Clinical Trials: Appropriate Selection of Test Articles

Joseph M. Betz
Office of Dietary Supplements
National Institutes of Health
USA
http://dietary-supplements.info.nih.gov

Views expressed are my own and do not reflect the views of ODS, NIH, HHS, or any other part of the U.S. government

“The Marketplace”

- AHPA estimates as many as 3000 plant species in commerce
  - 90% of market = top 30 or so plants
- Estimates of approximately 30,000-50,000 products
- Little pre-market scrutiny, no product or formula registration
  - Manufacturers may change formulations as costs dictate
- “Proprietary blend” concept

NIH Facts

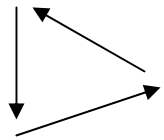
- **The US biomedical research agency**
- **27 Institutes and Centers, and a central Office of the Director**
- **In the same department (Health and Human Services) as Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), etc.**
- **Total NIH budget for 2005: $28 billion**
- **Support research**
  - **Universities, medical centers, hospitals, research institutions**
  - **US and other countries**
- **Grants, Contracts, Cooperative Agreements, etc.**
- **www.nih.gov**

NIH Funding for Dietary Supplement Research
(sources: HNRIM, CARDS)

Fiscal Yr	Total Grants	Dollars
1999	374	$ 98 million
2000	363	$118 million
2001	443	$127 million
2002	569	$171 million
2003	852	$260 million
	TOTAL	$774 million

1º Scientific Questions

- Do they work?
- Are they safe?
- Tools?
  - In vitro assays-relevance to intact humans
  - Animal studies-species relevance
  - Case reports-reliability
  - Randomized double blind placebo controlled clinical trial (RCT)



Medical Ethics

Photos ©Steven Foster

E. pallida (Nutt.) Nutt.

Echinacea

- Most published early trials were "positive"
  - Echinacea for preventing and treating the common cold Melchart, et al. (2000) *Cochrane Database Syst Rev* **2:**CD000530
    - 16 URI trials (8 prevention, 8 treatment) 3396 participants
    - Majority of the available studies report positive results

“Echinacea”

- Adequacy of blinding-open label
  - herbs have characteristic odors and tastes
- Sample size
- Appropriate dose?
  - Children, Comparability of “1 g root/day” to 300 mg product *3 x day*
- Timing of intervention
  - Continuous for prevention? “1st onset of symptoms?”
- Method of assessment-
  - self assessment, viral titer, parents keep log
- Nature of the test article

Trials

Turner *et al*. (2000) *Antimicrob Agents Chemother* 44:1708-9 (-)	Species, plant part (-) Chemistry (+)
Barrett et al. (2002) *Ann Int Med* **137:**939-946 (-)	Species, plant part (+) Chemistry (++)/other herbs
Taylor et al. (2003) *JAMA* **290:**2824-2830 (-/+)	Species, plant part (+) Chemistry(-)-post (-)
Goel et al (2004) *J Clin Pharmacy Ther* **29:**75-83 (+)	Species, plant part (+) Chemistry (++)

Trials

Cohen et al. (2004) *Arch Pediatr Adolesc Med* **158:**217-221 (+) (prevent, 1-4 yo)	Species, plant part (+) Chemistry (++)/other stuff (Propolis, vit C)
Sperber et al. (2004) *Clin Infect Dis* **38:**1367-1381 (?) Antibody titer/clinical colds	Species, plant part (+) Chemistry (-)
Turner et al. (2005) *NEJM 353:*341-348 (-)-dose?	Species, plant part (+) Chemistry (++)
Goel et al. (2005) *Phytother Res* **19:**689-694 (+)	Species, plant part (+) Chemistry(++)

“Echinacea”

- Nature of the test article
  - Species?
  - Plant part used?
  - Where collected/harvested, by whom?
    - Vouchers?
  - Processing?
    - Extraction solvent
    - Extract ratio
  - Standardized or not?
    - To what?
    - How? (methodology)
  - Evaluated for contaminants/adulterants?
  - Other ingredients-excipients, etc.

