PL-2

Evaluating Nutritional Supplements in America

James W. Daily III

Daily Manufacturing, Inc.

Nutritional supplements have been a controversial topic among American physicians, scientists, and the general public. While there is demonstrated efficacy of many dietary supplements for the prevention and treatment of diseases, there is considerable variability in the strength of the data as well as in the quality of products. The 1994 Dietary Supplement Health and Education Act (DSHEA) defined dietary supplements and provided for uniform labeling, but placed restrictions on health claims. Consumers invariably purchase supplements for real or perceived health benefits, and supplement manufacturers produce products to supply the demand for efficacious supplements. The lack of direct information results in confusion over quality and efficacy of products, with many illegal and dishonest health claims used in promotion of products. The most popular products include echinacea (for immune boosting), gingko biloba (prevention of Alzheimer's disease), saw palmetto (prostate health), and glucosamine (arthritis). Although all of these have convincing research supporting efficacy, the products are not standardized for either dose or type of product (whole herb or extract). Evaluating product quality is essentially the responsibility of the consumer. New regulations are proposed or recently added to address some of the questions and will provide for standardized manufacturing and testing of nutritional supplements. Organic certification is a recent regulation that addresses the quality of any product claiming to be organic. New Good Manufacturing Practices (GMPs) are proposed for the supplement industry and are expected to be implemented very soon. Almost immediately, all facilities manufacturing food or supplement products for use in the USA must be registered with the Food and Drug Administration and prior notification must be sent to the FDA of all shipments into the USA.

Dietary Supplement Health and Education Act of 1994 (DSHEA)

- Defines dietary supplements
- Established a framework for assuring safety
- Provides for "health claims" and "structure-function" claims
- Set labeling standards
- Mandated establishment of unique cGMP regulations for supplements

Dietary Supplement Definition

- A product intended to supplement the diet that contains: vitamin, mineral, botanical, amino acid, any dietary substance used to increase dietary intake, any metabolite, constituent or extract of the above.
- Is intended for ingestion in pill, capsule, tablet, or liquid form.
- Is not represented as a conventional food or sole item in the diet.
- Is labeled "dietary supplement"
- Can include a drug if it was marketed as a supplement before approval as a drug.

What is not Required

- FDA pre-market approval
- Clinical trials
- FDA testing
- Proof of efficacy
- Safety testing for substances sold in the USA before the Act. For a new substance being introduced into the food supply, the FDA must be notified 75 days prior to introduction and provided evidence of safety.

What is Required

- Uniform labeling that includes how much of an active ingredient and its form. Must include scientific name of botanical.
- FDA regulates labeling, FTC regulates advertisements
- Three types of claims allowed
  - 1. Nutrient content
  - 2. Disease claims if approved
  - 3. Nutritional support or "structure function" claims

Efficacy

- No claims can be made for efficacy, except for a few narrowly defined
- New products evaluated for safety
- FDA's attitude – as long as it is safe people are allowed to waste their money
- If supplements are nutritional products, that is consistent

Criteria FDA Uses to Determine if a Drug Claim has been Made

1. Has an effect on a specific disease or class of diseases.
2. Has an effect on a recognizable symptom characteristic of a disease
3. Has an effect on an abnormal condition that is unusual or causes harm.

FDA Criteria

4. Has an effect on a disease through one or more of these factors:
   a. Name of Product
   b. Claims that it contains a substance that is know to treat a disease.
   c. Citation of a reference that makes disease claim

FDA Criteria

5. Belongs to a class of products intended to diagnose, mitigate, treat, cure, or prevent a disease.
6. Is a substitute for a product that is a therapy for a disease
7. Augments a drug or therapy
8. Has a role in the body's response to a disease or to a vector of a disease.

FDA Criteria

9. Treats, prevents, or mitigates adverse events associated with a therapy for a disease.
10. Otherwise suggests an effect on a disease or diseases.

65 Federal Register: 56035
JAMA Sept 17, 2003 V0l. 290, p. 1507

Facing the Facts?

