



Medicinal Chemistry 420 (2 credits)

Alternative and Complementary Medicines

Thursdays 1:30-3:20 Room T639

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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.

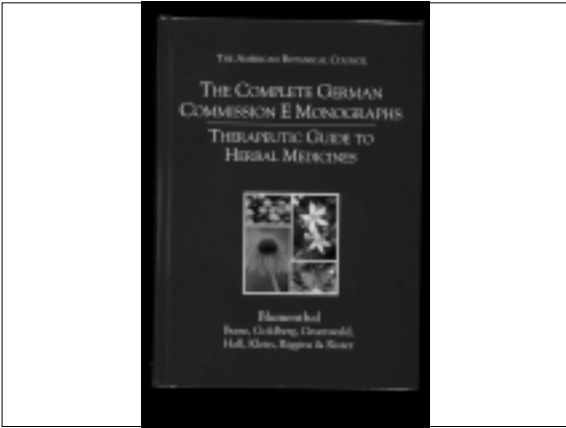
- available approximately one week before final exams
- due by 5pm on December 14.
- exam will be based on lecture material presented in class.

Attendance at the lectures.

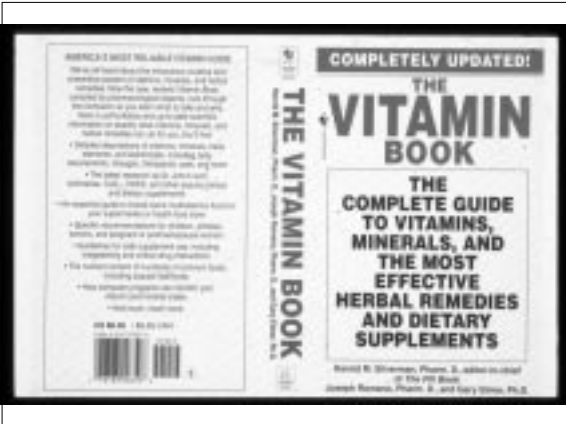
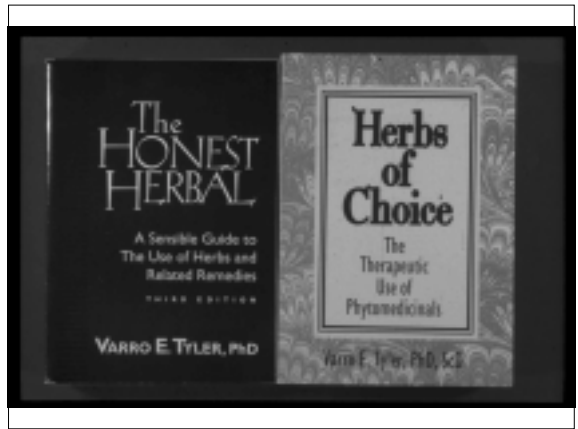
- Let Dr. Elmer or Mr. Lampe know if you will miss
- Occasional attendance checks will be taken.
 - There will be no midterm exams or quizzes.
 - Grades are on a credit/no credit format

General References on Herbal Products (comprehensive monographs)

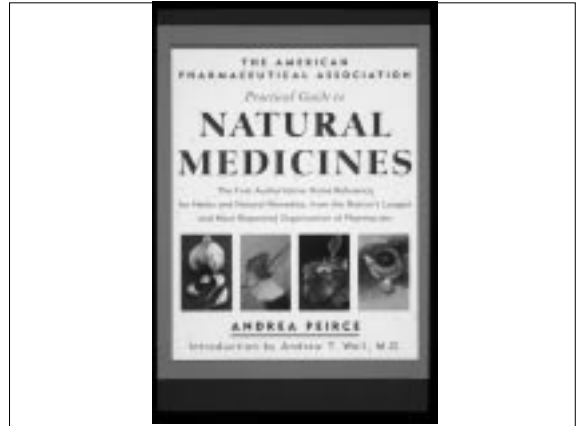
- The Review of Natural Products. *Facts and Comparisons Publishing Group*, St. Louis MO. 2000. Looseleaf format updated regularly in typical F&C fashion. Available at the UW Bookstore (Health Sciences) for \$99 including updates.
- Natural Medicines Comprehensive Database Excellent database available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