Herbal Drugs (EP)

- **Herbal** drugs are precisely defined by the scientific name
  - Identified using their macroscopic and microscopic descriptions and any further tests that may be required (for example, thin-layer chromatography)
- **EP**-the ***plant*** is the “active”

“Whole plant”

- Despite years of research, the actual “actives” remain unknown for most plants (even something as highly studied as SJW)
- Basic research into whether and how phytomedicines work is needed before true standardization can occur
- The underlying assumption behind phytomedicines is that the whole plant (or extract) is the “active”
  - Stermitz *et al.* (2000) *Proc Natl Acad Sci* 97:1433-7
  - Stermitz *et al.* (2000) *J Nat Prod* 63:1146-9

Quality

- What we measure and why we wish to measure it are subjects of another talk
  - Active Constituents
  - Marker Compounds
    - One or more constituents that occur naturally
    - Selected for special attention by researcher or manufacturer
- Efficacy?
- Safety?

Quality

- Correct plant-

Slifman *et al*., *NEJM* **339,** 806-811, 1998

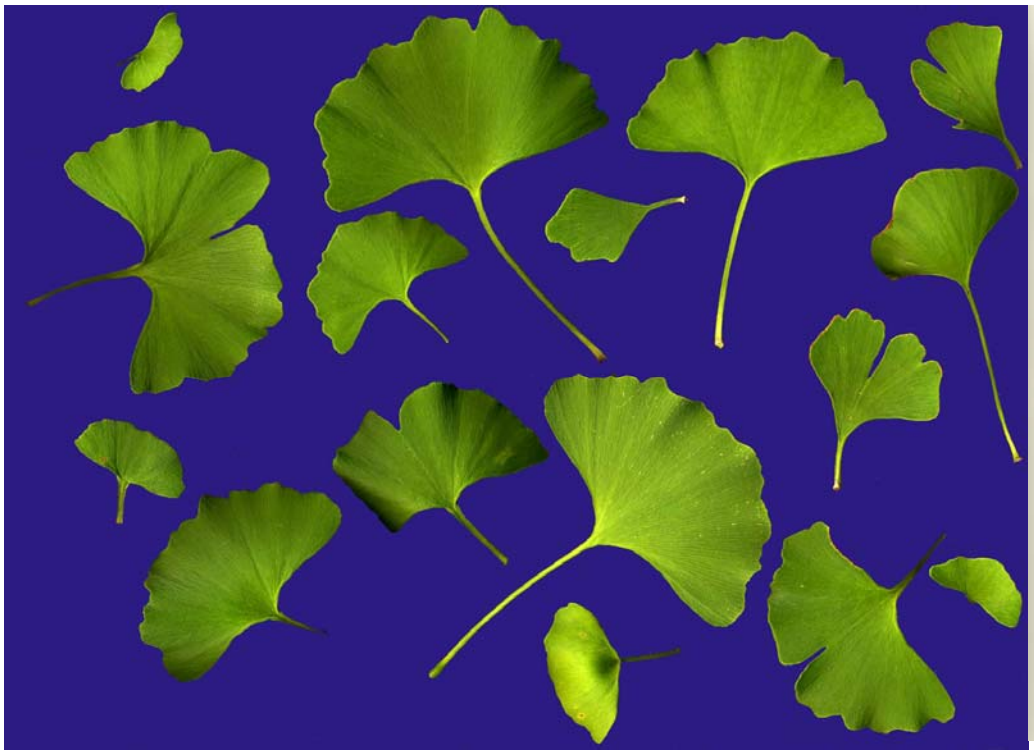
Quality

- Correct plant part

Lycopersicon esculenta

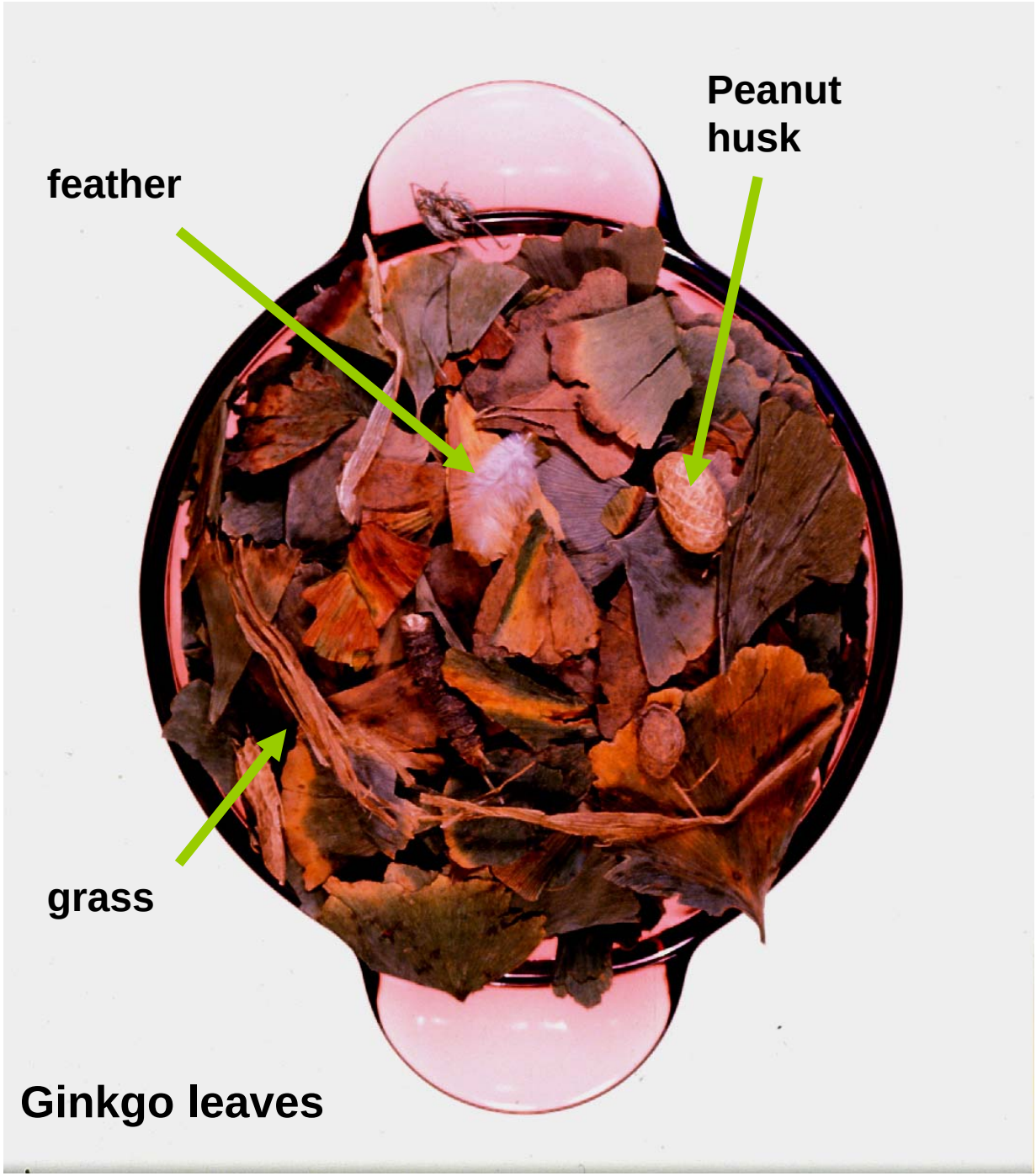
Quality

- Plant collected at proper time of year



Quality

- Pathogen free
- Not filthy or decomposed, not moldy
- Aflatoxin, pesticide, toxic elements within acceptable range
- No extraneous material



Herbal Drug Preparations (Plantae medicinales praeparatore)