- ◇ Fact: Consumers buy supplements to prevent or treat diseases
- ◇ Fact: Supplement manufacturers make supplements to meet the consumer demand for supplements to prevent or treat disease
- ◇ Question: Do supplements have efficacy
- ◇ Question: How do consumers know what works and what does not

Efficacy

- ◇ Many supplements have solid scientific backing
- ◇ Typically slower acting and preventive effects
- ◇ Not usually efficacious for acute disease
- ◇ Overselling may ultimately do more harm than good
- ◇ Example – Coral Calcium

Coral Calcium Internet Ad

- ◇ Research has revealed that this amazing coral calcium does wonders for allergies, kidney stones, insomnia and more. Now, you too can join the millions of people who have unlocked their bodies self-curing potential with all natural **100% pure Barefoot Coral Calcium Daily!** This amazing nutrient, with over 70 additional trace minerals, digests easily with **100% absorption in just 20 minutes**. One bottle contains 90 softgel capsules (a full month supply). Unleash your body's natural ability to live longer, better and without disease with the awesome power of Barefoot Coral Calcium from the waters of Okinawa, Japan

Einstein and Truth

"Whoever undertakes to set himself up as a judge of Truth and Knowledge is shipwrecked by the laughter of the Gods"

Supplements that Work Glucosamine for Arthritis

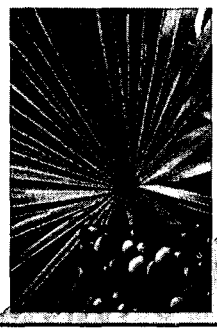
- Meta-Analysis of studies on the benefits of glucosamine and chondroitin for osteoarthritis
- 37 studies reviewed 15 included
- Conclusion: "Trials of glucosamine and chondroitin preparations demonstrate moderate to large effects, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.
- McAlindon et al. (2000) JAMA 2831469-1475.

Multivitamins and Heart Attack

- Stockholm Heart Epidemiology Program
- Odds Ratios for Myocaridal Infarction for supplement users
- Men: 0.79 (CI - 0.63-0.98)
- Women: 0.66 (CI – 0.48-0.91)
- Conclusion: "If the association is confirmed, then mulitvitamin therapy may provide a cheap, safe, and acceptable therapeutic option for the primary prevention of CVD.
- Holmquist et al. (2003) J. Nutrition 133: 2550-2654

Saw Palmetto and Prostate

- Common Plant in Florida
- Berries rich in β-sitosterol
- When compared with finasteride, similar efficacy. Wilde & Goa (1999) Drugs 57:557-581
- 50 men using 160 mg ext 2x/d. At 2, 4, and 6 months 21, 30, & 46% had improvements of 50% or more, respectively.
- Gerber et al. (1998) Urology 51: 1003-1007.



Other Supplements with Significant Evidence for Efficacy

- Vitamin E – Immunity
- Calcium – Osteoporisis
- Folic Acid – Neural Tube Defects
- Omega 3 FAs – Heart Disease
- Echinacea – Immunity
- Green Tea – Cancer Prevention
- Lycopene – Prevents Prostate Cancer
- Lutein – Prevents Macular Degeneration

Evaluating Specific Products

- What if a consumer determines that a supplement is worth trying
- Bewildering array of products
- Unlike drugs, supplements are not standardized – again more like foods
- What form, what dose, what brand
- Many claim that there product is the best

What Adult People Use & Why

Schaffer et al. (2003, Nov.) J. Am. Dietetic Assoc.103: 1500-1505

Use of non-vitamin/mineral supplements

- Echinacea 29.3% - Immunity
- Gingko biloba 14.7% - Alzheimer's
- Kava Kava – 10.9% Reduce Anxiety
- Saw Palmetto – 8.6% (men) Prostate
- Glucosamine – 5.3% Arthritis
- Melatonin - 4.7% Sleep aid
- St. John's Wort – 4.4 % Depression
- 32.7% used some non-vitamin/mineral

Example: Echinacea From Herbs and Health by Logan Chamerlain, Ph.D.

- I decide that cold and flu season may be bad. I Want to try boosting my immune system to stay healthy. Echinacea is the most popular herbal immune booster.

Echinacea Selection

- Seven products in capsule form
- 3 contained *E. angustifoia*, 2 *E. purpurea*, and 2 combined both
- 2 made from flowers, stems and leaves, 2 from root, 2 whole plant, and 1 from flowers.
- Two were standardized extracts and 5 were whole herb or root
- Four were organically grown, 3 were not.

Echinacea Selection Continued

- Six had batch numbers 1 did not
- Three had expiration dates, 4 did not
- All products had safety seals, 2 in brown glass bottles 5 in plastic
- One in vegetarian cellulose capsules others in gelatin capsules
- Both standardized products had around 200 mg total, whole plant products 380-450 mg per capsule

Echinacea Selection

- Some had structure function claims on labels
- Some had cautions – do not use if you have autoimmune disease etc.
- Prices for whole plant products were $8.39, $10.49, $11.98, $15.98, $18.95 for 100 capsules. Root products usually higher.
- Standardized extracts were $20.95 and $21.95 for bottles of 60 capsules.

