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Approaches by the US National Institutes of Health to support rigorous scientific research on dietary supplements and natural products

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Research relevant to dietary supplements (DS) is supported by many different components of the US National Institutes of Health (NIH), and spans the range from mechanistic through clinical and epidemiological. Reproducibility of DS research requires meticulous attention to the appropriate application of rigorous and comprehensive analyses of the DS (identity, stability, bioavailability, and metabolism), as well as the availability of relevant reference materials. The need for rigor is enhanced in cases where the DS studied include chemically complex natural products with unclear mechanisms of action. Here we describe some of the NIH components that support DS research, as well as some of the reference materials, methods and knowledge developed with NIH support that are germane not only to DS research but also useful to regulators and producers of DS.

The US Congress enacted the Dietary Supplement Health and Education Act of 1994 (DSHEA)^[1] to define and establish the regulatory framework for dietary supplements. DSHEA defines DS as products intended to supplement the diet that contain one or more vitamin, mineral, amino acid, herb or botanical (excluding tobacco), or other dietary substances, and which are not sold as conventional foods. DS may not be claimed to diagnose, mitigate, treat, cure, or prevent disease. In accordance with the provisions of DSHEA, DS product manufacture and safety are regulated by the US Food and Drug Administration (FDA). Manufacturers of DS are prohibited from marketing products that are adulterated or misbranded, they must comply with DS-specific current Good Manufacturing Practices (cGMP) and they must track and submit serious adverse event reports to the FDA. The FDA, the Federal Trade Commission (FTC), and Department of Justice Consumer Protection Branch are responsible for all regulatory investigations and actions against non-compliant manufacturers.

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DSHEA also authorized the establishment of the Office of Dietary Supplements (ODS) within the NIH. By design the NIH's role in the DS enterprise is to operate as a neutral scientific body distinctly separated from regulatory affairs. The NIH is focused on promoting rigorous biomedical research, supporting the development of cutting-edge analytical methodologies, and expanding the evidence-base to understand the potential health benefits and risks of DS use. The NIH has a leadership role on several Federal trans-agency committees and advisory panels covering issues of nutrition and dietary supplements. These include the Federal Working Group on Dietary Supplements, which is an ODS-led effort that facilitates communication between the NIH Institutes and Centers (ICs) and 16 other federal agencies, including the Centers for Disease Control and Prevention and the FDA. Furthermore, the NIH provides scientific expertise regarding research results and analytical approaches in response to specific requests from US Federal and State Agencies and Congress.

Dietary supplement research at the NIH

The DS market has experienced robust growth over the past 20 years in sales, as well as in the number and variety of products and ingredients.^[2,3] Approximately \$34.9 billion was spent on DS in the USA in 2013, with herbal and botanical products comprising about 17% of those consumer sales.^[3] It is in this context that the NIH supports research to better understand the potential health benefits and risks of DS use. The ODS budget for extramural research was \$21.1 million in 2014, but this constituted a relatively small percentage of the total NIH investment of \$250–300 million per year in DS research.^[4,5] The ODS's budget amount is reflective of ODS's role as a coordinator, as much as a funder, of DS research. Among the NIH Institutes and Centers, the National Center for Complementary and Integrative Health (NCCIH, formerly the National Center for Complementary and Alternative Medicine) has historically dedicated the largest proportion, over 20%, of its approximately \$124 million total extramural research budget to DS investigation.^[5]

Through the scientific peer-review process, the NIH strives to ensure that the dietary supplement formulations investigated in clinical research are pertinent to traditional or current usage, and that dosing regimens in pre-clinical studies are relevant to human use and bioavailability. This NIH-funded research is then cataloged and made publically available online via the NIH Research Portfolio Online Reporting Tools.^[6] Summary information for NCCIH-supported clinical trials has recently been reported,^[7] and [ClinicalTrials.gov](https://clinicaltrials.gov)^[8] allows for a selective search of all NIH-supported clinical trials and outcomes relevant to DS by using the term 'dietary supplements' in the Topic or Intervention query fields.

NCCIH-supported clinical studies have examined the safety and efficacy of commonly used DS for a variety of health outcomes, including cognitive decline, menopause, and infection rates.^[9–12] In some cases the clinical investigations have resulted in significant public health advances. The NIH-supported AREDS studies, for example, investigated combinations of vitamins C and E, zinc, and the carotenoids beta-carotene, lutein, and zeaxanthin, and demonstrated that a specific formulation could safely and effectively reduce the progression of age-related macular degeneration.^[13,14] However, most of the larger NIH-supported clinical trials of DS failed to demonstrate a significant benefit compared to control groups.^[7]

An important lesson learned from these trials was that in order to more fully leverage large research investments, future clinical trials using DS should be supported by rigorous preclinical data on molecular mechanisms, as well as better data on safety, pharmacokinetics and metabolism in both healthy and, where appropriate, more application-relevant human populations. The mechanistic data should include strong evidence pinpointing the key bioactive component(s) and the critical molecular targets in the organism. Both the NCCIH and the ODS share this commitment to support rigorous DS research and enhanced mechanistic understanding through improved analytical methods and approaches, though each NIH component has a unique mission.