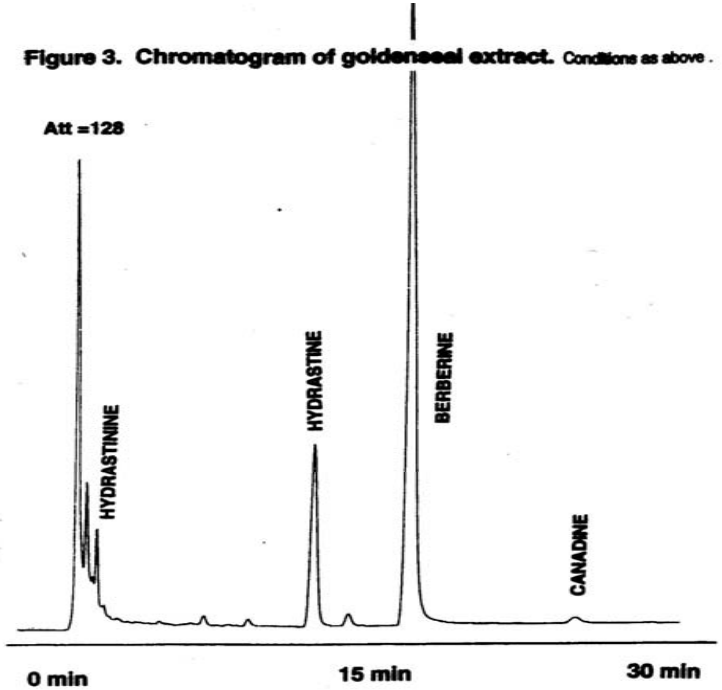
DEFINITION

- **Herbal** drug preparations are obtained by subjecting **herbal** drugs to treatments such as extraction, etc.
- **Extracts** are preparations of liquid (liquid extracts and tinctures), semi-solid (soft extracts) or solid (dry extracts) consistency

