

BACKGROUND

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Biologically Based Practices: An Overview

About This Series

“Biologically Based Practices: An Overview” is one of five background papers on the major areas of complementary and alternative medicine (CAM). The series was prepared as part of the National Center for Complementary and Alternative Medicine’s (NCCAM’s) strategic planning efforts for the years 2005 to 2009. These brief reports should not be viewed as comprehensive or definitive reviews. Rather, they are intended to provide a sense of the overarching research challenges and opportunities in particular CAM approaches. For further information on any of the therapies in this paper, contact the NCCAM Clearinghouse (see “For More Information”).

Introduction

Definition of Scope of Field

The CAM domain of biologically based practices includes, but is not limited to, botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics and probiotics, whole diets, and functional foods.

Dietary supplements are a subset of this CAM domain. In the Dietary Supplement Health and Education Act (DSHEA) of 1994, Congress defined a dietary supplement as a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet. The “dietary ingredients” in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and they can occur in many forms, such as tablets, capsules, softgels, gelscaps, liquids, or powders.¹

The Food and Drug Administration (FDA) regulates dietary supplements differently than drug products (either prescription or over-the-counter). First, drugs are required to follow defined good manufacturing practices (GMPs). The FDA is developing GMPs for dietary supplements. However, until they are issued, companies must follow existing manufacturing requirements for foods. Second, drug products must be approved by the FDA as safe and efficacious prior

to marketing. In contrast, manufacturers of dietary supplements are responsible for ensuring that their products are safe. While the FDA monitors adverse effects after dietary supplement products are on the market, newly marketed dietary supplements are not subject to premarket approval or a specific postmarket surveillance period. Third, while DSHEA requires companies to substantiate claims of benefit, citation of existing literature is considered sufficient to validate such claims. Manufacturers are not required, as they are for drugs, to submit such substantiation data to the FDA; instead, it is the Federal Trade Commission that has primary responsibility for monitoring dietary supplements for truth in advertising. A 2004 Institute of Medicine (IOM) report on the safety of dietary supplements recommends a framework for cost-effective and science-based evaluation by the FDA.²

History and Demographic Use of Biologically Based Practices

Dietary supplements reflect some of humankind's first attempts to improve the human condition. The personal effects of the mummified prehistoric "Ice Man" found in the Italian Alps in 1991 included medicinal herbs. By the Middle Ages, thousands of botanical products had been inventoried for their medicinal effects. Many of these, including digitalis and quinine, form the basis of modern drugs.³

Interest in and use of dietary supplements have grown considerably in the past two decades. Consumers state that their primary reason for using herbal supplements is to promote overall health and wellness, but they also report using supplements to improve performance and energy, to treat and prevent illnesses (e.g., colds and flu), and to alleviate depression. According to a 2002 national survey on Americans' use of CAM, use of supplements may be more frequent among Americans who have one or more health problems, who have specific diseases such as breast cancer, who consume high amounts of alcohol, or who are obese.⁴ Supplement use differs by ethnicity and across income strata. On average, users tend to be women, older, better educated, live in one- or two-person households, have slightly higher incomes, and live in metropolitan areas.

Use of vitamin and mineral supplements, a subset of dietary supplements, by the U.S. population has been a growing trend since the 1970s. National surveys—such as the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994); NHANES, 1999–2000; and the 1987 and 1992 National Health Interview Surveys—indicate that 40 to 46 percent of Americans reported taking at least one vitamin or mineral supplement at some time within the month surveyed.⁵⁻⁸ Data from national surveys collected before the enactment of DSHEA in 1994, however, may not reflect current supplement consumption patterns.

In 2002, sales of dietary supplements increased to an estimated \$18.7 billion per year, with herbs/botanical supplements accounting for an estimated \$4.3 billion in sales.⁹ Consumers consider the proposed benefits of herbal supplements less believable than those of vitamins and minerals. From 2001 to 2003, sales of herbs experienced negative growth. This was attributed to consumers' waning confidence and confusion. Within the herbal category, however, formulas led single herbs in sales; products became increasingly condition-specific; and sales of women's products actually increased by approximately 25 percent.¹⁰

In contrast to dietary supplements, functional foods are components of the usual diet that may have biologically active components (e.g., polyphenols, phytoestrogens, fish oils, carotenoids) that may provide health benefits beyond basic nutrition. Examples of functional foods include soy, nuts, chocolate, and cranberries. These foods' bioactive constituents are appearing with increasing frequency as ingredients in dietary supplements. Functional foods are marketed directly to consumers. Sales increased from \$11.3 billion in 1995 to about \$16.2 billion in 1999. Unlike dietary supplements, functional foods may claim specific health benefits.¹¹ The Nutrition Labeling and Education Act (NLEA) of 1990 delineates the permissible labeling of these foods for health claims.*

Whole diet therapy has become an accepted practice for some health conditions. However, the popularity of unproven diets, especially for the treatment of obesity, has risen to a new level as the prevalence of obesity and metabolic syndrome among Americans has increased and traditional exercise and diet "prescriptions" have failed. Popular diets today include the Atkins, Zone, and Ornish diets, Sugar Busters, and others. The range of macronutrient distributions of these popular diets is very wide. The proliferation of diet books is phenomenal. Recently, food producers and restaurants have been targeting their marketing messages to reflect commercially successful low-carbohydrate diets.