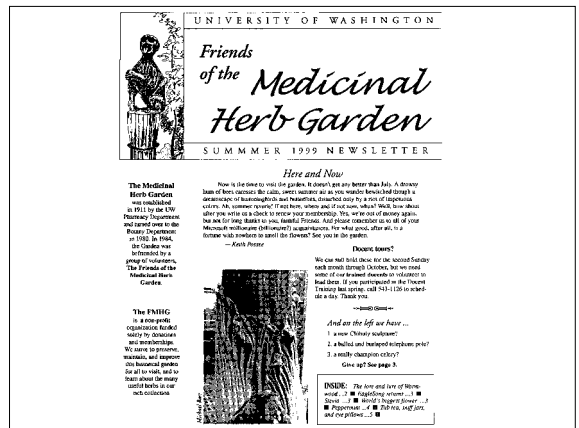
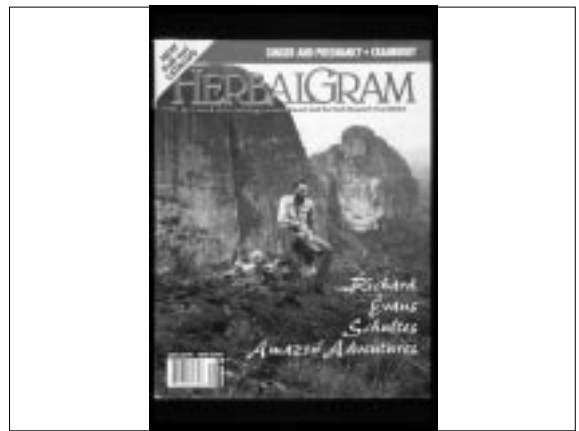
- General References on Herbal Products**
- **Tyler's The Honest Herbal.** Foster S and Tyler VE, Fourth Edition. *Haworth Press*, 1999. Excellent. Organized alphabetically. Referenced. Paperback. \$20
 - **Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals.** Robbers JE and Tyler VE. *Haworth Press*, 1998. Organized by disease state. Referenced. \$40
 - **The Vitamin Book.** Silverman HM, Romano J, Elmer G. *Bantam Books*, New York. 1999. Includes chapters on herbals and other dietary supplements. Objective treatment of the subject in an inexpensive paperback. Referenced. \$6.50



- References (continued)**
- **Rational Phytotherapy: A Physician's Guide to Herbal Medicine.** Schulz V, Rudolf H, Tyler VE. *Springer Verlag* 1998. Updated German book now in English. Emphasis on therapeutics with herbals. Excellent.
 - **The American Pharmaceutical Association Practical Guide to Natural Medicines.** Peirce, A. *William Morrow and Company*, NY. 1999. Very well done. Well documented and referenced. Written for the public but useful for all.



- Periodicals and Newsletters on Herbal Products**
- “HerbalGram” published by the American Botanical Council and the Herb Research Foundation; PO Box 201660, Austin TX 78720
 - “The Source” Association of Natural Medicine Pharmacists newsletter; 8369 Champs de Elysses, Forestville CA 95436.
 - “Friends of the Medicinal Herb Garden Newsletter” newsletter concerning the UW Medicinal Herb Garden
<http://www.nnlm.nlm.nih.gov/pnr/uwmhg/index.html>



Useful Internet Web sites

- The Natural Pharmacist. Great site with objective herbal info. With refs. <http://www.tnp.com/home.asp>
- 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>
- UW Healthlinks-Alternative Medicine. Links to many useful sites. http://healthlinks.washington.edu/clinical/alt_med.html
- University of Washington Medicinal Herb Garden. Home page includes access to photos of selected medicinal plants and a map of the garden. <http://www.nnlm.nlm.nih.gov/pnr/uwmhg/index.html>
- Association of Natural Medicine Pharmacists web site. Natural medicine information for the health professional. Useful site. <http://www.anmp.org/>
- American Botanical Council home page. Links to other sites of interest. <http://www.herbalgram.org>

