Approaches for Evaluating the Health Effects of Botanicals & Natural Products

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What are Botanicals & Natural Health Products?

Heterogeneous products derived from natural sources, as a finished product.
Natural Health Products & Botanicals

What they are not

- fermentation products (yeast, bacteria)
- highly purified or chemically modified substances derived from natural sources (paclitaxel)
- homeopathic drugs or elixirs
Natural Health Products

- From botanicals:
  - ginseng extracts, primrose oil, ginger root, “bee pollen”

- From animals:
  - fish oils, glandular materials
  - shark cartilage; elk antlers “velvet”
  - colostrum
Regulatory Impact on Scientific Assessment of Bioactives

How products are regulated in the United States affects the scientific assessment of Bioactives, as well as what can be done with the results of scientific assessment.
Principles of US Regulation

Products are regulated by their:

- Route
- Formulation
- Safety
- “Intended use”

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Route

Product

Parenteral
IV, IM, SC; PR, TD, IN

Oral

Topical

RX Drugs

OTC Drugs

Foods for Special Uses

Dietary Supplements

Food Additives

Conventional Foods

Cosmetics

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Formulation

**Product**

- **Parenteral:** liquid drops (eye/nose) transdermal patch; suppository; IV
- **Pill, Tab**: Cap, Chewable Tab; sachet; liquid drops
- **Food or Beverage**: gum, chewable, lozenge, etc.
- **Topical**: cream, spray; lotion; film ointment

**Categories**

- RX Drugs
- OTC Drugs
- Foods for Special Uses
- Dietary Supplements
- Food Additives
- Conventional Foods
- Cosmetics

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NHPs are ingredients regulated by their “Intended Use” as defined by their “Labeling”.

Many “faces” of Soy
Principles of US Regulation:

Labeling

includes:

• product container label or packaging
• package insert (if required)
• advertising and promotion (including video, spoken, internet, etc.)
• all other written, printed or graphic material accompanying the product.

see FD &C Act Sec. 201(m)
Garlic

**Intended Use**

- **Food Additive (GRAS)**
  - Powder added to micro-wavable pizza: “to impart flavor”

- **Cosmetic**
  - Spray & body lotion: “rejuvenates the skin and prevents the appearance of wrinkles”

- **Medical Device**
  - Earplugs: “prevents swimmers’ ear”

- **Conventional Food**
  - Fresh Garlic or Health Claims: “taken with a complete diet it may reduce your risk to heart disease.”

- **Dietary Supplement**
  - Odorless garlic capsule “boosts the immune system”

- **Foods for Special Dietary Use**
  - Enteral Formula “for the management of patients with heart disease”

- **Drug**
  - Any form: “cures cancer, lowers cholesterol, treats hypertension”

- **Biologic**
  - Injected garlic vaccine “for the prevention of garlic allergies”

From: FA Hoffman and T Garvey IV; Textbook of Legal Medicine, 5th ed/ 2001
“Intended Use”

Types of Labeling Claims

- Nutrient content claims
- Statements of nutritional support
- Health claims (risk reduction)
- Symptom relief
- Disease claims (to diagnose, treat, prevent, mitigate or cure)
- Structure or function claims
Dietary supplements are intended to supplement the diet and/or "Effect the Structure/Function of the Body" (DSHEA -1994)
“Structure/Function” Claims

Drugs are intended for to treat, prevent, diagnose, mitigate or cure disease, OR

“Effect the Structure/Function of the Body”
SAFETY

Foods <<<< >>>> Drugs

Opposing Legal Premises

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Legal Assumption: Foods

“generally recognized as safe”

OR

contain ingredients with

“a history of use or other evidence of safety”

which

“will reasonably be expected to be safe…..”
Legal Assumption:

**Drugs**

*not generally recognized as safe & effective*

under the conditions prescribed, recommended
or suggested in the labeling

[Definition of “new” drug: Section 201p FD&C Act]
Legal Assumptions: Risk

Dietary supplements are intended to supplement the diet of healthy (normal) individuals for which no risk is tolerable.

Drugs are intended for use by a population for which the benefit has been proven to outweigh the risk.

