

Review

In the Midst of Confusion Lies Opportunity: Fostering Quality Science in Dietary Supplement Research

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The Office of Dietary Supplements (ODS) was established at the National Institutes of Health (NIH) by Congress through the Dietary Supplement Health and Education Act (DSHEA) of 1994. The mission of the ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results and educating the public, all in an effort to foster an enhanced quality of life and health for the U.S. population. In pursuit of this mission, ODS takes into account an array of dietary supplement ingredients and products. This includes vitamin and mineral supplements and botanicals, as well as non-nutrient supplements. Toward that end, ODS has taken a number of steps. In collaboration with other Institutes and Centers at NIH, ODS has established a network of Dietary Supplement Research Centers around the country that provide the focus for multidisciplinary research efforts; it supports research activities and scientific conferences, it supports evidence-based reviews of supplements, and it maintains a public database of scientific literature on dietary supplements. The lack of credible information from well-controlled studies of many dietary supplements raises issues of caution and concern. The ODS is committed to providing and disseminating accurate and reliable scientific information on dietary supplements.

Key teaching points:

- The Office of Dietary Supplements at the National Institutes of Health was established to promote research on dietary supplements.
- The Dietary Supplement Research Centers program is key to developing new laboratory methodologies, as well as contributing to the development of scientifically-based guidelines for the use of supplements.
- Lack of well-controlled studies limits recommendations for use of dietary supplements.

INTRODUCTION

The use of dietary supplements is widespread among people motivated by general health concerns. Estimates of use range from 40 percent to 68 percent for the U.S. population [1, 2]. Americans have reported a variety of reasons for taking dietary supplements, including decreasing their susceptibility to health problems such as stress, colds, heart attacks and cancer and increasing their physical stamina [1,3–6].

Evidence is accumulating for a number of supplements supporting beneficial health effects from doses not usually achieved by individuals consuming a typical diet. For example, the periconceptional use of folic acid-containing supplements is associated with reduction of the first occurrence, as well as the recurrence, of neural tube defects [7]. Because 10 percent to 30 percent of older individuals may not fully absorb food-bound

vitamin B-12, older people have been advised to meet their RDA for vitamin B-12 by consuming foods fortified with B-12 or a supplement containing B-12 [7,8].

In contrast, it was recently announced that there was insufficient evidence to support taking antioxidant supplements, such as selenium and vitamins C and E, or carotenoids to prevent chronic disease [9]. The scientific literature relating to dietary supplements is proliferating, and it is important that nutrition and health professionals become knowledgeable about the use, formulation and properties of these supplements.

THE OFFICE OF DIETARY SUPPLEMENTS AT NIH

To assist scientists, health professionals and the public in interpreting the literature on dietary supplements, the Office of

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Dietary Supplements (ODS) was established at the National Institutes of Health (NIH) by Congress through the Dietary Supplement Health and Education Act (DSHEA) of 1994 [10]. The mission of the ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results and educating the public to foster an enhanced quality of life and health for the U.S. population [11]. The ODS seeks to encourage and foster research on the health benefits and risks of dietary supplements based on the merit of the underlying scientific evidence. Such research is warranted regardless of how ingredients or supplements might be currently incorporated into different categories of commercial products or their regulatory status in the commercial marketplace.

In this effort, over the past three years the ODS has co-funded 15 investigator-initiated research studies with other NIH Institutes and Centers and has sponsored or cosponsored over 35 workshops, symposia and conferences. Additionally, the ODS, along with the National Cancer Institute, has supported the development and promotion of a CD-ROM Nutrition in Medicine Series (website: <http://www.med.unc.edu/nutr/nim>) for integration initially into medical school curricula nationwide and then into the curricula for other health professionals.

In partnership with the Food and Nutrition Information Center and the National Agricultural Library at the USDA, the ODS developed the International Bibliographic Information on Dietary Supplements (IBIDS) database—a collection of over 400,000 national and international reference citations on dietary supplements. References are culled from MEDLINE, AGRICOLA, and AGRIS under one user-friendly search engine for researchers in industry and academia, as well as for the general public (for information on IBIDS and other ODS activities, visit our website: <http://dietary-supplements.info.nih.gov>). The NIH, with its sister federal agencies (CDC, NCHS, DoD, FDA and USDA) and Canadian partner, Health and Welfare Canada, supports the work of the Food and Nutrition Board (FNB) of the National Academy of Sciences in the development of the new Dietary Reference Intakes. The scientific reports issued by the FNB focus on nutrient needs for Americans, not only to support basic nutrition, but also to evaluate the role of nutrients in disease prevention and maintenance of optimal health [12].

DIETARY SUPPLEMENT RESEARCH ACTIVITIES

In the last two years, ODS has made four awards in collaboration with the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of General Medical Sciences (NIGMS) and the Office of Research on

Women's Health to establish NIH Centers for Dietary Supplements Research with an emphasis on botanicals. In 1999, competitive awards of approximately \$1.5 million per year for five years were made to the University of California at Los Angeles and to the University of Illinois at Chicago. In 2000, similar awards were made to Purdue University and to the University of Arizona.