Useful Internet Web sites

- Herbmed. A product of the Alternative Medicine Association. Monographs on popular herbal products. Not bad. <http://www.herbmed.org>
- American Herbal Products Association. Trade Association with links to member companies and publications. Useful. <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/index.html>
- Consumer Lab. A private testing service that is testing botanicals and other dietary supplements for accuracy in meeting label claims. There is a fee for access to results. <http://www.consumerlab.com>

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 allopathic drugs

ref. Eisenberg et al. *N.Engl.J.Med.* 1993;328:246-252; *JAMA* 1998;280:1569-1575

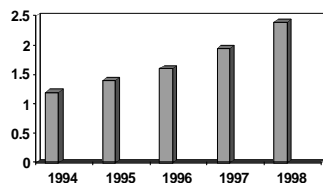
Another Survey on Public Use of Alternative Medicines

- 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)
- ref: Oldendick et al. *S. Med. J.* 93:375-381,2000

Trends

US Retail Sales of Herbals

(adapted from "Packaged Facts", 1998 and Pharmacy Today)



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)

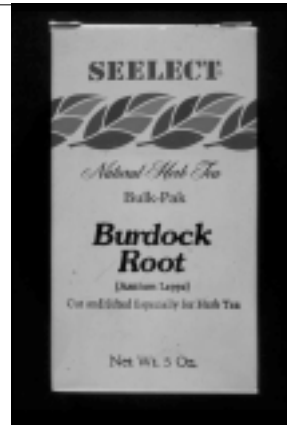
•Men (saw palmetto, pygeum)

•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 Herbs - Mass Market, 52 weeks ending Jan7,2001
from Food, Drug, and Mass Market Retail, HerbalGram vol 51

Product	M \$
- ginkgo	99.1
- ginseng	62.5
- garlic	61.2
- echinacea	58.4
- st. John's wort	56.0
- saw palmetto	43.8
- soy	41.0
- valerian	16.8
- kava	14.7
- evening primrose	8.9
- milk thistle	8.9
- grapeseed	7.9
- bilberry	6.2
- black cohosh	6.2

Top 20 Selling Herbs (continued)- Mass Market, 52 weeks ending Jan7,2001
from Food, Drug, and Mass Market Retail, HerbalGram vol 51

Product (continued)	M \$
- Pycnogenol	3.2
- Green Tea	3.2
- Ginger	2.2
- Yohimbe	2.1
- Feverfew	1.6
- Hawthorn	1.5
- Multi-herbs	2.6
- All other	60
- Total	591

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 uses
• ginseng	adaptogen, tonic
• grape seed	vision, antioxidant uses
• Evening primrose	dysmenorrhea
• Bilberry	vision, antioxidant uses
• Garlic	hyperlipidemias, hypertension
• yohimbe	erectile dysfunction, aphrodesiac

Herbal Products Deemed Unsafe

• Aconite (Bushi)	• Germander
• Belladonna	• Kombucha Tea
• Blue Cohosh	• Ma Huang (ephedra)
• Borage	• Lobelia
• Broom	• Pennyroyal Oil
• Calamus	• Poke Root
• Chaparral	• Sassafras
• Coltsfoot	• Scullcap
• Comfrey	• Tansy Ragwort
• Ephedra (Ma Huang)	• 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)

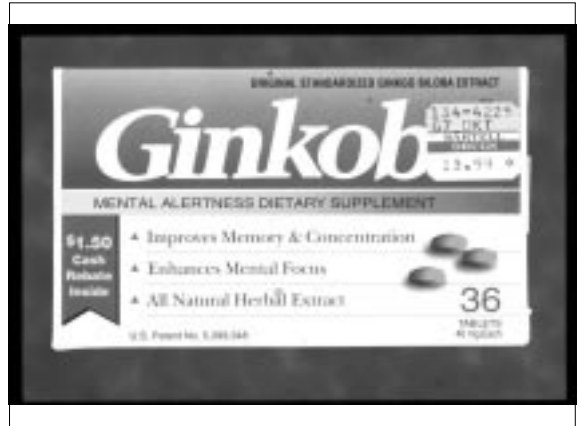
Regulatory Issues

- **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)

