Medicinal Chemistry 525
(2 credits)
Alternative and Complementary Medicines

Thursdays 1:30-3:20 Room T733

http://courses.washington.edu/medch525/

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Lecture Topics

• Sept 25	Introduction	Gary Elmer
• Oct 2	Herbal Products 1 (M-Z)	Gary Elmer
	Tour of the Medicinal Herb Garden (A-L)	Doug Ewing
• Oct 9	Herbal Products 1 (A-L)	Gary Elmer
	Tour of the Medicinal Herb Garden (M-Z)	Doug Ewing
• Oct 16	Herbal Products 2	Gary Elmer
• Oct 23	Herbal Products 3	Gary Elmer
• Oct 30	Herbal Products 4	Gary Elmer
	Other Dietary Supplements	
• Nov 6	Herbal-Drug Interactions	Gary Elmer
• Nov 13	Probiotics	Gary Elmer
	Homeopathic Products	Gary Elmer
• Nov 20	Toxic Herbals	Sid Nelson
• Nov 27	Thanksgiving Holiday	
• Dec 4	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, fish oil, glucosamine, chondroitin, melatonin, CoQ10,and homeopathic products.
  - If taking Pharm 500, the guidelines specified for the research paper for this course and a 3.0 grade or better on the paper will be accepted. See http://courses.washington.edu/pharm500.
  - If not taking 500, write the paper following guidelines for the paper for Pharm 500 (see above) except you do not need to indicate the database search source location of your cited references.
  - You will need to read and cite results from the PRIMARY literature for credit for the paper. SOME secondary citations are OK to use.
  - Due date will be Nov 21.

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 one quiz with the lowest score.
- 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 Comparison Publishing Group*, St. Louis MO. 2004. Available at the UW Bookstore. Also available online through the UW at (http://healthlinks.washington.edu/)

- Natural Medicines Comprehensive Database Excellent database, the "gold standard", available in print version ($92/yr) or online ($92/yr). Online updated "daily" Available online at UW at (http://healthlinks.washington.edu/)

- Natural Standard. Excellent database with an expert editorial board. $99/year. Online available at UW at http://healthlinks.washington.edu/

Books

- Desk Reference to Nature's Medicines Stephen Foster and Rebecca L. Johnson. National Geographic 2006 $40

- Essential Guide to Herbal Safety
  Simon Mills and Kerry Bone.. 2005
  Elsevier – excellent.
  $65

- The ABC Clinical Guide to Herbs
  By M. Blumenthal, et al. 2003. ABC Press. $70.
-

Books (continued)

- **Rational Phytotherapy: A Reference Guide for Physicians and Pharmacists**. Schulz, Hansel, Blumenthal and Tyler. *Springer Verlag.* 2005. Emphasis on therapeutics with herbals. Excellent. $60

- **Natural Therapeutics Pocket Guide, 2nd edition**. Krinsky, DL et al. APhA. 2003. Very well done. Has disease conditions as well as monographic information. $32

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.

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 $29/yr. The subscription will also provide you access to The Natural Products Encyclopedia, an excellent database of monographs on herbals and other dietary supplements. www.consumerlab.com**
- **NIH Nat Center for Complementary and Alternative Medicine (NCCAM). Programs and information of this important NIH program. 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. CE programs. http://www.anmp.org/**
- **American Botanical Council home page. Links to many sites of interest. http://www.herbalgram.org**