The eventual goal of the program is to develop a network of Dietary Supplement Research Centers, at which dietary supplement research encompassing all classes of dietary supplements can be fostered and at which training and career development in the field can take place. Information on the Centers' program can be found on the ODS Internet homepage.

Additional NIH-sponsored programs intended to support dietary supplements research are being implemented through NCCAM, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Environmental Health Sciences' National Toxicology Program (NTP). NCCAM has initiated a multi-center clinical trial with the National Institute on Aging to evaluate the safety and efficacy of ginkgo biloba in the prevention of dementia in older individuals. Additionally, there are funded clinical trials of St. John's wort in depression (NCCAM and the National Institute of Mental Health) and glucosamine and chondroitin sulfate in osteoarthritis (NCCAM and National Institute of Arthritis and Musculoskeletal and Skin Diseases). The NTP is charged with coordinating toxicology research and testing activities within the DHHS and providing information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities and the public. The NTP has undertaken to study the chemistry, pharmacology, clinical efficacy and safety of many of the popular herbal products. NTP "Executive Summaries" of studies are available for seven herbs and/or herbal ingredients, and four additional herbs are under review for study (website: <http://ntp-server.niehs.nih.gov>). The NHLBI and National Institute of Diabetes and Digestive and Kidney Diseases have also recently announced the Nutrition Academic Award, an initiative to encourage the development and enhancement of nutrition training in the medical school curricula. The goal of the award is to increase opportunities for students, house staff, faculty and practicing physicians to learn nutrition principles and clinical practice skills with an emphasis on preventing cardiovascular diseases, obesity, diabetes and other chronic diseases.

Recently a three-day NIH Consensus Conference on Osteoporosis Prevention, Diagnosis and Therapy was held on March 27–29, 2000, for which a summary statement is available (<http://consensus.nih.gov>). Similarly a Consensus Development Conference on Screening and Management of Phenylketonuria was held in October 2000. The ODS supported a conference with the NIGMS, entitled "Metals in Medicine: Targets, Diagnostics, & Therapeutics" (website: www.nigms.nih.gov/news/meetings/metals), and in February 2001 with the National Institute of Child Health and Human

Development to investigate the use of dietary supplements in children (www.nichd.nih.gov/prip/).

Released in December 2000, the Annual Bibliography of Significant Advances in Dietary Supplement Research 1999 is a joint effort of the ODS and the Consumer Healthcare Products Association. The purpose of this bibliography is to help develop an overall perspective on how the dietary supplement field is advancing through quality research. Copies may be downloaded from the ODS Internet homepage.

OTHER FEDERAL PROGRAMS SUPPORTING ACTIVITIES ON DIETARY SUPPLEMENTS

Other federally-sponsored programs to support research on and encourage awareness of dietary supplements include the FDA Center for Food Safety and Applied Nutrition *Dietary Supplements Strategy*—a 10-year plan. FDA's "Program Goal by the year 2010 is to have a science-based regulatory program that fully implements the Dietary Supplement Health and Education Act of 1994, thereby providing consumers with a high level of confidence in the safety, composition, and labeling of dietary supplement products [13]." Additionally, the Federal Trade Commission, Bureau of Consumer Protection, has published *Dietary Supplements: An Advertising Guide for Industry* [14] to assist industry in the conduct of sound promotional and advertising practices.

IN THE MIDST OF CONFUSION LIES OPPORTUNITY

Along with this new emphasis on the use of dietary supplements, there is confusion, caution and concern. Much confusion stems from how dietary supplements were to be regulated by the DSHEA. Unlike prescription drugs or over-the-counter (OTC) preparations, dietary supplements are not required by the government to meet any standards of quality. DSHEA allows manufacturers to introduce more products rapidly into the marketplace, increasing the potential for compromises in quality control or in standardization. Botanicals used in folk and traditional medicine, and products available commercially as dietary supplements, usually contain many diverse compounds rather than a single active pharmacological agent. In many instances, the active ingredients are not known. The quality, strength and purity of botanical products may vary greatly due to factors such as the plant part used, the time of year that the plant was gathered and the manufacturing processes employed. Active ingredients of botanical products can potentially vary from batch to batch. The need for sound analytical methods for determination of bioactive constituents in a complex matrix as they exist in dietary supplements continues to grow.

