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NCCIH Priorities for Natural Products Research#

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ABSTRACT

The National Center for Complementary and Integrative Health (NCCIH) is the lead agency within the U. S. federal government for complementary and integrative health research, which includes natural products. Although NCCIH is one of the smaller components of the National Institutes of Health (NIH), NCCIH funds a disproportionately high percentage of natural products research at NIH. This stems from NCCIH being the only NIH grant issuing component that includes natural products as an explicit part of its mission. This perspective provides an overview of the NCCIH mission and summarizes NCCIH funding priorities for natural products research across basic and mechanistic as well as clinical sectors. These priorities are guided by the recently released NCCIH strategic plan. A primary element of this new plan is a focus on whole person health instead of the frequent focus on the treatment of diseases. The NCCIH focus on whole person health includes how natural products and multicomponent therapeutic approaches, which often include natural products, can help move individuals towards health restoration and promotion.

Introduction

NIH, which resides within the U. S. Department of Health and Human Services, is the largest funder of biomedical research in the world. NIH comprises 27 Institutes and Centers, each focused on a specific area of research. The NCCIH is the lead agency within NIH for research on complementary and integrative health practices, but the NCCIH budget is less than 1% of total NIH appropriations. Fortunately, many other NIH components also fund research on complementary and integrative health approaches. In fiscal year 2020, NCCIH awarded nearly $130 million in research grants while the rest of NIH awarded more than $350 million in additional research funding on complementary and integrative health research [1].

A wide range of complementary and integrative health approaches are used in the United States by an equally diverse collection of consumers and practitioners. NCCIH defines and groups these approaches based on the therapeutic input involved: nutritional, physical, or psychological. Traditionally, physical and psychological inputs were classified as mind and body approaches whereas nutritional inputs were classified as natural products. The NCCIH website (https://www.nccih.nih.gov/grants/natural-products-research-information-for-researchers) defines natural products as "a large and diverse group of substances from various natural sources such as plants, bacteria, fungi, insects, arachnids, marine organisms, and higher-order animals. The term 'natural products' also refers to complex mixtures from these products and the isolated compounds derived from them. In addition, the NCCIH definition also includes vitamins, minerals, probiotics–i.e., live microorganisms, bacteria in most cases, that are intended to have health benefits–and special diets for medical conditions or health outcomes". Under either the new or old classifications, about half of NCCIH research funding is devoted to grants for physical and psychological input (i.e., mind and body) research

Dedicated to Professor Dr. A. Douglas Kinghorn on the occasion of his 75th birthday.

and about half is devoted to grants for nutritional input (i.e., natural products) research. It is noteworthy that NCCIH is the only grant making NIH component for which natural product research is an explicit part of its mission.

NIH maintains a public database of all funded research, the Research Portfolio Online Reporting Tools (RePORT) (https://reporter.nih.gov/advanced-search), that can be mined for information about NIH support on any topic. Capturing all natural products funding using this database is challenging because of the incredible breadth of research endeavors that could be classified under that topic. An approximation can be made by combining search terms, but it certainly underestimates the true investment. For example, using a combination of the search terms "herbal", "natural product", "natural products", "botanical", "botanicals", "dietary supplements", "probiotics", "herb-drug", "medicinal herbs", "medicinal plants", and "phytochemical" for fiscal year 2020 yields more than $530 million in NIH grant funding. Of this sum, NCCIH provided more than $36 million which represented the fourth largest investment among NIH Institutes and Centers [1]. Thus, although NCCIH has the 23rd largest budget, the Center provides a disproportionate amount of funding for natural products research.

In early 2021, NCCIH issued its new strategic plan [2] (https://www.nccih.nih.gov/about/nccih-strategic-plan-2021-2025) which laid out a new and bold vision for the next 5 years. In particular, the new plan includes a renewed focus on whole person health. This is not new for NCCIH. The Center's mandate has always included research on the whole person. What is new in this plan is an effort to explicitly study how the nutritional, physical and psychological components of complementary and integrative health approaches can work together across multiple organ systems to move the whole person towards health restoration, also known as salutogenesis [3]. In addition to laying out a range of scientific research priorities, the plan also includes a specific objective focused on improving workforce diversity. NCCIH wishes to emphasize support for groups underrepresented in the sciences, including racial and ethnic minorities, a position that aligns well with the NIH-stated interest in diversity (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html). Although the plan is comprehensive in scope, this perspective focuses on how the plan shapes NCCIH priorities for natural products research.

Rigor, Reproducibility, and Regulations

Underlying all research funded by NCCIH is adherence to the highest standards for research integrity and quality. Within the Center's natural products research portfolio, these standards are embodied by NCCIH's Natural Product Integrity Policy (https://www.nccih.nih.gov/research/nccih-policy-natural-product-integrity). Instituted more than 15 years ago, this policy requires that investigators describe specific details about the identity, source, handling, and chemistry of the products used in NCCIH-funded research. This information is required before any award is made. Given the inherent heterogeneity of natural product preparations, even within the same botanical species, the information provided becomes critical for proper interpretation of the resulting data when comparing them with other research using similar products. These details also provide the necessary blueprint for reproducing the results, if necessary.