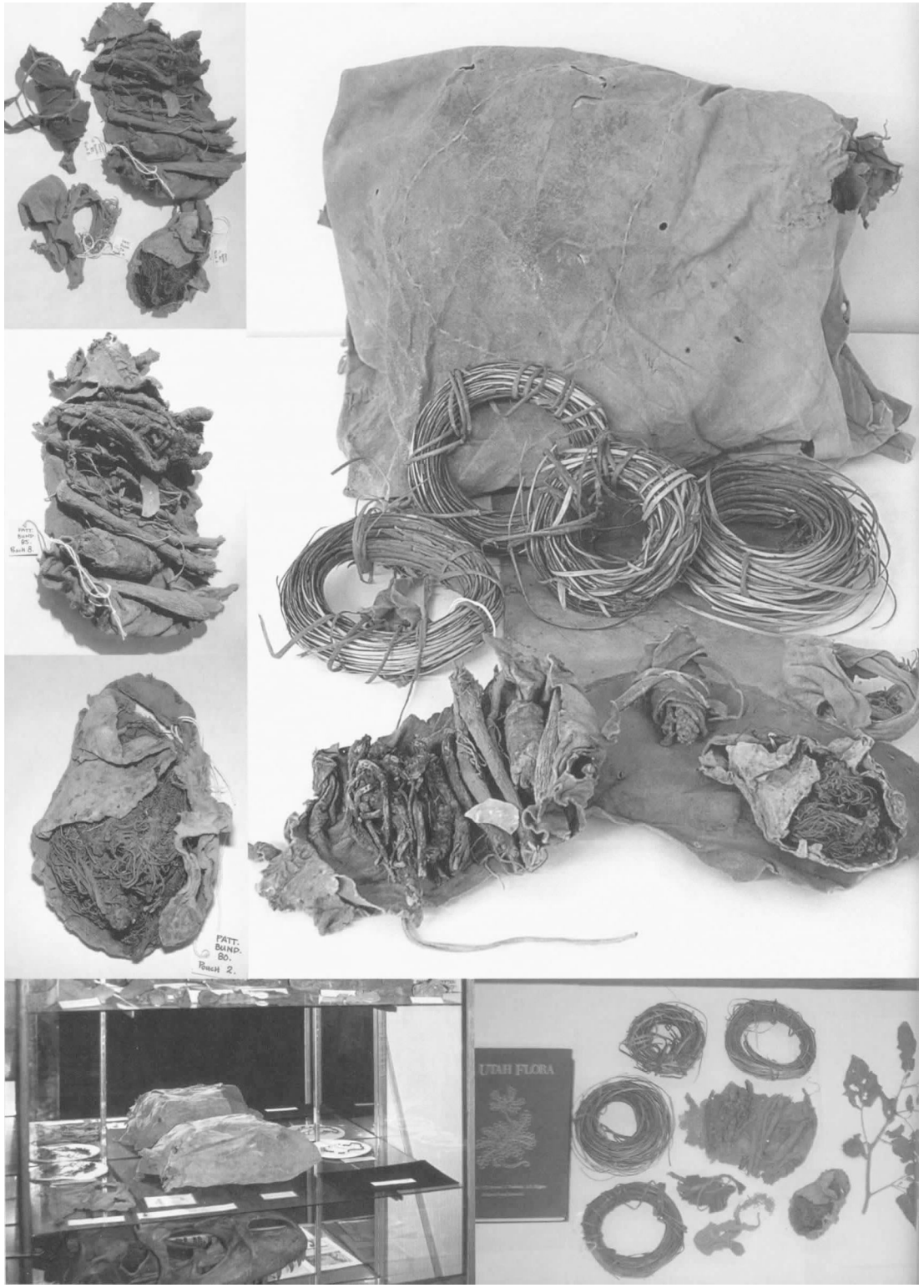
Useful Internet Web sites

- **Office of Dietary Supplements, NIH. Mandated by DSHEA, their mission is to promote research and provide objective information on dietary supplements. Link to IBIDS database on scientific literature on dietary supplements and other databases. Use is free to all. . 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/**
- **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**

Free Electronic Newletters

- Dietary Supplement/Food Label News from the FDA http://www.cfsan.fda.gov/~dms/infonet.html
- Nutrition News Focus http://www.NutritionNewsFocus.com
- Arbor Clinical Nutrition Updates (Dr. Tony Heilman) http://arborcom.com

1000 year old "Patterson Bundle", a Native American bundle of medicinal herbs. HerbalGram 2002;55:35-41



Herbal Products

- sales of about $14 billion $ in USA for dietary supplements
- sales of about 5 billion $ in USA for botanicals
- Mass market herbal sales increased dramatically in the 1990s but have dropped in recent years. Total sales from all channels have generally shown a slow increase.
- In 1990 5.8% used “alternative medicines”
- In 2002, 25.2% used “alternative medicines”
- most do not tell their “traditional” provider what they are taking and many take alternative and complementary products together with alopathic drugs

ref. Eisenberg et al. *JAMA* 1998;280:1569-1575; HerbalGram 2006;71:64.

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

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

Table 1. Enrollees in CHS Study [a]

Total enrolled: 5849
White: 4925 (84)
Black: 924 (16)
Male: 2478 (42)
Female: 3371 (58)

Study period	1	2	3	4
Total users	4373	4351	3919	3561
Rx users	3994 (91)	3891 (89)	3533 (90)	3259 (92)
CAM users	278 (6)	295 (7)	504 (13)	533 (15)
Vitamin/mineral users	1713 (39)	1707 (39)	1678 (43)	2081 (58)
OTC users	2635 (60)	2720 (63)	2263 (58)	2219 (62)
Rx plus CAM	238 (5)	243 (6)	411 (11)	463 (13)
Rx, CAM, OTC	264 (6)	270 (6.2)	459 (11.7)	511 (14.4)

[a] The number in parentheses is the percent of the enrolled

Elmer et al. Ann Pharmacother (in press for Oct 07)