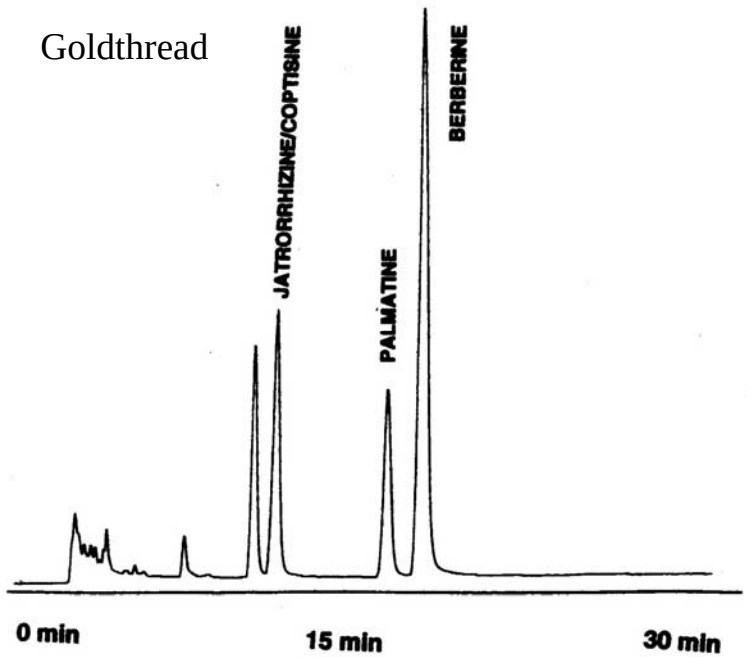
Goldenseal Root
Hydrastis canadensis

Several good RP ion-pair methods for UV

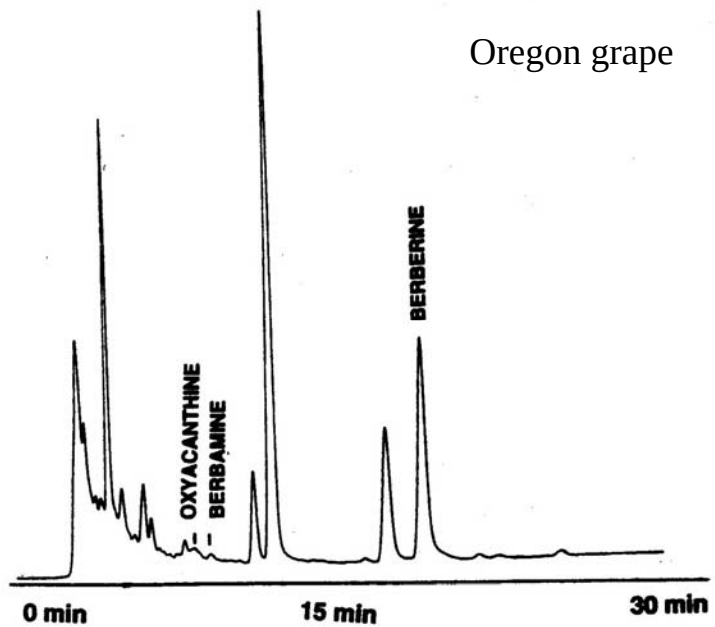
C4 Column, volatile buffer for MS

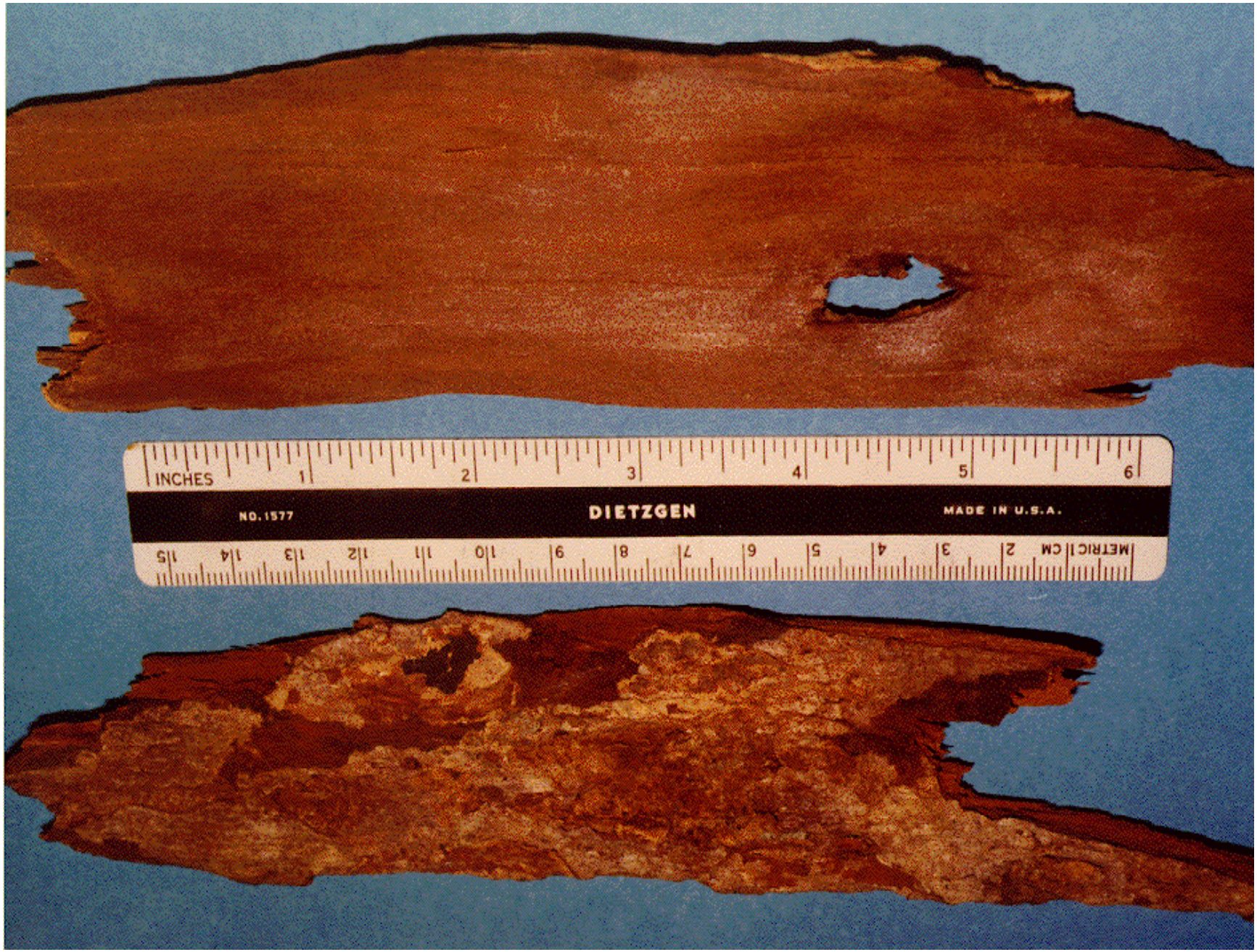


Goldthread

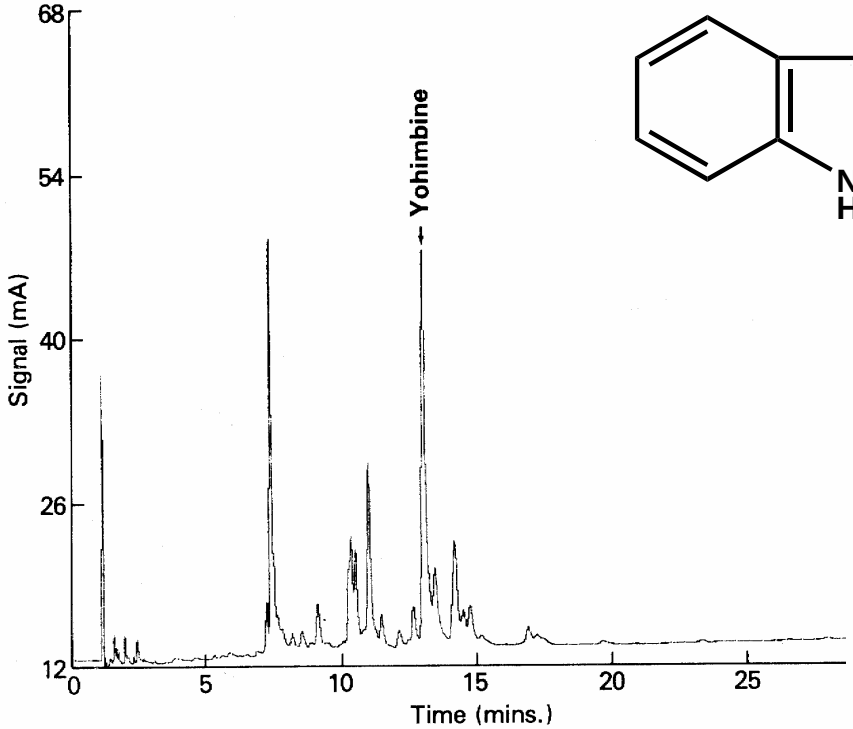


Oregon grape



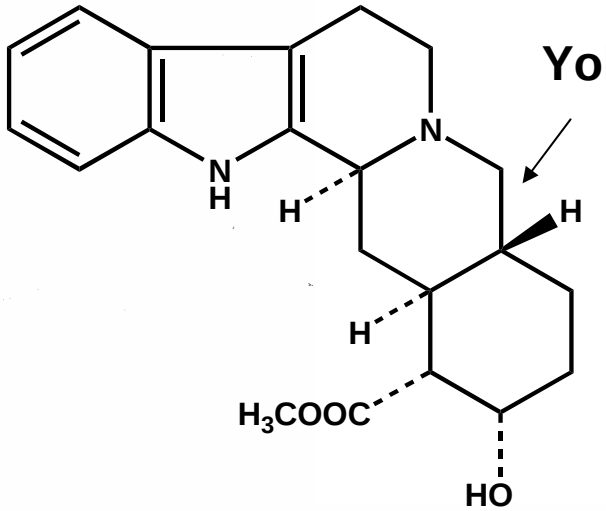


- ***Pausinystalia yohimbe* bark = Herbal Drug**



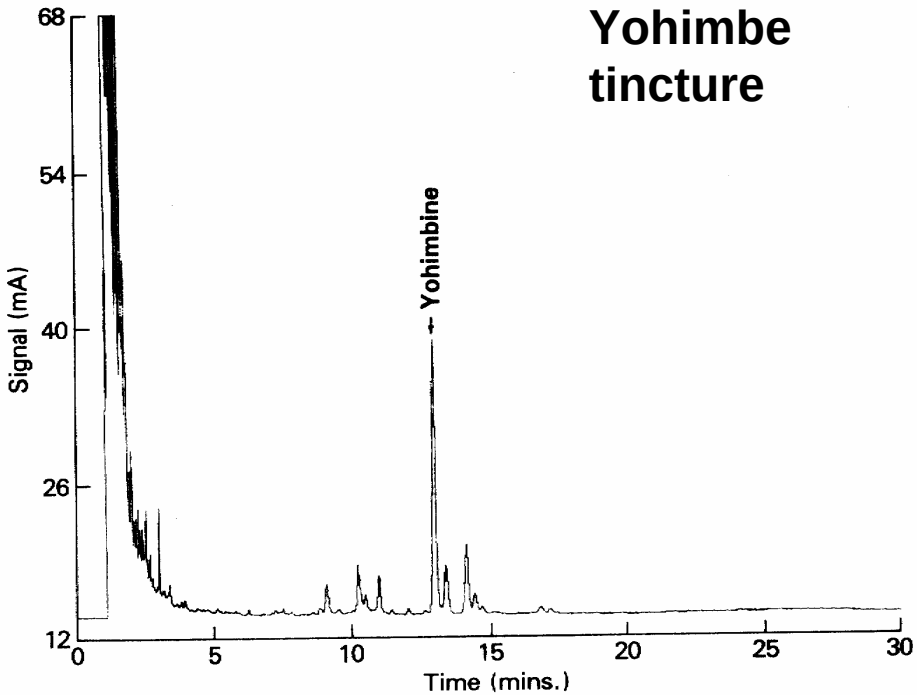
7.1 mg/g

Yohimbe



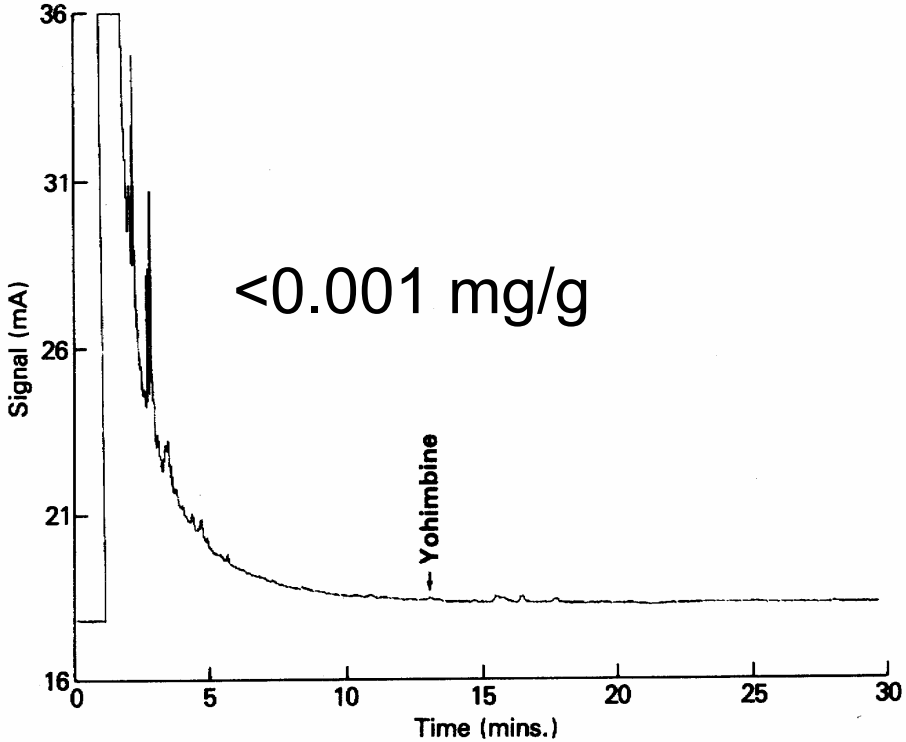
Yohimbine

Yohimbe tincture

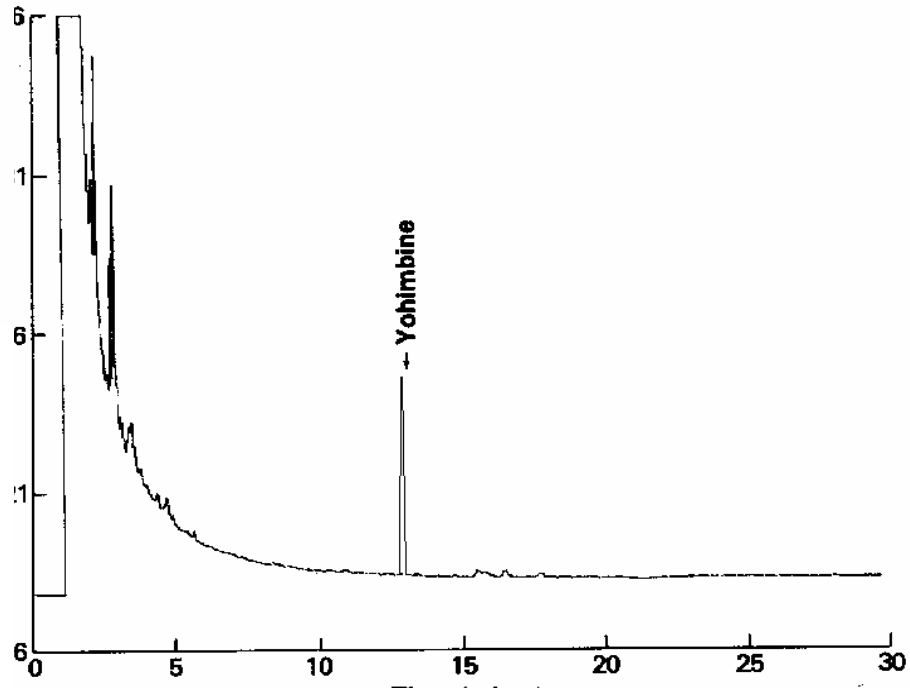


0.3 mg/g

Yohimbe products



<0.001 mg/g



Drugs/Toxic Substances Found in Dietary Supplements

- "Black Pearl"-arthritis pre-DSHEA
  - hydrochlorothiazide, diazepam, indomethacin, and mefenamic acid
- *Chiu Fong*-arthritis pre-DSHEA
  - Aminopyrine, phenylbutazone
- "Sleeping Buddha"-sleep aid post-DSHEA
  - Estazolam (a benzodiazepine tranquilizer)
- "PC SPES"-warfarin post-DSHEA
    - http://dietary-supplements.info.nih.gov/Research/CARDS_Database.aspx