The National Center for Complementary and Integrative Health

The NCCIH is one of 27 NIH Institutes and Centers (ICs). The NCCIH's mission is 'to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care'. The interventions encompassed by this mission include DS and natural products. The NCCIH supports both basic and translational research on natural products, as well as studies on efficacy and interactions. At its inception, the NCCIH's research funding portfolio was divided between large phase III clinical trials and basic research initiated by academic investigators. As described above, the NCCIH has recently emphasized a need for improving the understanding of the biological mechanisms of DS and of the interactions between natural products and pharmaceutical drugs.

The DS market in the USA is large and diverse (estimated at more than 55 000 different products in 2012^[15]), and many natural products are chemically complex with inherently variable compositions.^[16,17] Appropriate and rigorous characterization of DS products are needed to ensure the presence of expected ingredients and to detect any contaminants or adulterants. The NCCIH established policies to promote thorough characterization in all DS research they support^[18] in the wake of high-profile cases of product adulteration^[19,20] but such stringent and appropriately comprehensive product analysis is also critical for reproducibility in studies of both biological mechanisms and health outcomes^[21–25] Validated methods for the analysis of natural products are therefore critically important not only for DS manufacturers and regulators, but also researchers.^[26]

Since 2005, investigators have been required to provide evidence that the natural products used in NCCIH-supported research are well characterized in identity and composition. More recently, the NCCIH has additionally required natural product analysis independent of the manufacturer. These characterization requirements for complex and refined products are outlined in the NCCIH Natural Product Integrity Policy,^[27] and are similarly applied by the ODS. The demands of a randomized, controlled clinical trial require that the DS products used are not only well-characterized, but also have prior evidence of safety in the context of the study protocol and are available in sufficient supply (and within previously determined specifications) to complete the trial. Thus, although products used in NIH-supported clinical trials may be commercially available, they are often obtained under a Materials Transfer Agreement (MTA), a contract that governs the transfer of tangible research materials between organizations. The use of an MTA to obtain a product for use in a clinical trial

supports the exchange of proprietary product information (e.g. processing methods not included on the label) in order to demonstrate product integrity, and also facilitates researchers' ability to ensure that a large enough batch (or a sufficiently similar batch, if stability or other issues require the use of multiple batches over the course of the study) of product can be obtained. In some cases, custom processing of a product may be required to ensure the availability of a well-matched placebo intervention. An MTA can also be used to ensure that it is clearly understood that the manufacturer will not have control of resulting publications.

Comprehensive characterization is particularly important for complex mixtures where the identities of the bioactive components and their mechanisms of action are not fully understood. Additionally, the development of methods for the comprehensive analysis of natural product composition could potentially yield important insights into the mechanistic reasons for equivocal preclinical and clinical research results for DS products. To foster the advancement of such methodologies, the NCCIH and the ODS offer funding opportunities that support novel characterization methods and approaches in natural products research.^[28,29] The NCCIH and the ODS have also collaborated to encourage the validation of analytical methods developed as part of relevant NIH awards.^[30]

Office of Dietary Supplements (ODS)

The ODS was created in 1995 with a mission to strengthen the scientific understanding of DS, in part by stimulating and supporting relevant research and disseminating the results of that research. As an NIH extramural programme office, all ODS-supported activities are performed through grant co-funding agreements with the NIH ICs, contracts, or interagency agreements. The majority of the ODS budget is committed to extramural research.^[4] Much of this investment is in the co-funding of NIH grants focused on epidemiological studies and DS effects on biological processes relevant to health^[5,31] The ODS may also support research on disease prevention or treatment if there is a strong rationale that the biological mechanisms studied will be relevant to improving our understanding of DS effects on risk reduction and/or health promotion.

Many of the ODS's efforts relevant to the analysis of natural product composition are supported through the ODS Analytical Methods and Reference Materials (AMRM) Program^[32] The AMRM Program is designed to assist researchers by developing validated analytical tools, methods, and reference materials that can be used to enhance the verification of DS product ingredients and formulations. In this way the AMRM Program can in turn support a strong evidence base for clinical studies. Additionally, the validated analytical methods and reference materials developed through the AMRM Program can be used by both DS manufacturers and regulators to demonstrate or investigate product identity and integrity, and they may therefore assist with cGMP compliance.^[33,34] To accomplish its goals, the AMRM Program operates in three main areas: (1) analytical method development, validation, and dissemination; (2) development and dissemination of reference materials; and (3) educational outreach to promote the adoption of best practices and improve the quality of laboratory DS measurements. Along with analytical laboratories, the FDA and DS trade associations are among the stakeholders in the AMRM Program and participate in the

identification of mutual analytical needs through a formal process. To date, the AMRM Program has resulted in numerous publications and AOAC International Official Methods of Analysis,^[35] as well as the production of standard and certified reference materials by the National Institute of Standards and Technology^[36] AMRM-developed methods have focused on compositional analysis of raw materials and finished products (like the measurement of soy isoflavone or coenzyme Q₁₀ content), identity analysis (like spectral fingerprinting of botanicals), and the identification of adulterants (like aconitum alkaloids, aristolochic acid, and PDE-5 inhibitors). The AMRM Program has also worked directly with the FDA through an interagency agreement process to provide funding for FDA-led method development for the analysis of pesticides, toxic elements, and mycotoxins.