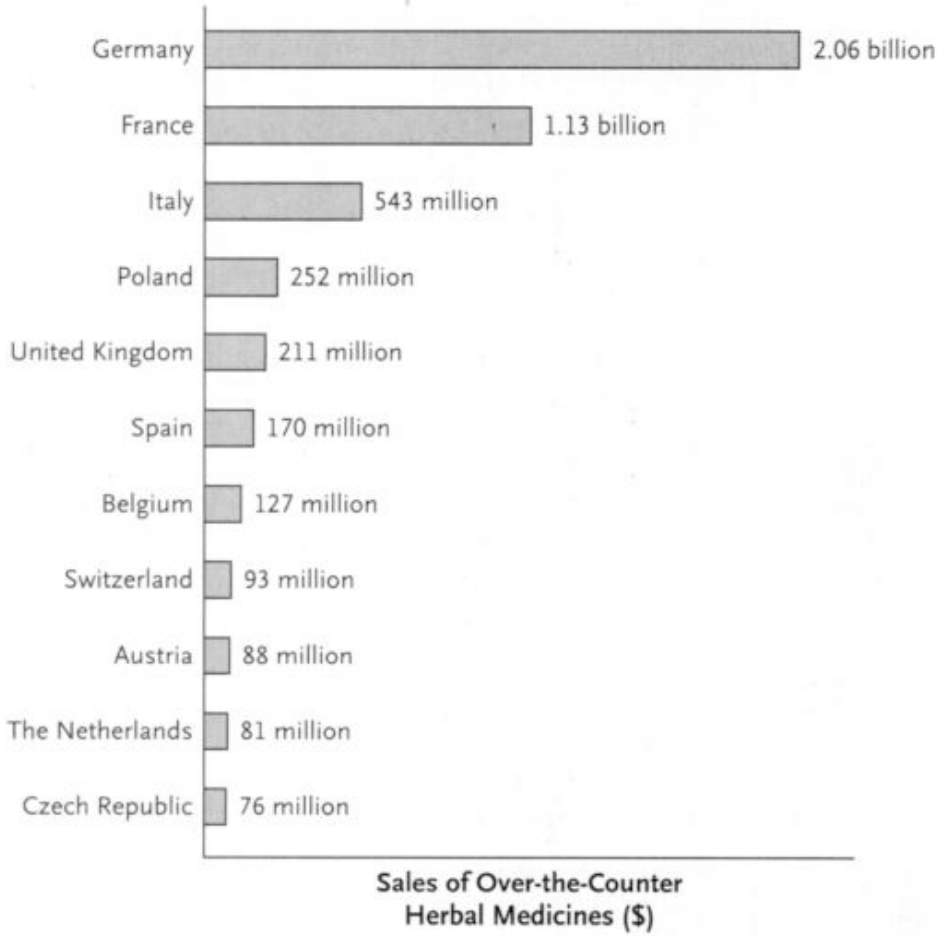
Elmer et al. Ann Pharmacother. 2007;40:1617-24.

Table 3 All users of the top 20 CAM products by race [a]

CAM Product	All (%)	Black (%)	White (%)
Garlic	5.86	7.76	5.48
Ginkgo	4.20	3.34	4.37
Glucosamine	2.45	0.48	2.85
Lecithin	1.92	0.36	2.23
Cod Liver Oil	1.82	4.30	1.33
Ginseng	1.11	1.67	1.00
CoQ10	0.97	0.24	1.12
Alfalfa	0.91	0.48	1.00
Antioxidant	0.91	0.72	0.95
Chromium picolinate	0.85	0.24	0.97
melatonin	0.65	0.48	0.69
Saw palmetto	0.63	0.36	0.69
Echinacea	0.61	0.84	0.57
Aloe	0.53	0.48	0.55
St. John's wort	0.51	0.24	0.57
Chromium	0.49	0.36	0.52
Bilberry	0.48	0.24	0.52
l-lysine	0.42	0.12	0.47
Bee pollen	0.36	0.36	0.36
Shark cartilage	0.32	0.36	0.31