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REVIEW

Lack of herbal supplement characterization in published randomized controlled trials

Peter M. Wolsko, MD, MPH,[a] David K. Solondz, BSE,[b] Russell S. Phillips, MD,[c] Steven C. Schachter, MD,[d,e] David M. Eisenberg, MD[e]

[a]Kaiser Permanente Medical Group, Denver, Colo; [b]Tufts University School of Medicine; [c]Division of General Medicine and Primary Care at Beth Israel Deaconess Medical Center; [d]Office of Clinical Trials and Research, Beth Israel Deaconess Medical Center; and [e]Division for Research and Education in Complementary and Integrative Medical Therapies at Harvard Medical School, Boston, Mass.

KEYWORDS:
Plants, medicinal;
Herbal medicine;
Dietary supplements;
Review, systematic;
Drug impurity;
Complementary therapies

ABSTRACT

PURPOSE: Herbal supplements in the United States and abroad have poor quality control and high content variability. We assessed the extent to which recently published randomized controlled trials of herbal supplements characterized and verified the content of the supplement under study.

METHODS: We identified all MEDLINE-indexed English language randomized controlled trials evaluating single-herb preparations of echinacea, garlic, ginkgo, saw palmetto, or St. John's wort that were published between January 1, 2000, and February 9, 2004. From each article we extracted information characterizing the herbal supplement studied.

Table 1 Studies fulfilling important quality-control criteria

Quality-control criteria	Studies fulfilling criteria (n = 81) n (%)
Part A: Testing	
Studies performing quantitative analysis	12 (15)
Echinacea (n = 6)	2 (33)
Garlic (n = 17)	3 (18)
Ginkgo (n = 30)	1 (3)
Saw palmetto (n = 23)	6 (26)
St. John's wort (n = 5)	0 (0)
Studies reporting analytic results	8 (10)
Part B: Description	
Plant source identified	
Latin binomial listed	40 (49)
Part of plant used identified	8 (10)
Manufacturer identified	53 (65)
Brand name identified	33 (41)
Report processing/extraction method	23 (28)
Report at least one expected constituents and amount (ie, contains 12 mg ginkgolides)	41 (51)
Report dosing	
Form (eg, gel-cap, powder, etc)	64 (79)
Total daily amount	74 (91)
Frequency (times/day)	61 (75)
Report number of batches used	14 (17)

Biologically Active Agents Used in CAM and Placebo Materials--Policy and Guidance

The policy and guidance documents address biologically active products such as:

- Botanicals
- Products derived from animals
- Probiotics
- Nutrients
- Small molecules
- Functional foods

Read the policy on product quality, scope of research, and Investigational New Drug application.

Use the guidance to determine the type of information that you should include in your grant application and to learn what type of information NCCAM may request of you before grant award.

Note: This policy supersedes NCCAM's Policy Announcement on the Quality of Natural Products (July 2003).

NCCAM, National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892 USA
Web: nccam.nih.gov
E-mail: info@nccam.nih.gov