Public need for information about dietary supplements, functional foods, and selected strict dietary regimens has driven research on the effectiveness and safety of these interventions and the dissemination of research findings.

Scope of the Research

Range of Studies

Research on dietary supplements spans the spectrum of basic to clinical research and includes ethnobotanical investigations, analytical research, and method development/validation, as well as bioavailability, pharmacokinetic, and pharmacodynamic studies. However, the basic and preclinical research is better delineated for supplements composed of single chemical constituents (e.g., vitamins and minerals) than for the more complex products (e.g., botanical extracts). There is an abundance of clinical research for all types of dietary supplements. Most of this research involves small phase II studies.

The literature on functional foods is vast and growing; it includes clinical trials, animal studies, experimental *in vitro* laboratory studies, and epidemiological studies.¹² Much of the current evidence for functional foods is preliminary or not based on well-designed trials. However, the foundational evidence gained through other types of investigations is significant for some functional foods and their "health-promoting" constituents. The strongest evidence for effectiveness is that developed in accordance with the NLEA guidelines for preapproved health claims (e.g., oat bran or psyllium).

*Information on NLEA and the scientific review of health claims for conventional foods and dietary supplements is available at <http://vm.cfsan.fda.gov/~dms/ssaguide.html#foot1>.

An important gap in knowledge concerns the role of diet composition in energy balance. Popular diets low in carbohydrates have been purported to enhance weight loss. Shorter-term clinical studies show equivocal results. In addition, mechanisms by which popular diets affect energy balance, if at all, are not well understood. Although numerous animal studies assessing the impact of diet composition on appetite and body weight have been conducted, these studies have been limited by availability and use of well-defined and standardized diets. The research on weight loss is more abundant than that on weight maintenance.

Primary Challenges

Many clinical studies of dietary supplements are flawed because of inadequate sample size, poor design, limited preliminary dosing data, lack of blinding even when feasible, and/or failure to incorporate objective or standardized outcome instruments. In addition, the lack of reliable data on the absorption, disposition, metabolism, and excretion of these entities in living systems has complicated the selection of products to be used in clinical trials.^{13,14} This is more problematic for complex preparations (e.g., botanicals) than for products composed of single chemical moieties (e.g., zinc).

The lack of consistent and reliable botanical products represents a formidable challenge both in clinical trials and in basic research. Most have not been sufficiently characterized or standardized for the conduct of clinical trials capable of adequately demonstrating safety or efficacy, or predicting that similarly prepared products would also be safe and effective in wider public use. Consequently, obtaining sufficient quantities of well-characterized products for evaluation in clinical trials would be advantageous. Several issues regarding the choice of clinical trial material require special attention, for example:

- Influences of climate and soil
- Use of different parts of the plants
- Use of different cultivars and species
- Optimal growing, harvesting, and storage conditions
- Use of the whole extract or a specific fraction
- Method of extraction
- Chemical standardization of the product
- Bioavailability of the formulation
- Dose and length of administration

Some nonbotanical dietary supplements, such as vitamins, carnitine, glucosamine, and melatonin, are single chemical entities. Botanicals, however, are complex mixtures. Their putative active ingredients may be identified, but are rarely known for certain. Usually, there is more than one of these ingredients, often dozens. When active compounds are unknown, it is necessary to identify marker or reference compounds, even though they may be unrelated to biological effects. Qualitative and quantitative determinations of the active and marker compounds, as well as the presence of product contaminants, can be assessed by capillary electrophoresis, gas chromatography, liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry, high-performance liquid chromatography, and liquid chromatography-

multidimensional nuclear magnetic resonance. Fingerprinting techniques can map out the spectrum of compounds in a plant extract. New applications of older techniques and new analytical methods continue to be developed and validated. However, there remains a paucity of analytical tools that are precise, accurate, specific, and robust. Steps are currently being taken to apply molecular tools, such as DNA fingerprinting, to verify species in products, while transient expression systems, and microarray and proteomic analyses, are beginning to be used to define the cellular and biological activities of dietary supplements.