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**Impact of US Regulation on Bioactives:**

**Foods vs Drugs?**

<table>
<thead>
<tr>
<th>Foods</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ taste, aroma, flavor,</td>
<td>◆ safe/effective to treat, prevent,</td>
</tr>
<tr>
<td>nutritional supplementation</td>
<td>diagnose, mitigate, cure</td>
</tr>
<tr>
<td>◆ for general population</td>
<td>◆ for target population</td>
</tr>
<tr>
<td>◆ documented safety</td>
<td>◆ documented safety/efficacy</td>
</tr>
<tr>
<td>◆ <strong>no risk:</strong> safety is</td>
<td>◆ **risk:**benefit: safety is relative</td>
</tr>
<tr>
<td>absolute</td>
<td>◆ consistency very crucial</td>
</tr>
<tr>
<td>◆ consistency not crucial</td>
<td>◆ consistency very crucial</td>
</tr>
<tr>
<td>◆ manufacturing is not</td>
<td>◆ manufacturing is vetted by FDA</td>
</tr>
<tr>
<td>reviewed by FDA</td>
<td></td>
</tr>
</tbody>
</table>
Health Effects: What you can say

Joints: Study Objectives, Product Claims

◆ **Disease Claim (drug):**
  - “treat/prevent [symptoms of] arthritis”

◆ **Structure/Function Claim (drug):**
  - “reduce the inflammation associated w/ arthritis”

◆ **Structure/Function Claim (diet. supplmt):**
  - “maintain/promote healthy joint range of motion”

◆ **Health Claim (food/diet.supplmt):**
  - “may reduce the risk of developing arthritis…”
Health Effects: *Who you should study*

**Joints: Subjects**

- **Drug:**
  - patients diagnosed with arthritis

- **Dietary Supplement:**
  - healthy volunteers

- **Food:**
  - general public, OR
  - those at high risk to develop arthritis (for FDA-approved “Health Claim”)
Health Effects: *What you must assess*

**Joints: Outcome Measurements**

**Drug:** “perceived (clinical) benefit”
- clinical improvement of disease parameters, symptoms, quality of life, along with improvement of joint space in those who had abnormal studies

**Dietary Supplement/Food:** “surrogates”
- range-of-motion data; maintain normal joint space in “normal” subjects [SF Claim]
- lack of progression to disease state (“reduce risk”) [Health Claim]
Health Effects: 

Requirements your “test article” must meet

Quality Standards

◆ Drug:
  – “drug” Good Manufacturing Practices (GMPs)
  – focus on lot-to-lot consistency, potency, purity

◆ Dietary Supplement/Food:
  – dietary supplement or food GMPs
  – focus on filth, adulteration, contamination
Health Effects of Botanicals and Natural Health Products

Existing Approaches

USDA Historical Photos
Existing Approaches:

Pulling the “Bioactive” out of the food:

- Identification of “bioactive”
- Isolation
- Purification
- Synthesis

Historical approach works well for vitamins, minerals, and many nutrients

Beta-carotene from Carrots

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Caffeine in Foods and Drugs

“Botanical Caffeine”

- Cup of coffee: 90-150mg
- Instant coffee: 60-80mg
- Tea: 30-70mg
- Mate: 25-150mg
- Cola drink: 30-45mg
- Chocolate bar: 30mg

“Chemical Caffeine”

- Vivarin: 200mg
- Stay-awake pill: 100mg
- Cold relief tablet: 30mg
- Headache tablet: 32mg
Existing Approaches: Chemically Defined Molecules

Preclinical Screens

- Focus on pharmacology of Bioactives & “Mechanisms of Action”
- “Lock & Key” model -
  - Must have the “lock” (molecular targets)
  - If target is unknown, no way to find a ‘new’ active
Attributes of Botanical and other “Natural” Bioactives

- Complex mixtures
- True “actives” rarely are known
  - ginkgolides in *Ginkgo biloba* are the exception!! - not the rule
- Major AND minor active(s): what are thought to be “impurities” usually contribute to the biological effect
- “Mechanisms of action” generally unknown
- Product is “process-defined” (not chemically defined)
Single Chemical vs Complex Botanical
Health Benefit “Targets”

Synergy = Botanical

‘Magic Bullet’ = Single Chemical

Single Active → Multiple Actives

Probability of useful Biological Response

Polymorphic Target

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Health Effects of Botanicals and Natural Health Products

New Paradigm
Why Heterogeneous Products?

*When the whole is greater than the parts*
Consumption of antioxidant vitamins may reduce the risk of certain kinds of cancer.
FDA Denies “Health Claim”

- No support for antioxidant vitamins, alone or in combination.

- Data “….did not resolve whether the protective effects of fruit and vegetable consumption….are due to a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant function… OR ….to other nutritive components of such foods…, ….to unmeasured components of such diets, … ….to displacement of other known risk components… within the total diets.”

From: FDA denial of Health Claim for Antioxidant Vitamins & Cancer ‘93
“FDA has determined that although some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer, this evidence is limited and not conclusive.”

