inquire their patients if they are using HMPs
• Consumers that seek professional advise often find that their pharmacist or doctor is not able to answer their questions
• In many cases information about certain HMP is not available
• At present time many health professionals are not adequately informed about HMP in particular about their quality, safety, and efficacy
• Purchasers of HMP include patients with serious medical conditions, e.g. cancer, HIV/AIDS, asthma, rheumatoid arthritis, etc.
• Pregnant and breastfeeding women, children, and patients taken conventional medications are also consuming HMPs
• Patients are unaware of the possibility of drug-herb interactions
# NATURAL PRODUCT- DERIVED DRUGS INTRODUCED (2000-2005)

<table>
<thead>
<tr>
<th>Source Organism Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terrestrial Plants</td>
<td>5</td>
</tr>
<tr>
<td>(apomorphine HCl, arteether, nitisinone, galanthamine HBr, tiotropium Br)</td>
<td></td>
</tr>
<tr>
<td>Terrestrial Microorganisms</td>
<td>5</td>
</tr>
<tr>
<td>(amrubicin HCl, biapenem, caspofungin acetate, cefditoren pivoxil, daptomycin, ertapenem, everolimus, gemtuzumab ozogamicin, micafungin Na, miglustat, mycophenolate Na, pimecrolimus, rosvuastatin Ca, telithromycin, tigecycline)</td>
<td></td>
</tr>
<tr>
<td>Marine Organisms</td>
<td>1</td>
</tr>
<tr>
<td>(ziconotide)</td>
<td></td>
</tr>
<tr>
<td>Terrestrial Invertebrate and Vertebrate Animals</td>
<td>2</td>
</tr>
<tr>
<td>[bivalirudin; exenatide (synthetic versions)]</td>
<td></td>
</tr>
</tbody>
</table>

Botanical Products

• Botanical products are finished, labeled products that contain vegetable matter as ingredients.

• A botanical product may be a food (including a dietary supplement), a drug (including a biological drug), a medical device (e.g., gutta-percha), or a cosmetic under the Act. An article is generally a food if it is used for food (21 U.S.C. 312(f)(1)).

• Whether an article is a drug, medical device, or cosmetic under the Act turns on its "intended use" (21 U.S.C. 312(g)(1)(B) and (C), (h)(2) and (3), (i)).

• "Intended use" is created by claims made by or on behalf of a manufacturer or distributor of the article to prospective purchasers, such as in advertising, labeling, or oral statements.

http://www.fda.gov/cder/guidance/4592fnl.htm
Botanical Drugs

• A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC indication may be eligible for consideration in the OTC drug monograph system.

• Currently, there are several botanical drugs, including cascara, psyllium, and senna, that are included in the OTC drug review.

• For a botanical drug substance to be included in an OTC drug monograph, there must be published data establishing general recognition of safety and effectiveness, usually including results of adequate and well-controlled clinical studies (see §§ 314.126(b) and 330.10).

• Requirements related to safety, effectiveness, and labeling for drugs to be included in an OTC drug monograph are set forth in 21 CFR part 330.
1st Botanical Drug approved in the USA

FDA approved to treat both existing and newly emerging external genital and perianal warts

- Veregen® (sinecatechins) Ointment, 15% is a botanical drug product for topical use.
- The drug substance in Veregen® is sinecatechin.
- Sinecatechin is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze (Theaceae) and is a mixture of catechins and other green tea components.
Significance

• This is the first time that a complex herbal preparation has been approved by FDA as prescription drug in more than half a century

• In 1962 Congress approved the Kefauver-Harris* Amendment to the Federal Food, Drug, and Cosmetic Act. in response to the thalidomide tragedy “drugs must be both safe and effective”

• Most botanical drugs marketed at that time disappeared in the United States

*US representative Oren Harris from Arkansas
How many more in the pipeline?