Choosing an Echinacea

Jim Daily III, Ph.D.

- Chose standardized extract for known potency
- Did not care about plant part, as long as the active ingredients were present

L. Chamberlain, Ph.D.

- Chose whole plant product to obtain all synergistic components.
- Chose root product because it is more potent, although more expensive

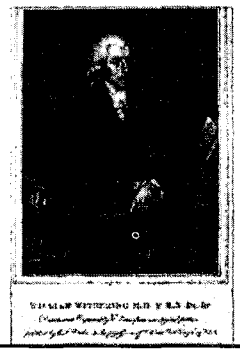
Jim Daily III, Ph.D.

- Preferred organic
- Preferred vegetarian capsules, but not too important
- Preferred *E. purpurea* but unsure
- Chose an extract that costs $ 20.95 for 60 capsules

L. Chamberlain, Ph.D.

- Preferred organic
- Preferred vegetarian capsules, but not too important
- Preferred *E. purpurea*
- Chose a whole root product that cost $18.95 for 100 capsules.

William Wuthering, M.D.



Dr William Wuthering was said to be kind, but extremely conservative an cautious. A rather boring person, but persistent. That was part of the reason he made one of the greatest drug discoveries of all drug discoveries.

He was a member of the "Lunar Society" a group of elite scientists started in 1776 who met one night per month dinner and discussion. They always met on the full moon, thus the name lunar society – others used the term – Lunatics.

Withering Continued

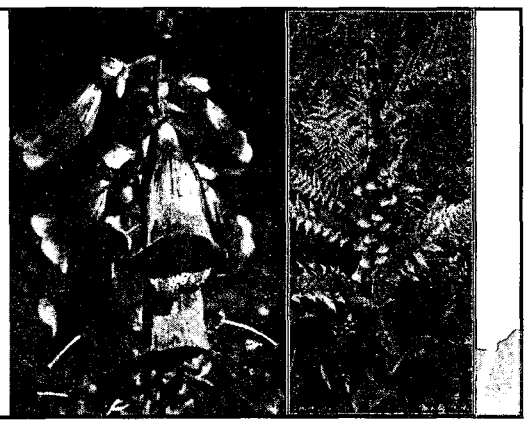
Withering was also interested in botany, and wrote a botanical book with a title beginning with "*A Botanical Arrangement of all the Vegetables Naturally Growing in Great Britain...*" the title proceeded for 24 lines. One of his fellow lunatics, Erasamus Darwin (grandfather of Charles) suggested a more modest title such as "English Botany", but Withering would not consider it, it had to be precise!

Withering Continued

In 1775 one of Withering's patients was dying, and he thought the case hopeless. But the patient, being unwilling to simply die, took a gypsy's remedy – and recovered. Withering hunted down the gypsy and found that the major ingedient was a common flower, foxglove.

Withering Continued

Withering was intrigued and began studying foxglove and began experimenting with different parts of the plant on numerous patients. He finally concluded that powered leaf was best and could be given orally. This was the discovery of digitalis, a drug in common use for heart conditions to this day.



Withering vs Today

- Too often an adversarial relationship between orthodox and alternative professionals
- That is slowly changing.
- Dieticians have been very opposed to supplements – now 46% entry level and 42% of non-entry level dieticians either use or plan to use alternative supplements in their practice. Touger-Decker et al. (2003 Nov.) J. Am. Dietetic Assoc. 103: 1465-1467.

Evaluating Supplements - Efficacy

- Does the supplement have a strong history of traditional use.
- Does the supplement have scientific backing.
  - Epidemiological
  - Mechanistic Cell Studies
  - Animal
  - Human
  - Well Designed

Evaluating Supplements - Safety

- For Drugs there is a cost/benefit analysis. Benefits are weighed against adverse side effects.
- For Supplements no efficacy can be claimed, therefore no cost/benefit analysis. Must be almost totally safe.
- Side effects need to be better studied and communicated.
- PDR for nutritional supplements a good start.

Evaluating Supplements - Dose

- Many supplements have inadequate amounts of active ingredients to be effective.
- Very few herbs are potent enough for whole herb capsules to be effective
- Standardized extracts give potent doses, but lose characteristics of whole herbs.