[a] n=5052 for all participants; n=838 for blacks; n=4214 for whites

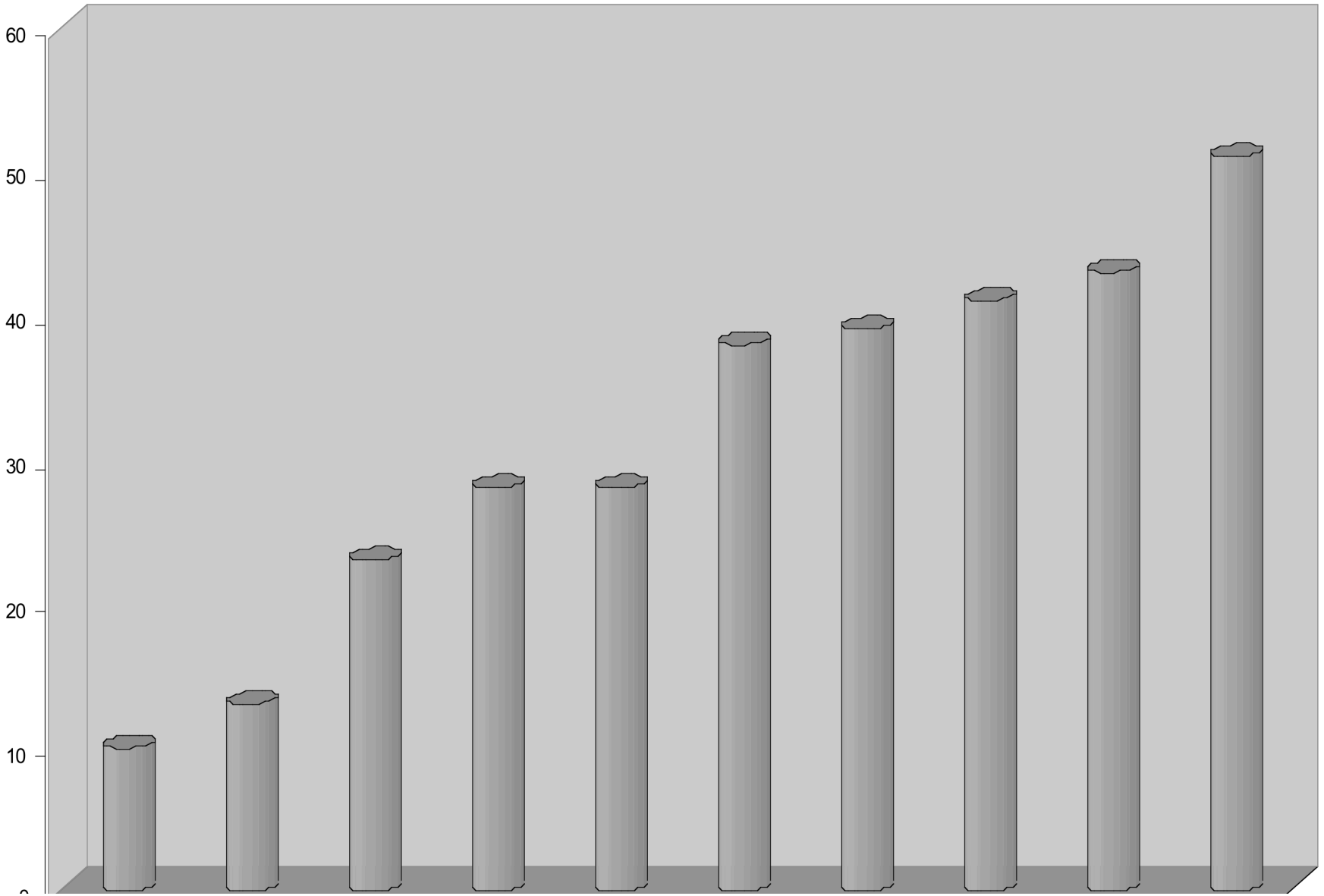
Elmer et al. Ann Pharmacother (in press for Oct 07)



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.

Where People Get Info (Prevention 1999)



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)

Types of Herbal and Alternative Medicines

- “Crude” dried herbs *
- “European” Phytopharmaceuticals
  - extracts
  - standardized extracts *
- Traditional Chinese Medicines*
- Ayurvedic Medicines
- Homeopathic Medicines*
- Functional Foods/Nutraceuticals *
- Probiotics **
- “other” dietary supplements (e.g. melatonin)

Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	M $	% change	rank in 2006
1. soy	25	-17	1
2. cranberry	24	+24	3
3. garlic	20	-13	2
4. ginkgo	18	+12	5
5. saw palmetto	17	- 6	4
6. echinacea	16	- 9	6
7. black cohosh	09	-0.5	8
8. milk thistle	09	-0.4	7
9. ginseng	08	+ 3	10
10. St. John's wort	08	- 6	9
11. Green tea	05	- 7	11
12. Evening primrose oil	04	- 9	12
13. valerian	03	- 9	13
14. Horny goat weed	02	- 2	14

Red indicates risk for drug interactions

Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	**M $**	**% change**	**rank in 2004**
– 15. bilberry	02	- 9	15
– 16. grape seed	02	- 9	16
– 17. Yohimbe	01	-15	17
– 18. red clover	01	-13	18
– 19. Horse chestnut seed	01	-21	19
– 20. ginger	0.7	-20	20
Total (all herbs)	268	+7.6	

Red indicates potential risk for drug interactions

Note: total herbal sales are estimated at $4.7 billion

The above figures include only sales from food stores, drug stores, and mass market retailers but with Wal-Mart figures not included. It does not include warehouse buying clubs (Costco), convenience stores, natural foods stores, multilevel marketers, health professional sales, mail order or internet sales.