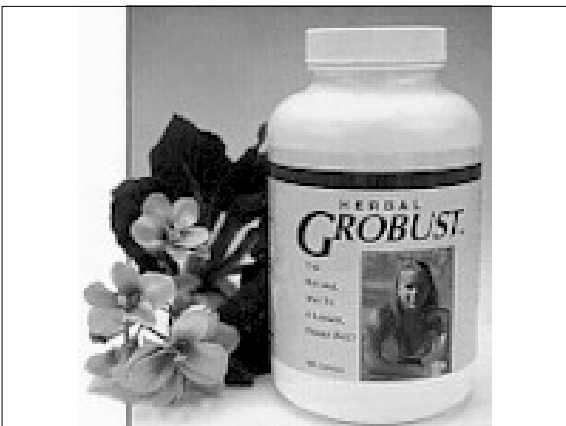
- dietary supplements are not considered foods, food supplements or drugs
- no "therapeutic claims" unless approved by FDA
- no "health claims" unless approved by FDA
- limited "structure/function" claims allowed if there is some evidence to support them
 - examples of structure/function claims
- FDA 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 (thru MedWatch and Special Nutritionals Adverse Event Monitoring System)




“When I started on GroBust I measured myself. After two weeks on GroBust I could feel a difference, so I measured myself again. Sure enough I had already grown a full 1/2 inch! I have been on the product for 3 1/2 months now and I am 4 inches larger! Thank you for this wonderful natural alternative to surgery!” — J.S., St. George, Utah



Just listen to what Herbal V has done for the sex lives of people like you!

 "On a scale of 1 to 10, it's a 15. Electrifying. It's like a wonder pill!"
— Bill B., Bellwin, Missouri

 "I haven't had sexual relations in 11 years. Then with Herbal V it was... wow! It works again!"
— Brian Q., Sunrise, Florida

- 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 noncritical books and literature* not meaningful package insert**
 - **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**
 - example: ginseng*
 - example: contamination of plantain with dig* (NEJM 339:839-841,1998)
 - other examples
 - **Unethical and criminal elements in industry**
 - example: adulteration

Ginseng Tests
6 major ginsenosides
adapted from Consumer reports, Nov 1995

– Product-	-%-
• Walgreen's Gin-Zing	7.6
• Herbal Choice	6.8
• American Ginseng	5.5
• Natual Brand Korean	3.9
• Ginsana (extract)	2.8
• KRG Korean Red	2.2
• Solgar Korean	2.0
• Naturally Korean	0.2
• Rite Aid Imperial	0.2

Ginseng Tests
6 major ginsenosides
adapted from Cui et al., Lancet 344:134,1994

– Product-	% --
• Walgreen's Gin-Zing	7.5
• American Ginseng	5.4
• Natual Brand Korean	3.7
• Herbal Choice	3.1
• Ginsana (extract)	3.1
• Nature Resource Korean	2.1
• KRG Korean Red	2.1
• Naturally Korean	0.3
• Rite Aid Imperial	0.1
• Herbal Harvest	<0.01
• Nature's Herbs	<0.01

Content of Ginkgo Products (24/6)

adapted from Consumer's Reports, March, 1999

– 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
• Pharmanex 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

adapted from LA Times, Aug 31,1998

– 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

adapted from Consumer's Reports, March, 1999

– 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)
- **“Adulterants in Asian Patent Medicines”** Ko, R. J. NEJM 339:847,1998. (83/260 products adulterated)
- **“Butyrolactone-Induced Central Nervous System Depression after Ingestion of RenewTrient, a Dietary Supplement”** LoVecchio et al. NEJM 339:847-848, 1998. (CNS depression)
- **“Alternative Therapies for the Treatment of Childhood Cancer”** Coppes et al. NEJM 339:846,1998.
- **“Alternative Medicine - The risks of untested and unregulated remedies”** Editorial NEJM 339:839-841,1998.

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**
 - Commission 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**

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)

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**