A need for caution stems from the fact that many supplements are being promoted for multiple intended uses and are available in many different formulations. This can result in a variety of beneficial—as well as not so beneficial—health effects, depending on the targeted population. Results from some recent clinical studies suggest that caution is warranted. Recall that, not so long ago, beta-carotene was touted for prevention of cancer and heart disease, among other uses. Well-designed clinical trials found that not only was there essentially little benefit from beta-carotene for the prevention of cancer and heart disease, but also it found that it was associated with higher lung cancer incidence in certain subpopulations [15]. Recently, concerns have been raised about one of the most commonly used herbs in the world, St. John's wort, as more and more instances have been reported of significant interactions with other drugs dependent on metabolism by the liver [16]. In March 2000, the American Society of Anesthesiologists released an advisory urging patients to stop taking herbal medicines at least two to three weeks prior to surgery. However, we must remember that plants or plant parts supply healing remedies for an estimated 80% of the world's population and serve as chemical models for pharmaceutical drugs [17]. There are a number of plant-derived products that have withstood the rigors of clinical trials and have proven to be valuable contributions to medical treatment as prescription and OTC drugs, such as digoxin from foxglove, psyllium from plantago seeds, morphine from poppies, aspirin from willow bark, paclitaxel (taxol) from the bark of the Pacific yew tree and capsaicin from cayenne pepper or chili pepper. Psyllium seed (*Plantago psyllium*) is a component of many bulk-forming OTC laxatives. Recent studies [18] have also shown that psyllium-enriched cereals may lower blood cholesterol levels when consumed regularly with a heart-healthy diet. Topical capsaicin, derived from *Capsicum*, has been used to treat a variety of conditions to include arthritic pain, diabetic neuropathy and pain associated with herpes shingles (herpes zoster) [19]. Capsaicin's mechanism of action is believed to act through the depletion of substance P, a peptide neurotransmitter, from sensory nerve terminals.

Concern exists regarding the safety and efficacy of supplements and their potential toxicity, as adverse effects are not systematically tabulated, reviewed, evaluated and reported. Compared to drugs that produce quantitative effects on target organ systems, dietary supplements often produce a more generalized and qualitative response, making it difficult to establish cause and adverse effect, as well as to attribute benefit to use. Digitalis (*Digitalis purpurea*), one of the most effective drugs ever developed from a plant, provides a most dramatic example of the difficulties encountered in identifying adverse effects from herbal products because it has a relatively narrow therapeutic-to-toxic ratio. A recent case report highlighted the serious adverse effects incurred by two women who consumed a botanical product contaminated with the poisonous plant *Digitalis lanata* containing cardiac glycosides [20].

Another illustrative example involves soy and soy constituents. After reviewing the evidence, the FDA has recently authorized a health claim for soy protein in that it may aid in lowering the risk of heart disease, but the claim was not extended to other soy constituents, such as the soy isoflavones that occur naturally in soy products or that may also be found in concentrated form as dietary supplements. "While isoflavones may have beneficial effects at some ages or circumstances, this cannot be assumed to be true at all ages. Isoflavones are like other estrogens in that they are two-edged swords, conferring both benefits and risks [21]." Recent findings suggest that maternal ingestion of bioflavonoids (e.g., flavones, flavanones and isoflavones) found in foods such as tea, onions, soy and wine may induce MLL (mixed-lineage leukemia) gene breaks and potentially translocations in utero leading to infant and early childhood leukemia [22]. It should be noted that prior epidemiologic studies were not designed to measure the disease impact of phytochemicals ingested either as foods or as dietary supplements. Needed to move the research forward are the epidemiologic studies with biomarkers to more accurately quantify phytochemical intake and excretion while controlling for confounders in carefully selected populations with a wide range of intakes.

FUTURE EXPECTATIONS

Until the state of the science catches up to the public demand for dietary supplements, where does this leave the health professional? *The Journal of the American College of Nutrition* is initiating a new series on dietary supplements to assist scientists and health professionals in acquiring the information they need in order to stay abreast of this dynamically evolving field. In each issue, a review article will appear on a dietary supplement of current or "hot" interest. The primary objective of these reviews will be to present a well-balanced academic review of the current state of the science on a selected dietary supplement. What is meant by a well-balanced academic review? Each review submitted to the Journal will highlight and discuss the standards of evidence of effectiveness for a dietary supplement. There is no single agreed-upon standard; however, models do exist (e.g., FDA, United States Pharmacopeia, Institute of Medicine) and numerous reference monographs are available (United States Pharmacopeia, German Commission E, European Scientific Cooperative on Phytotherapy, WHO Monograph on Selected Medicinal Plants). The sources of evidence must be those that one would rely upon for any substance used for health or therapeutic purposes: clinical trials, epidemiologic studies and other sources, and these may be ranked according to a hierarchy of evidence [23]. Systematic reviews of the literature and meta-analyses to evaluate the totality of the clinical evidence, such as those performed by the

Agency for Health Care Research and Quality (AHRQ) Evidence-based Practice Centers (evidence-based reports are available at <http://www.ahrq.gov/clinic/epicx.htm#reports> for garlic and milk thistle), Cochran Collaboration and other organizations are increasingly utilized to evaluate clinical interventions. This type of review may be equally valuable in judging efficacy for dietary supplements as it has been for drugs. There are all kinds of information, all kinds of studies. The issue is not quantity, but quality. The hallmark of a good study is its design, execution, analysis and conclusions. Execution refers to how well the study and confounding variables have been controlled. Experimental design is the road map and is particularly key for botanical dietary supplements, where product selection and standardization are still poorly defined and reproducibility of results is critical.

The ODS is pleased to support this new *JACN* featured section on dietary supplements in a continuing effort to bring forward, discuss and evaluate the state of the science on dietary supplements for the health professional.

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