Total Estimated Herb Sales for All Channels

Year	M $	% change
1996	2990	21
1997	3557	19
1998	4002	13
1999	4110	3
2000	4260	4
2001	4397	3
2002	4276	-3
2003	4178	-2
2004	4320	3
2005	4410	2
2006	4590	4.1
2007	4791	4.4

Ref: HerbalGram 2008;78:61-62

Herb Sales by Channel 2007

Channel	M$	% change
Mass market	752	5.5
Natural and health food	1537	2.9
Direct sales	2501	5.0
Total	4790	4.3

Ref: HerbalGram 2008;78:61-62

Herb Sales by Category 2007

	M$	% change
Single Herbs	3090	4.6
Combination Herbs	1701	3.9
Total	4791	4.4

Ref: HerbalGram 2008;78:61-62

Kaufman et al. JAMA 2002;287:337-344

Table 3. Ten Most Commonly Used Herbals/Supplements: 1-Week Prevalence, %, by Sex and Age*

		Men			Women			
Rank	Herbal/Supplement	18-44 y (n = 528)	45-64 y (n = 388)	≥65 y (n = 243)	18-44 (n = 595)	45-64 y (n = 485)	≥65 y (n = 351)	Total (N = 2590)
1	Ginseng	4	4	<1	2	5	2	3.3
2	*Ginkgo biloba* extract	<1	4	1	1	4	5	2.2
3	*Allium sativum*	<1	4	4	1	3	3	1.9
4	Glucosamine	<1	2	4	<1	5	4	1.9
5	St. John's wort	<1	2	0	2	3	<1	1.3
6	*Echinacea augustifolia*	1	1	0	1	3	<1	1.3
7	Lecithin	<1	<1	1	1	3	1	1.1
8	Chondroitin	<1	1	1	0	3	2	1.0
9	Creatine	4	0	0	0	0	0	0.9
10	*Serenoa repens*	1	1	4	0	<1	0	0.9
	Any use	12	17	11	10	23	14	14

*Percentages weighted according to household size.

Useful Herbal Products

(some evidence in support of uses)

• **Echinacea**	**immune stimulant**
• **Saw Palmetto**	**BPH**
• **Ginkgo**	**circulation**
• **Milk Thistle**	**liver**
• **Ginger**	**nausea**
• **Chamomile**	**indigestion**
• **Fever Few**	**migraine**
• **St. John's Wort**	**mild/mod depression**
• **Hawthorn**	**heart/circulation**
• **Soy**	**menopause symptoms**
• **Kava**	**anxiolytic**
• **Black cohosh**	**menopause symptoms**
• **Green tea**	**stimulant (antioxidant)**
• **Cranberry**	**UTI prevention**

Possibly Useful Herbal Products

(less evidence or conflicting evidence)

• **pycnogenol**	**vision, antioxidant uses**
• **ginseng**	**adaptogen, tonic**
• **grape seed**	**vision, antioxidant uses**
• **Evening primrose**	**dysmenorrhea, other**
• **Bilberry**	**vision, antioxidant uses**
• **Garlic**	**hyperlipidemias, hypertension, heart**
• **yohimbe**	**erectile dysfunction**
• **Valerian**	**sleep**

Herbal Products Deemed Unsafe

- Aconite (Bushi)
- Aristolochia sp.
- Belladonna
- Blue Cohosh
- Borage (internal)
- 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 Ammendments 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)

- 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

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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**
- **just passed in 2007, the Adverse Event Requirement bill (AER Bill). Now manditory reporting to FDA of serious adverse events for supplements and OTC products**