It is also important to note that NCCIH works collaboratively with various U. S. regulatory bodies to make sure the research we fund adheres to all relevant federal regulations. This collaboration becomes particularly important if the research involves a controlled substance (https://www.dea.gov/drug-information/drug-scheduling), such as cannabis, or involves a clinical trial that may use the natural product as a drug as defined by the U. S. Food and Drug Administration (FDA). In these instances, NCCIH also requires that the researcher demonstrate compliance with regulations established by the U. S. Drug Enforcement Administration (DEA) for use of controlled substances or the FDA for clinical trials.

Methodology

NCCIH has a long-standing interest in improving the tools and methodologies used by natural products researchers. This priority was based on a desire to break through the persistent bottlenecks that prevented rapid identification of compounds responsible for activity in an extract. Over the past 7 years, NCCIH has supported the Center for High Content Functional Annotation of Natural Products (https://hifan2.sites.ucsc.edu/) which is dedicated to development of novel methods for the chemical and biological characterization of natural products. The new NCCIH strategic plan extends the Center's interests to development and application of novel computational, artificial intelligence, and systems biology methods to model, predict, and quantify complex interactions of natural products across multiple biological systems.

NCCIH support for innovative methodology applies to the Center's clinical natural product research portfolio as well in which NCCIH is interested in studies that test the reliability and validity of diagnostic systems used by multicomponent therapeutic approaches such as traditional Chinese and Ayurvedic medicines. These studies may involve omics approaches that measure systems level changes in response to treatments. Studying such multicomponent interventions and multisystem outcomes may also require innovative clinical trial designs and advanced statistical methods to explore which components are responsible for an observed effect. Machine learning using big data and systems science has the potential to further unlock these complex interactions and may identify subpopulations for which certain interventions may be more effective.

Mechanistic Research

The NCCIH strategic plan highlights several priorities related to mechanistic natural products research. The most common type of mechanistic research determines the effect of a natural product on a mechanistic measure assessed at a biological, behavioral, psychological, or social level, either in a model system or in human subjects. NCCIH is interested in how natural products, including pre- and probiotics work together across multiple biological systems to elicit biological effects, with special focus on health and on resilience against various environmental, biological, and psychological stressors. There are several types of mechanistic studies relevant to natural product research. The first type of

mechanistic study has the objective to understand the mechanism(s) of action of an intervention, a biological or behavioral process, or the pathophysiology of a disease or condition. In such studies, the primary outcomes are mechanistic. The second type of mechanistic study involves the prospective use of a natural product where the intent is to obtain biospecimens or other psychosocial or environmental factors to identify genetic risk associations and novel biomarkers, examine the disease process, characterize therapeutic responses, or predict treatment outcomes, using preclinical models or human participants. Some mechanistic studies may use a natural product to answer basic science questions about normal physiological function or the pathophysiology of a disorder, but do not aim to demonstrate efficacy on clinical outcomes. Studies to develop, validate, and/or apply novel measures contributing to healthy behaviors in humans, or biomarkers of physiological or pathological processes, are also important examples of mechanistic research relevant to natural products. For studies that involve human subjects, especially in a specific patient population, there is a need to distinguish clinical mechanistic studies, which could be any one of the mechanistic study types described earlier, from those clinical studies geared toward safety, tolerability, feasibility, efficacy and/or effectiveness.

Many natural products are consumed as complex mixtures. The NCCIH mechanistic research program also supports studies that aim to identify the active components of these mixtures and better understand how they interact with each other and potentially multiple biological targets. These mechanistic insights are necessary for the design of maximally informative clinical trials. Importantly, NCCIH includes probiotics in our definition of natural products. Thus, NCCIH is equally interested in furthering knowledge of the mechanisms through which the gut microbiome interacts with pre- and probiotics to influence health outcomes. In the current strategic plan, NCCIH places emphasis on gaining mechanistic insight into how natural products can influence and improve salutogenesis, well-being, and resilience. On the bidirectional continuum between health and sickness there exists predisease states. On that continuum, a phase also exists during which an acute injury or exposure transitions to a more chronic condition. Natural product interventions may be particularly helpful during these critical time points. NCCIH encourages basic and mechanistic research in this window where functional or biochemical abnormalities exist but are still reversible.

Clinical Research Priorities

The NCCIH strategic plan outlines several priorities for clinical research on natural products. NCCIH continues to place emphasis on studying products that have compelling preclinical evidence of potential biological activity or products that are widely used by the American public. NCCIH has designed its funding opportunities to support all phases of clinical research from Phase I trials through fully powered Phase III efficacy trials. Clinical trials of natural products are maximally informative if they incorporate well-formulated biological hypotheses, are built on a sound foundation of basic mechanistic and pharmacologic understanding, and incorporate assessment of defined signatures of biological effects. Consistent with NIH's goals for rigor and reproducibility, NCCIH requires that the signature of biological effects be reproducible in two independent clinical trials before it will support efficacy trials, unless the biological impact of a natural product is impossible or impractical to measure directly. Priorities include clinical trials for isolated natural product compounds as well as for the complex mixtures from which they originate.