Particular attention should be paid to the issues of complex botanicals and clinical dosing. Quality control of complex botanicals is difficult, but must be accomplished, because it is not ethical to administer an unknown product to patients. The use of a suboptimal dose that is safe but ineffective does not serve the larger goals of NCCAM, the CAM community, or public health. Although the trial would indicate only that the tested dose of the intervention was ineffective, the public might conclude that all doses of the intervention are ineffective, and patients would be denied a possible benefit from the intervention. Overdosing, on the other hand, might produce unnecessary adverse effects. Phase I/II studies should be conducted first to determine the safety of various doses, and the optimal dose should then be tested in a phase III trial. As a result, maximum benefit would be seen in the trial; also, any negative result would be definitive.

To a great extent, the difference between a dietary supplement and a drug lies in the use of the agent, not in the nature of the agent itself. If an herb, vitamin, mineral, or amino acid is used to resolve a nutritional deficiency or to improve or sustain the structure or function of the body, the agent is considered a dietary supplement. If the agent is used to diagnose, prevent, treat, or cure a disease, the agent is considered a drug. This distinction is key when the FDA determines whether proposed research on a product requires an investigational new drug (IND) exemption. If the proposed investigation of a lawfully marketed botanical dietary supplement is to study its effects on diseases (i.e., to cure, treat, mitigate, prevent, or diagnose a disease and its associated symptoms), then the supplement is more likely to be subject to IND requirements. The FDA has worked with NCCAM to provide direction to investigators and recently created a Botanical Review Team to ensure consistent interpretation of the document *Guidance for Industry—Botanical Drug Products*.[†] Such FDA guidance is currently unavailable for other products (e.g., probiotics).

Similarly, little attention has been paid to the quality of probiotics. Quality issues for probiotic supplements may include:

- Viability of bacteria in the product
- Types and titer of bacteria in the product
- Stability of different strains under different storage conditions and in different product formats
- Enteric protection of the product

Therefore, for optimal studies, documentation of the type of bacteria (genus and species), potency (number of viable bacteria per dose), purity (presence of contaminating or ineffective microorganisms), and disintegration properties must be provided for any strain to be

[†] See www.fda.gov/cder/guidance/index.htm under “Chemistry.”

considered for use as a probiotic product. Speciation of the bacteria must be established by means of the most current, valid methodology.

Many of the challenges identified for research on dietary supplements, including issues of composition and characterization, are applicable to research on functional foods and whole diets. In addition, challenges of popular diet research include adherence to the protocol for longer-term studies, inability to blind participants to intervention assignment, and efficacy versus effectiveness.

Summary of the Major Threads of Evidence

Over the past few decades, thousands of studies of various dietary supplements have been performed. To date, however, no single supplement has been proven effective in a compelling way. Nevertheless, there are several supplements for which early studies yielded positive, or at least encouraging, data. Good sources of information on some of them can be found at the Natural Medicines Comprehensive Database and a number of National Institutes of Health (NIH) Web sites. The NIH Office of Dietary Supplements (ODS) annually publishes a bibliography of resources on significant advances in dietary supplement research. Finally, the ClinicalTrials.gov database lists all NIH-supported clinical studies of dietary supplements that are actively accruing patients.[‡]

For a few dietary supplements, data have been deemed sufficient to warrant large-scale trials. For example, multicenter trials have concluded or are in progress on ginkgo (*Ginkgo biloba*) for prevention of dementia, glucosamine hydrochloride and chondroitin sulfate for osteoarthritis of the knee, saw palmetto (*Serenoa repens*)/African plum (*Prunus africana*) for benign prostatic hypertrophy, vitamin E/selenium for prevention of prostate cancer, shark cartilage for lung cancer, and St. John's wort (*Hypericum perforatum*) for major and minor depression. The results of one of the depression studies showed that St. John's wort is no more effective for treating major depression of moderate severity than placebo. Other studies of this herb, including its possible value in treatment of minor depression, are under way.

Reviews of the data regarding some dietary supplements have been conducted, including some by the members of the Cochrane Collaboration[§]. The Agency for Healthcare Research and Quality has produced a number of evidence-based reviews of dietary supplements, including garlic, antioxidants, milk thistle, omega-3 fatty acids, ephedra, and S-adenosyl-L-methionine (SAME). The following are examples of findings from some of these reviews:

- Analysis of the literature shows generally disappointing results for the efficacy of antioxidant supplementation (vitamins C and E, and coenzyme Q10) to prevent or treat cancer. Because this finding contrasts with the benefits reported from observational studies, additional research is needed to understand why these two sources of evidence disagree.¹⁵

[‡]The Natural Medicines Comprehensive Database is accessible at www.naturaldatabase.com. Related NIH Web sites include nccam.nih.gov/health, ods.od.nih.gov, and www3.cancer.gov/occam/information.html. The ODS annual bibliographies can be found at ods.od.nih.gov/research/annual-bibliographies.aspx. ClinicalTrials.gov can be accessed at www.clinicaltrials.gov.