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)**

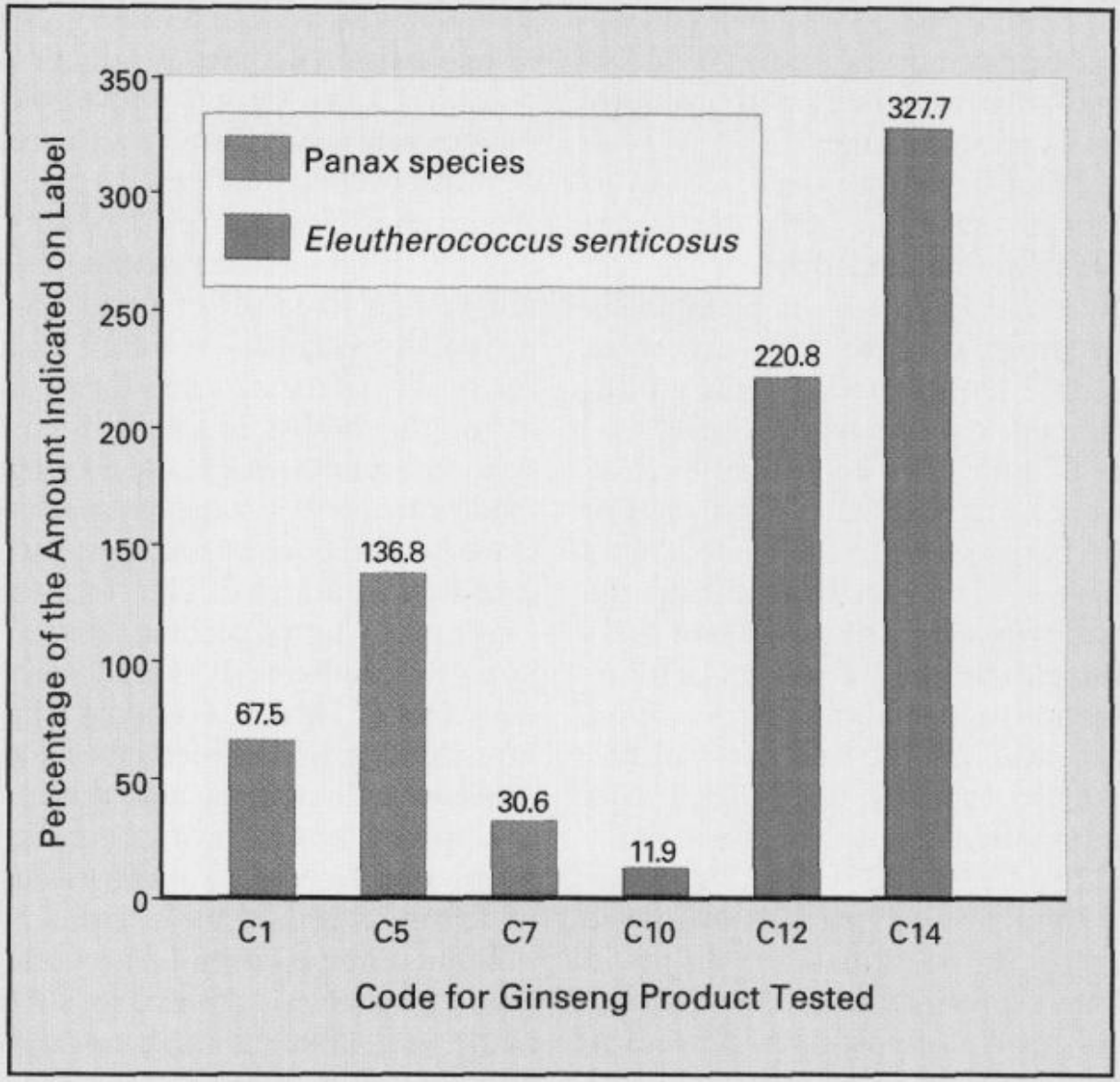
Problems with Existing Regulations

- **Still huge problems in quality control**
- **Unethical and criminal elements in industry**
  - **example: adulteration**

Hypericin and Hyperforin in Eight Brands of St. John's Wort

De Los Reyes and Koda, Am J Health-syst Pharm 59:545-547.2002

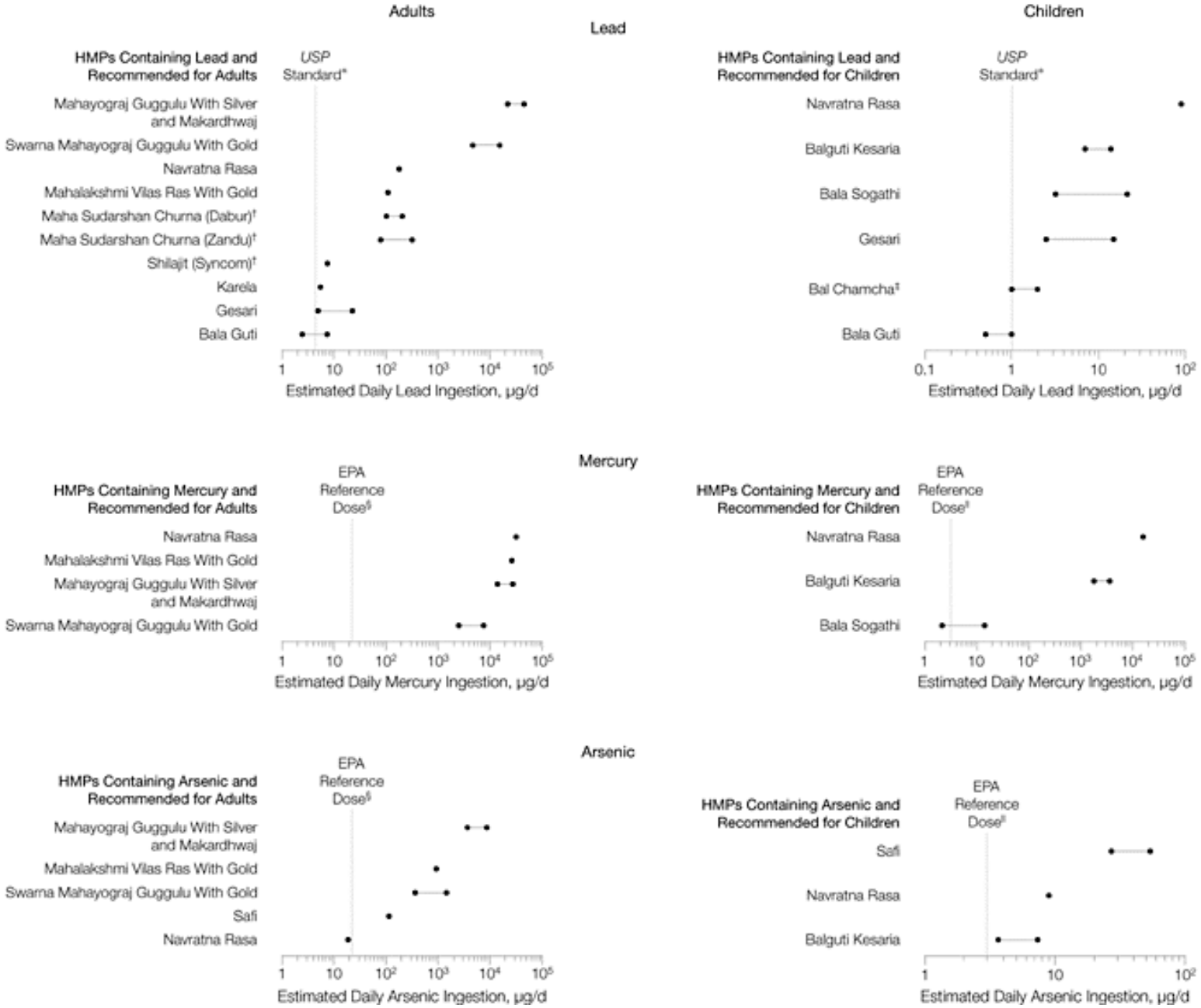
Product-	hypericin (%)	hyperforin (%)
Hyperifin	0.29	1.89
PNC	0.12	0.20
Brite-Life	0.22	1.16
ShopKo	0.26	0.05
Shurfine	0.17	0.29
YourLife	0.28	0.19
Nature's Balance	0.03	0.01
Natrol	0.25	0.48



