Clinical Trials: Appropriate Selection of Test Articles

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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)

<table>
<thead>
<tr>
<th>Fiscal Yr</th>
<th>Total Grants</th>
<th>Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>374</td>
<td>$98 million</td>
</tr>
<tr>
<td>2000</td>
<td>363</td>
<td>$118 million</td>
</tr>
<tr>
<td>2001</td>
<td>443</td>
<td>$127 million</td>
</tr>
<tr>
<td>2002</td>
<td>569</td>
<td>$171 million</td>
</tr>
<tr>
<td>2003</td>
<td>852</td>
<td>$260 million</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>852</strong></td>
<td><strong>$774 million</strong></td>
</tr>
</tbody>
</table>
1° 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
E. pallida (Nutt.) Nutt.
Echinacea

- Most published early trials were “positive”
  - Echinacea for preventing and treating the common cold
    - 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Species, plant part</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al. (2000)</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><em>Antimicrob Agents Chemother</em> 44:1708-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrett et al. (2002)</td>
<td>(+)</td>
<td>(++)/other herbs</td>
</tr>
<tr>
<td><em>Ann Int Med</em> 137:939-946</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor et al. (2003)</td>
<td>(+)</td>
<td>(-)/post(-)</td>
</tr>
<tr>
<td><em>JAMA</em> 290:2824-2830</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>J Clin Pharmacy Ther</em> 29:75-83</td>
<td></td>
<td></td>
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</table>
## Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal/Reference</th>
<th>Species, plant part</th>
<th>Chemistry</th>
<th>Other stuff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al. (2005)</td>
<td>NEJM 353:341-348 (-)-dose?</td>
<td>(+)</td>
<td>(++)</td>
<td></td>
</tr>
<tr>
<td>Goel et al. (2005)</td>
<td>Phytother Res 19:689-694 (+)</td>
<td>(+)</td>
<td>(++)</td>
<td></td>
</tr>
</tbody>
</table>
“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”
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-
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
Yohimbine

Yohimbine tincture

7.1 mg/g

Yohimbe

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
REVIEW

Lack of herbal supplement characterization in published randomized controlled trials

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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.

RESULTS: Of 47 studies, 11 (23.4%) did not attempt to characterize or verify the herbal supplement administered.
<table>
<thead>
<tr>
<th>Quality-control criteria</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part A: Testing</strong></td>
<td></td>
</tr>
<tr>
<td>Studies performing quantitative analysis</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Echinacea (n = 6)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Garlic (n = 17)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Ginkgo (n = 30)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Saw palmetto (n = 23)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>St. John’s wort (n = 5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Studies reporting analytic results</td>
<td>8 (10)</td>
</tr>
<tr>
<td><strong>Part B: Description</strong></td>
<td></td>
</tr>
<tr>
<td>Plant source identified</td>
<td></td>
</tr>
<tr>
<td>Latin binomial listed</td>
<td>40 (49)</td>
</tr>
<tr>
<td>Part of plant used identified</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Manufacturer identified</td>
<td>53 (65)</td>
</tr>
<tr>
<td>Brand name identified</td>
<td>33 (41)</td>
</tr>
<tr>
<td>Report processing/extraction method</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Report at least one expected constituents and amount (ie, contains 12 mg ginkgolides)</td>
<td>41 (51)</td>
</tr>
<tr>
<td>Report dosing</td>
<td></td>
</tr>
<tr>
<td>Form (eg, gel-cap, powder, etc)</td>
<td>64 (79)</td>
</tr>
<tr>
<td>Total daily amount</td>
<td>74 (91)</td>
</tr>
<tr>
<td>Frequency (times/day)</td>
<td>61 (75)</td>
</tr>
<tr>
<td>Report number of batches used</td>
<td>14 (17)</td>
</tr>
</tbody>
</table>
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).