[§] The Cochrane Database is accessible at www.cochrane.org.

- Similarly, the literature on the roles of the antioxidants vitamins C and E and coenzyme Q10 for cardiovascular disease also shows discordance between observational and experimental data. Therefore, the thrust of new research into antioxidants and cardiovascular disease should be randomized trials.¹⁶
- The clinical efficacy of milk thistle to improve liver function is not clearly established. Interpretation of the evidence is hampered by poor study methods or poor quality of reporting in publications. Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferase levels. Liver function tests are overwhelmingly the most common outcome measure studied. Available evidence is not sufficient to suggest whether milk thistle is more effective for some liver diseases than others. Available evidence does suggest that milk thistle is associated with few, and generally minor, adverse effects. Despite substantial *in vitro* and animal research, the mechanism of action of milk thistle is not well defined and may be multifactorial.¹⁷
- The review of SAME for the treatment of depression, osteoarthritis, and liver disease identified a number of promising areas for future research. For example, it would be helpful to conduct (1) additional review studies, studies elucidating the pharmacology of SAME, and clinical trials; (2) studies that would lead to a better understanding of the risk-benefit ratio of SAME compared to that of conventional therapy; (3) good dose-escalation studies using the oral formulation of SAME for depression, osteoarthritis, or liver disease; and (4) larger clinical trials once the efficacy of the most effective oral dose of SAME has been demonstrated.¹⁸
- Two high-quality randomized controlled trials provide good evidence that cranberry juice may decrease the number of symptomatic urinary tract infections in women over a 12-month period. It is not clear if it is effective in other groups. The fact that a large number of women dropped out of these studies indicates that cranberry juice may not be acceptable over long periods of time. Finally, the optimal dosage or method of administration of cranberry products (e.g., juice or tablets) is not clear.¹⁹

There has been some study of other popular dietary supplements. For example, valerian is an herb often consumed as a tea for improved sleep, and melatonin is a pineal hormone touted for the same purpose.²⁰⁻²² Small studies suggest that these two supplements may relieve insomnia, and there may be little harm in a trial course of either one. Echinacea has long been taken to treat or prevent colds; other supplements currently used for colds include zinc lozenges and high doses of vitamin C. As yet, only moderate-sized studies have been conducted with echinacea or zinc, and their outcomes have been conflicting.²³⁻²⁶ Large trials of high doses of oral vitamin C showed little, if any, benefit in preventing or treating the common cold.²⁷⁻³⁰

Because of widespread use, often for centuries, and because the products are “natural,” many people assume dietary supplements to be inert or at least innocuous. Yet, recent studies show clearly that interactions between these products and drugs do occur. For example, the active ingredients in ginkgo extract are reported to have antioxidant properties and to inhibit platelet aggregation.³¹ Several cases have been reported of increased bleeding associated with ginkgo’s use with drugs that have anticoagulant or antiplatelet effects. St. John’s wort induces a broad range of

enzymes that metabolize drugs and transport them out of the body. It has been shown to interact with a number of drugs that serve as substrates for the cytochrome P450 CYP3A enzymes responsible for metabolism of approximately 60 percent of current pharmaceutical agents.^{32,33} Other dietary supplements shown to potentiate or interfere with prescription drugs include garlic, glucosamine, ginseng (*Panax*), saw palmetto, soy, valerian, and yohimbe.¹⁴

In addition to interacting with other agents, some herbal supplements can be toxic. Misidentification, contamination, and adulteration may contribute to some of the toxicities. But other toxicities may result from the products themselves. For example, in 2001, extracts of kava were associated with fulminant liver failure.^{34,36} More recently, the FDA banned the sale of ephedra after it was shown to be associated with an increased risk of adverse events.^{37,38}

Given the large number of dietary supplement ingredients; that dietary supplements are assumed to be safe in general; and that the FDA is unlikely to have the resources to evaluate each ingredient uniformly, a 2004 Institute of Medicine report offers a framework for prioritizing evaluation of supplement safety.² Among the report's recommendations are:

- All federally supported research on dietary supplements conducted to assess efficacy should be required to include the collection and reporting of all data on the safety of the ingredient under study.
- The development of effective working relationships and partnerships between the FDA and NIH should continue.
- The FDA and NIH should establish clear guidelines for cooperative efforts on high-priority safety issues related to the use of dietary supplements.

The FDA lists warnings and safety information on dietary supplements (e.g., androstenedione, aristolochic acid, comfrey, kava, and PC SPES) as they become available.**

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** See www.cfsan.fda.gov/~dms/ds-warn.html.

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For More Information

NCCAM Clearinghouse

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