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



Saper, R. B. et al. JAMA 2004;292:2868-2873. (Ayervedic Herbal Medicine Products)

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**
  - USP monographs (USP24-NF14) and label logo
  - Micromedex and other objective “use monographs”
  - WHO Monographs on Selected Medicinal Plants
- **GMPs for Dietary Supplements are now in effect**

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

Oriental Ginseng

» Oriental Ginseng consists of the dried roots of *Panax ginseng* C.A. Meyer (Fam. Araliaceae).

Packaging and storage—Store in a cool, dry place, in well-closed containers.

Labeling—The label states the Latin binomial name and, following the official name, the part of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Oriental Ginseng Extract RS.*

Botanic characteristics—

Macroscopic: Fusiform or cylindrical roots, sometimes branched, 5 to 12 cm or sometimes up to 20 cm in length and up to 2.5 cm in diameter at the crown, with one or more stem scars; pale yellow or cream surface, smooth in the upper part but with fine longitudinal ridges and root scars in the lower parts; some fine rootlets may be attached; fracture short; fractured surface light yellowish brown, exhibiting a ring of secretory canals in the cortex and a distinct brownish yellow cambium.

Histology: When reduced to a powder and examined under a microscope, the powder shows the following: traces of cork composed of thin-walled polygonal cells but mainly with phelloderm on the outside; wide cortex of parenchymatous cells with numerous secretory canals arranged in concentric zones; parenchymatous xylem with nonlignified tracheids and slightly lignified vessels with spiral and reticulate thickening, isolated or in small groups; small granules of starch 0.5 to 1.0 μm in diameter in all the parenchymatous cells and occasional cluster crystals of calcium oxalate in the cells of the central region.

Identification—Transfer 1.0 g of finely powdered Oriental Ginseng to a 25-mL flask fitted with a reflux condenser. Add 10.0 mL of a mixture of methanol and water (7:3), and heat under reflux for 15 minutes. Cool, filter, and dilute the filtrate with methanol to 10.0 mL. Apply separately, as bands, 20 μL of the test solution and 20 μL of a standard solution containing about 5 mg per mL each of arbutin and escin in methanol to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture, and allow the bands to dry. Develop the chromatograms in an unsaturated chamber containing a solvent system consisting of the upper layer of a mixture of butyl alcohol, water, and ethyl acetate (10:5:2.5) until the solvent front has moved about 10 cm from the origin. Remove the plate from the chromatographic chamber, and allow it to dry. Spray with a solution prepared as follows. Dissolve 0.5 mL of anisaldehyde in 10 mL of glacial acetic acid, add 85 mL of methanol, and mix. Carefully add 5 mL of sulfuric acid to this mixture, and mix. Heat the plate at 105° to 110° for about 10 minutes, and examine the plate. The chromatogram of the standard solution shows, in the upper third, a brown zone corresponding to arbutin and, in the lower third, a gray zone corresponding to escin. Between these two zones, the chromatogram of the test solution exhibits violet-gray zones corresponding to ginsenoside Rg_1 in the upper portion and to ginsenoside Re in the middle. A violet-gray zone corresponding to ginsenoside Rb_1 is located at the same R_f value as the gray zone corresponding to escin in the chromatogram of the standard solution. Other, less intense bands may be observed between the zones due to ginsenosides Rb_1 and Re, and the zone closest to the origin corresponds to ginsenoside Rc. Other spots may be visible in the lower third of the chromatogram.