Evaluating Supplements - Quality

- Difficult to know, even testing does not always tell whole truth
- Sometimes chemical actives can be added – St. John's Wort
- Difficult to distinguish whole herbs –digitalis and plantain
- Contamination difficult, many ingredients coming from third world countires – especially China. See the link: http://www.beta-glucan-info.com/pdf/buyerbeware.pdf

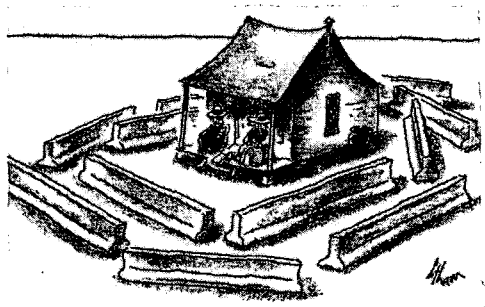
Evaluating Supplements – Source

- It is important to know the source of supplements. Consumers are no match for dishonest manufacturers
- Internet – made supplements accessible but full of bad information
- For many supplements, testing is not the only factor. Dissolution, absorption, and synergistic ingredients may all be important determinants of quality and effectiveness.

New Laws

- Currently there is no way to communicate reliable information on supplements effectively & legally
- A lot of confusion on quality and safety - much of it is not justified
- New laws are attempting to address these issues
- Whether the laws will be improvements remains to be seen

New Laws: Bioterrorism Act



Bioterrorism Act

Public Health Security and Bioterrorism Preparedness and Response Act of 2002

- Registration of Food Facilities by December 12, 2003. Foreign facilities must register unless products are further processed by other foreign company before shipped to the USA
- Establishment and Maintenance of Records - established requirements for manufacturers to maintain records of immediate and previous sources
- Prior notice of Imported Food Shipments

Bioterrorism Act – Foods Covered

- Dietary supplements and dietary ingredients
- Infant formula
- Beverages (including alcoholic beverages and bottled water)
- Fruits and vegetables
- Fish and seafood
- Dairy products and shell eggs
- Raw agricultural commodities for use as food or components of food
- Canned and frozen foods
- Bakery goods, snack food, and candy (including chewing gum)
- Live food animals
- Animal feeds and pet food

Bioterrorism Act – Prior Notice

- ***When must prior notice be submitted?*** Prior notice must be received and confirmed electronically by FDA no more than 5 days before arrival and, as specified by the mode of transportation below, no fewer than:
- 2 hours before arrival by land by road
- 4 hours before arrival by air or by land by rail
- 8 hours before arrival by water
- The time consistent with the timeframe established for the mode of transportation for an article of food carried by or otherwise accompanying an individual if it is subject to prior notice (The food must also be accompanied by the FDA confirmation.)
- *In addition, prior notice must be received and confirmed* electronically by FDA before food is mailed by international mail. (The parcel must be accompanied by confirmation of FDA receipt of prior notice.)

Organically Certification

- Until recently "organically grown" has not had a consistent definition
- There were many private certification organizations with different standards
- Now there are government standards for organic

Organic Certification

- No GMO products
- No Irradiated Products
- Very strict limitations on fertilizers
- Very strict limitations on pesticides and herbicides
- Very strict limits on preserveatives
- Covers both growing and processing
- Product levels in mixed products

Advantages of Organic

- Good for the environment
- Good for health - reduces exposure to chemicals
- Reduces dependence on expensive chemicals and technology
- Works well for small sized farms
- Higher prices realized for products
- Greater consumer acceptance

Foreign Organic Certification Organizations Accepted or Applied

- Germany (9)
- Israel (2)
- Spain (5)
- Argentina (3)
- Costa Rica (2)
- Australia (2)
- Italy (7)
- Turkey
- Hungary
- Peru
- Bolivia
- Canada (9)
- Egypt (2)
- Chile
- Mexico
- Greece
- France
- Switzerland
- Brazil
- Guatemala
- Thailand
- China
- Japan
- Netherlands (3)
- United Kingdom

Current Good Manufacturing Practices (cGMPs) for Supplements

- Will be very strict on record keeping, cleanliness, final product testing, stability testing
- Will be difficult for small companies to comply with - FDA estimates 150-200 companies will not survive
- Proposed regulations published, final version could be released any time.

Links to USA Regulatory Web Sites

- Information on Bioterrorism Act Registration and Notification
- http://www.fda.gov/oc/bioterrorism/bioact.html
- Register and Make Notifications Under Bioterrorism Act
- https://www.access.fda.gov/
- Information on Organic Farming and Certification
- http://www.ams.usda.gov/nop/indexIE.htm
- FDA Industry Information
- http://www.fda.gov/oc/industry/default.htm