- 242 pre-NDAs and NDAs (June, 05)
  - 1-2 new pre-NDA or NDA submissions per month
  - 192 INDs, 50 pre-INDs
    - 128 active files
    - 64 inactive files

IND = Investigation New Drug
NDA = New Drug Application
DSHEA: The Dietary Supplement Health and Education Act of 1994

- In the early 1990s, Congress began considering two bills to greatly strengthen the ability of federal agencies to combat health frauds. One would have increased the FDA's enforcement powers as well as the penalties for violating the Food, Drug, and Cosmetic. The other would have amended the Federal Trade Commission Act to make it illegal to advertise nutritional or therapeutic claims that would not be permissible on supplement labels. During the same period, the FDA was considering tighter regulations for these labels.

- Alarmed by these developments, the health-food industry and its allies urged Congress to "preserve the consumer's freedom to choose dietary supplements." Industry leaders warned retailers that they would be put out of business. Consumers were told that unless they took action, the FDA would take away their right to buy vitamins. These claims, although bogus, generated an avalanche of communications to Congress.

- The end result was passage of DSHEA (Sponsored by Senators Hatch and Kennedy, and Congressman Bill Richardson), which defined "dietary supplements" as a separate regulatory category and liberalized what information could be distributed by their sellers. DSHEA also created an NIH Office of Dietary Supplements and directed the President to appoint a Commission on Dietary Supplement Labels to recommend ways to implement the act. The Commission's final recommendations were released on November 24, 1997.
Dietary Supplements

• Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), an orally ingested product that meets the definition of a "dietary supplement" under section 201(ff) of the Act may be lawfully marketed with a statement that

  • (1) claims a benefit related to a classical nutrient deficiency disease (and discloses the prevalence of the disease in the United States),

  • (2) describes how the product is intended to affect the structure or function of the human body,

  • (3) characterizes the documented mechanism by which the product acts to maintain such structure or function, or

  • (4) describes general well-being from consumption of the product (section 403(r)(6)(A) of the Act).

• A dietary supplement statement of the type described above may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases (section 403(r)(6) of the Act).
Common Botanical Dietary Supplements sold in the USA

- Goldenseal: *Hydrastis canadensis* L., Ranunculaceae
- German Chamomile: *Matricaria recutita* L., Asteraceae
- Milk thistle: *Silybum marianum* (L.) Gaertn., Asteraceae
- Fenugreek: *Trigonella foenum-graecum* L., Fabaceae
- Ephedra: *Ephedra sinica* Stapf, Ephedraceae
- Black Cohosh: *Cimicifuga racemosa* (L.) Nutt., Ranunculaceae
- Echinacea: *Echinacea purpurea* (L.) Moench, Asteraceae
- Saw Palmetto: *Serenoa repens* (W. Bartram) Small, Arecaceae
- Ginseng: *Panax ginseng* C.A. Mey., Araliaceae
- Ginkgo: *Ginkgo biloba* L., Ginkgoaceae
- St. John’s Wort: *Hypericum perforatum* L., Hypericaceae
- Valerian: *Valeriana officinalis* L., Caprifoliaceae
- Garlic: *Allium sativum* L., Amaryllidaceae
Dietary Supplements

• Although the general public often considers botanical supplements *natural and safe* alternatives to conventional synthetic pharmaceuticals, there is relatively little scientific evidence behind this belief.

• In 1999 the global market for herbal supplements exceeded **US$15 billion**, with a US$7 billion market in Europe, US$2.4 billion in Japan, US$2.7 in the rest of Asia and US$3 billion in North America. Most of the published studies suggest that the use of herbal medicine is widespread, with as many as three in ten Americans using botanical remedies in a given year.
Dietary Supplements

• The demand for dietary supplements is driven by a variety of factors that include an aging population, a growing trend to self-medicate, mistrust in the conventional medical establishment, increasing difficulty to obtain health insurance, and the perception that natural is healthy and that plant products are safe.

• Botanical supplements are frequently criticized for poorly proven efficacy and safety, lack of standardization and quality standards.
Key Concepts

• CAM is multifaceted and refers to an array of diverse medical practices

• In the Western world – our primary use of plant-based CAM comes in the form of “dietary supplements”
  – More botanical drugs in the future?

• Regulatory actions dictate much of how we use CAM in the US