From: FDA Letter – Apr 1, 2003
GARLIC: *Health Benefits may vary with the product*

- **ANTI-INFECTIVE**
  - Antibacterial
  - Antifungal
  - Antiviral

- **CARDIOVASCULAR**
  - Antihypertensive
  - Antiarrhythmic
  - Antithrombotic
  - Antiplatelet
  - Lipid lowering

- **ANTICANCER**
  - Tumor initiation
  - Immune enhancing
  - Tumor promotion
  - Modification of carcinogenesis

“Throwing out baby with bath-water”

Evaluating “Negative” Results

- *JAMA* article reports a *steam-distilled garlic oil* preparation tableted with beta-cyclodextrin (binder) “*lacks lipid-lowering effect*”
- Formulation: <40% release of oil from tablet binder
- Authors failed to address bioavailability AND dismissed 17 (out of 20) studies that were positive for the health effect!
- But press reported all garlic products were “ineffective”

“It’s often not what you know – but what you don’t know that counts”

Garlic (*Allium sativum, L.*)

- >100 compounds identified in garlic
- “Process defines the product:”
  - Fresh Garlic, garlic juice, volatile garlic oil, garlic oil macerates, dried garlic powder, aged garlic extracts
- **Standardized extracts may not always be the “answer:”**
  - Some products are standardized on *Allicin*
  - But health benefits were observed using products containing no *Allicin* (e.g., cooked, steamed, aged garlic extract)

*Compounds other than Allicin are responsible for some health benefits of garlic*
“Don’t believe everything you read...”

Deficiencies in the Scientific Literature

“[Clinical investigators]...are apparently unaware that no standards of quality exist for herbal products...

Accustomed to working with drugs that must conform to official specifications, [investigators] often fail to define adequately the botanicals employed [in studies]...”

---Varo Tyler

Botanical Product Forms

*each form contains varying levels of bioactive compounds*

- **Powders** — dry, crushed, minimally processed
- **Infusions** - near-boiling water poured over botanical, steeped (e.g., tea)
- **Decoction** - botanical placed in water, boiled; strained liquid (e.g., coffee)
- **Tincture** - botanical in solvent, steeped days/wks
- **Fluid extract** - similar to tincture, but product concentrated through distillation process
- **Solid extract** - solvent evaporated off, leaving solid residue
- **“Standardized” extract** - guaranteed amounts of constituents; given as % total weight of extract
New Paradigm: Heterogeneous Products

“Identification”

- Taxonomy/nomenclature not internationally harmonized
- Identification must use a variety of approaches (organoleptic, gross & microscopic, DNA, etc.)
Heterogeneous Products

“Screening”

- By history:
  - prior human use, traditional use, historical use

- Bioassay
  - Study the whole product, not the components
  - Test in a “matrix” (*in vivo* or *in vitro* – using entire systems) because effect may be indirect, i.e., through complex metabolic pathways, cellular recruitment, etc.
New Paradigm: Heterogeneous Products

“Methodology”

- Manufacturers do not use comparable assays to quantify actives
- No high quality, pure standards are available
- Even the term “standardized” -- is not standardized!
New Paradigm: Heterogeneous Products

“Testing”

- Quality standards will rely on a combination of tests and controls
- Toxicology
- But standard pharmacology is not feasible for complex bioactives
Heterogeneous Products (Botanicals)

Evolving Regulatory Milieu

- FDA Guidance for Industry: Development of Botanical Drugs (June 2004)
Evolving Regulatory Milieu

New Class of Drugs

- Synthetic, small molecular weight
- Recombinant, large molecular weight
- Natural products, multi-component
  *(including botanicals)*
Guidance for Industry Botanicals

**BOTANICAL DRUG**

*Intended for OTC Use?*

- **YES**
  - US Marketed for Material Time & Material Extent
    - **YES**
    - Evidence of Safety & Efficacy for OTC Monograph?
      - **YES**
      - Is marketing exclusivity desired?
        - **YES**
        - NDA
      - **NO**
      - OTC Monograph
    - **NO**
  - **NO**

*Indicate which of the following actions is desired:*

- **IND**
  - Safety, Efficacy & CMC data to Support NDA?
    - **YES**
    - NDA
    - **NO**
  - OTC Monograph
  - **NO**

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Botanicals as Future Drugs:
Number of Pre-IND & IND Applications submitted to the US FDA

- 1990 - 1998: 50
- 1999 - 2005: >200
- 2002 - 2005: 1 to 3 per month
Botanical Drug IND Sponsors

2002
[From S. Chen, CDER-FDA]
Summary

- To assess health benefits, “whole” bioactives should be defined --not just their chemical components.
- Regulatory status of “test articles” can have an impact on scientific investigation and results.
- Complex bioactives may be particularly useful against polymorphic biologic targets.
- Existing approaches for single molecular bioactives may be inappropriate for heterogeneous bioactives.
- Recent changes in US regulatory policies open new avenues for developing beneficial complex bioactives from natural sources.
Thank you!

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Ginkgo biloba
Ginkgo
Photo: Ginger Webb