In addition to its interest in the classic clinical trial designed to assess the effect of a single natural product on a single primary outcome, NCCIH is interested in studying the effect of natural products on interconnected systems and multi-organ outcomes (e.g., on the nervous, gastrointestinal, and immune systems). NCCIH also has interest in studying the effects of multicomponent interventions which may include one or more natural products on single outcomes or on multi-system outcomes. Multicomponent therapeutic systems such as traditional Chinese medicine, naturopathy and Ayurvedic medicine often use a package of treatment approaches that frequently include one or more natural product. NCCIH supports research that defines and develops treatment algorithms from these therapeutic systems to establish if they can be delivered with fidelity and reproducibility.

Investigators proposing research hypotheses to examine multicomponent interventions or multisystem outcomes will likely need to use more advanced analytic techniques and may incorporate computational or machine learning approaches. Once multicomponent interventions have demonstrated efficacy or effectiveness, the question then becomes how to accomplish adoption, implementation and sustainability of these interventions into health care delivery. To address these questions, pragmatic trials or implementation science trials can be done to assess the effectiveness of the multicomponent intervention or the strategies used to integrate the intervention into health care delivery. It is critical that the participants in clinical trials represent the racial and gender diversity of the population with the study condition in the United States.

As described above, the strategic plan emphasizes the study of natural products on whole person health. Some of the outcomes relevant to whole person health include health promotion and restoration, resilience, and disease prevention across the lifespan. Many Americans use natural products to promote their overall health and NCCIH is interested in supporting clinical research that will develop and validate measures of health as well as evaluate the safety and efficacy of natural products to improve these measures of health. In addition to promoting health, natural products are used by the public to address the symptoms of pain, anxiety, depression, and sleep difficulties. For the management of these symptoms, clinical research that identifies biologically active natural products and evaluates the safety and efficacy of these products is of high priority to NCCIH.

NCCIH Peer Review Alignment with Strategic Plan Priorities

Peer review across NIH is framed by policies that promote the fair and unbiased evaluation of applications submitted in response to funding opportunity announcements (FOAs). Applications fo-

cused on natural products are reviewed at the Center for Scientific Review (CSR) or NCCIH based on the locus of review for the relevant FOA. To reflect its strategic plan for natural products research, NCCIH has added additional review language to many of its FOAs. For example, for the PAR-20-228 (Pilot Projects Increasing the Impact of the NIH Centers for Advancing Research on Botanicals and Other Natural Products, R03) FOA, reviewers evaluate how rigorously the experimental design addresses similarities to or differences from humans. In the review language, the emphasis on translational validity at the pilot stage is reflects the strategic plan objectives for advancing research on the whole person. In particular, the plan prioritizes conducting clinical and translational research on multicomponent interventions and studying the impact of these interventions on multiple physiological systems (NCCIH strategic plan, objective 2, strategies 1 and 2).

Reviewers also evaluate, for example, whether a proposed study responding to the PAR-20-218 and PAR-20-217 (Natural Product Early Phase Clinical Trial Phased Innovation Award, R61/R33) FOA could advance knowledge of the natural product's effect on a biological signature, whether the results are positive or negative. This additional review language reflects NCCIH's prioritization of support for trials of natural products that assess whether the effects of these products on biological signatures are reproducible (NCCIH strategic plan objective 2, strategy 2). Reviewers evaluate appropriate characterization of the natural product in proposed studies responding to the aforementioned FOAs (i.e., PAR-20-218, PAR-20-217, PA-20-228) which reflects the NCCIH Natural Product Integrity Policy of ensuring that natural products used in NCCIH-supported research are fully identified, characterized, and standardized.

Conclusion

The NCCIH strategic plan sets a bold and ambitious vision for the next 5 years. The goals and strategies of the plan influence all aspects of NCCIH research priorities. Within its natural products portfolio, NCCIH will continue to adhere to the highest standards of rigor and reproducibility through the implementation of the long-standing Natural Product Integrity Policy. NCCIH continues to support research on complex natural product mixtures as well as on identification of active components within those mixtures. NCCIH is especially interested in exploring and better understanding how the components of natural product mixtures work together to elicit biological effects in both mechanistic and clinical settings. Furthermore, NCCIH will prioritize research investigating how natural products can improve whole person health and increase resilience through coordinated effects on multiple biological systems. NCCIH looks forward to working with the investigator community to enact these priorities.

Contributors' Statement

Conception of the work: P. Still, W. Chen, W. Weber, D. C. Hopp; data collection: P. Still, W. Chen, W. Weber, D. C. Hopp; drafting the manuscript: P. Still, W. Chen, W. Weber, D. C. Hopp; critical revision of the manuscript: P. Still, W. Chen, W. Weber, D. C. Hopp.

Conflict of Interest

The authors declare that they have no conflict of interest.

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