Total ash ⟨561⟩: not more than 8.0%, determined on 1.0 g of finely powdered Oriental Ginseng.

Acid-insoluble ash ⟨561⟩: not more than 1.0%.

Foreign organic matter ⟨561⟩: not more than 2.0%.

Loss on drying ⟨731⟩—Dry 1.0 g of finely powdered Oriental Ginseng at 105° for 2 hours: it loses not more than 12.0% of its weight.

Alcohol-soluble extractives, *Method 2* ⟨561⟩: not less than 14.0%.

Microbial limits ⟨61⟩—The total bacterial count does not exceed 10,000 per g. The total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Salmonella* species, *Escherichia coli*, and *Staphylococcus aureus*.

Content of ginsenosides Rb_1 and Rg_1—

Solution A—Use water.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*.

Standard solution—Transfer an accurately weighed quantity of USP Oriental Ginseng Extract RS, equivalent to about 2 mg of ginsenoside Rg_1, to a suitable container, add 20 mL of water, and mix. [NOTE—The concentrations of ginsenoside Rg_1 and ginsenoside Rb_1 in this solution are not expected to be equal, and are determined on the basis of the labeled quantities present in the USP Oriental Ginseng Extract RS.] Transfer the mixture to a freshly conditioned solid-phase extraction column containing about 360 mg of packing L2. Wait for 15 minutes, elute with 20 mL of water, and discard the eluate. Elute with 15 mL of a mixture of water and methanol (7:3), and discard the eluate. Elute with 100 mL of methanol, collect the eluate, and evaporate the eluate in a rotary evaporator at 50° to dryness. Dissolve the residue in 10.0 mL of methanol.

Test solution—Reduce about 100 g of Oriental Ginseng to a powder, and transfer about 1.0 g of the powder, accurately weighed, to a 100-mL round-bottom flask fitted with a reflux condenser. Add 50 mL of a mixture of water and alcohol (6:4) and a few grains of pumice, and boil on a water bath under reflux for 1 hour. Cool, and filter. Wash the flask and the residue with 20 mL of a mixture of water and alcohol (6:4), and filter through the same filter. Combine the filtrates, and evaporate in a rotary evaporator at 50° to dryness. To the residue so obtained add 20 mL of water, mix, and proceed as directed for *Standard solution*, beginning with "Transfer the mixture to a freshly conditioned solid-phase extraction column."

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 203-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per minute. The system is programmed to provide a *Mobile phase* consisting of variable mixtures of *Solution A* and *Solution B*. The percentage of *Solution B* is 18% at the time the specimen is injected into the chromatograph and is held at that composition for 10 minutes, then the percentage of *Solution B* is increased linearly to 40% over the next 40 minutes, and held at that composition for the next 30 minutes before the next injection. [NOTE—This system separates ginsenosides Rb_1, Re, Rf, Rg_2, Rg_1, Rc, Rb_2, and Rd.] Chromatograph about 10 μL of the *Standard solution*, and record the peak responses as directed under *Procedure:* the relative retention times for ginsenoside Rg_1 and ginsenoside Re are 1.0 and 1.03, respectively, the resolution, R, between the ginsenoside Rg_1 and ginsenoside Re peaks is not less than 0.9, the resolution between ginsenoside Rb_1 and a neighboring minor peak, at relative retention times of 1.86 and 1.89, respectively, is not less than 1.0, the column efficiency determined from the ginsenoside Rg_1 and ginsenoside Rb peaks is not less than 17000 and 11000 theoretical plates, respectively, the tailing factors for ginsenoside Rg_1 and ginsenoside Rb_1 are not greater than 1.0 and 1.2, respectively, and the relative standard deviation for replicate injections is not more than 4.0% for ginsenoside Rg_1 and ginsenoside Rb_1.

Procedure—Separately inject equal volumes (about 10 μL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the peak responses. Calculate the percentages of ginsenosides Rb_1 and Rg_1 in the portion of Oriental Ginseng taken by the same formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of ginsenoside Rg_1 or ginsenoside Rb_1 in the *Standard solution*, W is the weight, in mg, of Oriental Ginseng taken to prepare the *Test solution*, and r_U and r_S are the peak responses of ginsenoside Rg_1 or ginsenoside Rb_1 obtained from the *Test solution* and the *Standard solution*, respectively: not less than 0.2% each of ginsenoside Rg_1 and ginsenoside Rb_1 is found.

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.

www.usp.org

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.