In partnership with the NCCIH and other NIH ICs, the ODS coordinates the NIH Botanical Research Centers (BRC) Program,^[37] a group of competitively awarded centers focused on collaborative, trans-disciplinary, preclinical, and early phase clinical studies on botanical DS conducted by extramural (usually academic) researchers. Research in the BRC has sought to elucidate the biological mechanisms of DS health effects, to better understand potential synergy in complex DS mixtures, and to investigate herb-drug interactions. The more than 600 published research papers citing support by this Program span the range from methods for botanical identification, characterization, and product standardization, through research to elucidate mechanisms of action in cells, preclinical models, and humans. The BRC has also conducted small, hypothesis-generating early phase clinical trials. For example, one recent series of studies has raised the possibility that African Americans may be at greater risk of producing some inflammatory mediators from certain plant-derived fatty acids than the majority of Caucasian Americans - but this remains to be fully tested in the clinic.^[38] Another recently funded project is expected to culminate in clinical assessments of potential botanical DS-drug interactions.^[39]

The BRC is also required to provide strong support for the training and career development of transdisciplinary natural products researchers via additional competitively awarded or institutional funding. Researchers trained in the BRC are currently working in both academic research and industry, and have also served in regulatory roles. The NCCIH and the ODS recently awarded five research centers that will focus on pioneering novel and innovative characterization approaches in natural products research^[37]

Smaller, individual DS research projects are also supported by the ODS Research Scholars Program through competitive, one-year awards to NIH intramural young investigators^[40] The ODS has also co-funded nationally representative surveys that track the prevalence of DS use in the USA, in particular the National Health and Nutrition Examination Survey^[41] and the National Health Interview Survey^[42] In all of their research-funding activities, the ODS and the NCCIH emphasize the application of appropriate and rigorous analytical methods to address the inherent variability of botanical raw materials and natural products^[43] in addition to requiring thorough and transparent reporting to optimize the reproducibility of DS research. This emphasis on research reproducibility and transparency has been recently highlighted for all NIH-funded research^[44,45]

In addition to the AMRM and the BRC Programs and other research funding, the ODS accomplishes its mission to generate, evaluate, and disseminate DS knowledge through a number of complementary approaches. The ODS sponsors systematic reviews of DS efficacy and safety through the Evidence-Based Review Program^[46] These reviews of DS like vitamin D and Omega-3 fatty acids are intended to inform health professionals and the public about the DS evidence base, and to help the NIH identify research gaps. The Evidence-Based Review Program has also produced a RAND Corporation systematic review (co-sponsored by the ODS and the NCCIH) which evaluated the safety and efficacy of ephedra and ephedrine in weight loss supplements^[47] This seminal report on the effects of ephedra was among the data utilized by the FDA in its efforts to ban the sale of ephedra-containing products, and it serves as an important example of how independent research supported by the NIH can be used to inform public safety analysis and regulatory decisions.^[48]

The ODS and NIH ICs also develop and co-sponsor numerous DS research workshops and initiatives. Workshops have focused on DS characterization,^[49–51] as well as public health issues. Recent workshops of note have brought together federal, academic, and industry experts to discuss the evidence base and research needs for topics such as the use and biology of energy drinks^[52] high intakes of folic acid,^[53] and DS-induced liver injury.^[54]

In efforts to further support natural product researchers, the ODS has been engaged in the ongoing development of a database of all federally funded DS research projects,^[55] as well as partnerships with the National Library of Medicine and the US Department of Agriculture, respectively, to develop DS label^[56] and ingredient databases^[57] These publically available databases can also be used by healthcare professionals and consumers, in conjunction with information for navigating the market place and expert-vetted summaries of knowledge about dietary supplements and health^[58] to aid in assessing the quality of dietary supplement products and identifying those that have shown health benefits in clinical studies.

Conclusion

The NIH NCCIH and the ODS are committed to stimulating and supporting rigorous, mechanistic, pre-clinical, clinical, and epidemiological research on DS. The NCCIH's purview spans research on all integrative health approaches, while the ODS's focus is DS research and related activities. Consistent with (and in support of) NIH-wide efforts, both the NCCIH and the ODS endeavour to ensure that supported research advances the understanding of the effects of DS on human health, and the specific biological and biochemical mechanisms mediating those effects. The individual and collaborative efforts of these two NIH components support the development, validation, and appropriate deployment of innovative and state-of-the-art methods for research on natural products used in or as DS, including methods for comprehensive and rigorous characterization. Combined with the development of approaches expected to advance the elucidation of biological activities and mechanisms of action, NIH policies and programmes are designed to improve the reproducibility of DS research, and thus accelerate the generation of information that can be

applied by other researchers, healthcare practitioners, industry, government agencies, and the general public to enhance health.

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