

## STRATEGIC OBJECTIVE 2

### ADVANCE RESEARCH ON CAM NATURAL PRODUCTS

CAM also includes a large and diverse group of orally or topically administered substances such as herbal medicines, botanicals, and probiotics referred to in this plan as CAM natural products.\* They are widely marketed and readily available, often sold as dietary supplements. Although research has explored many of these products, in most instances scientific evidence regarding efficacy or safety to support or refute their use is insufficient. Nonetheless, they are used for the treatment of health problems or as a means to improve or maintain general health. Herbal medicines and botanicals are also prominent elements of most systems of traditional medicine, and this vast body of historical experience with them may provide leads for further scientific investigation. These approaches are grouped together in this plan because research on CAM natural products relies heavily on the methods and tools of the scientific disciplines of pharmacology and pharmacognosy.

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\*Terminology: CAM natural products replaces *biologically based practices* used previously by NCCAM. The term *biologically based* is no longer used because other CAM modalities also exert biologically based effects. *Natural* refers to the source in nature of most CAM natural products. It does not imply safety.





## Research Challenges and Needs

In recent years, several issues have emerged that are critical to defining future directions for research on CAM natural products funded by NCCAM.

### *Need for Mechanistic Research and Signatures of Biological Effect*

During NCCAM's first decade, a number of large, randomized efficacy trials of CAM natural products were launched. In most cases, study design was based on a combination of previous clinical experience and preliminary clinical studies. Generally, however, the studies failed to show hypothesized clinical outcomes. As a result, many questions about key aspects of study design (e.g., choice of product, dose, schedule of administration, choice of outcome measures) have been raised, casting uncertainty about the validity of the observed “negative” findings.

Thus it has become clear that maximally informative clinical efficacy studies of CAM natural products should be based on a scientifically sound hypothesis grounded in basic mechanistic research. In addition, the level of mechanistic insight should be sufficient to allow measurement of signatures of biological effect, biomarkers, or surrogate markers relevant to the hypothesis and validated in preliminary translational research, in addition to clinical outcome. This approach will increase greatly the information gleaned from efficacy trials, lessen the likelihood of uncertain “negative” outcomes, and elucidate leads for further research and development.

### *The Continuum of Exploratory Research and Targeted Development*

At one end of the continuum of research aimed at building rigorous evidence regarding CAM natural products are exploratory studies that have the potential to yield new, fundamental, mechanistic, or physiological insight and to identify signals of useful effects in ongoing clinical experience. This work also allows for serendipitous discoveries. The range of CAM natural products appropriate for such exploratory research is extensive and is best supported through investigator-initiated research project grants.

At the other end of the continuum are targeted and goal-directed studies (e.g., large clinical trials) aimed at developing definitive clinical evidence. Given available resources, the expectation is that the number of CAM natural products entering large, advanced clinical trials will be small and that these CAM natural products will have been designated as high priority by NCCAM because of particularly promising preliminary results in smaller studies or because of a compelling public health need (e.g., safety information).

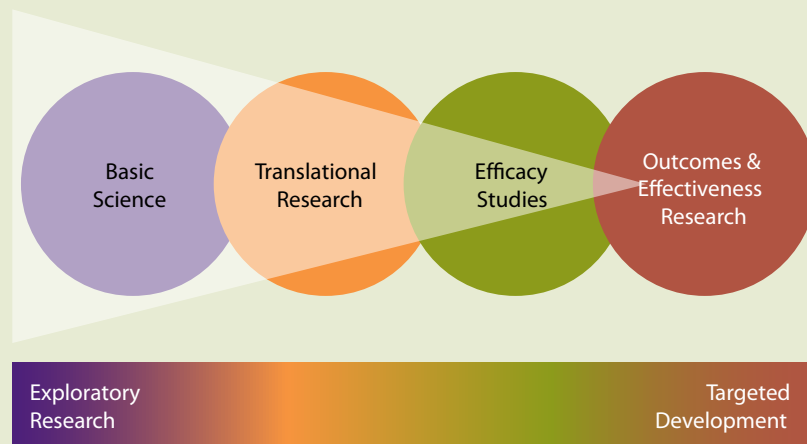


## CAM Natural Products Research

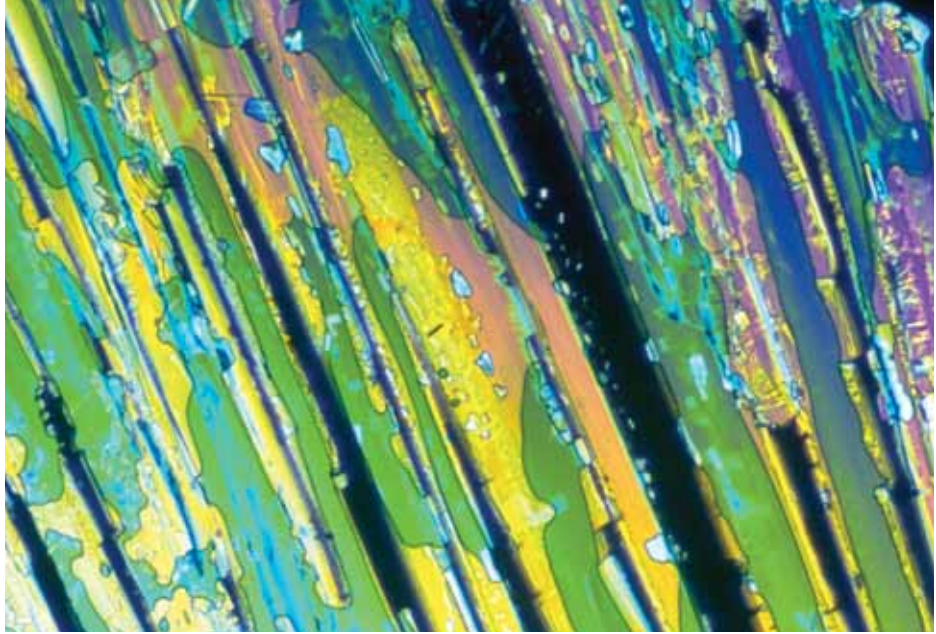
### Categories of CAM Natural Products

- Dietary supplements
- Herbal or botanical products
- Traditional medicine formulations
- Folk medicines
- Homeopathic remedies
- Probiotics
- Food-based phytochemicals

### The Continuum of CAM Natural Products Research



Although CAM natural products are readily available to consumers, rigorous evidence regarding usefulness and safety of many does not exist. Research priorities for most are at the exploratory end of the research and development continuum. Targeted development and large clinical trials will be warranted only when basic and translational research allows rigorous testing of evidence-based hypotheses. For most natural products, better understanding of safety and interactions with drugs or other natural products is needed.



Historically, NCCAM has supported the vast majority of basic and translational research and development activities relevant to CAM natural products through general solicitations for investigator-initiated research grants. This broad-based approach has yielded a large body of basic mechanistic information and promising leads for future research, and support of similar research in the future remains essential. Going forward, however, it has become clear that a portion of NCCAM's natural product efforts should be targeted to more directed translational and clinical research needed to expedite the development of the evidence base regarding specific, high-priority CAM natural products.

*There remain major gaps in knowledge about the adult and pediatric safety profiles of most CAM natural products.*

### ***Need for Continued Attention to Product Integrity and Safety***

During its first decade, NCCAM led NIH in establishing rigorous standards and policies regarding the quality and integrity of CAM natural products used in both mechanistic and clinical research supported by the Center. The overarching goal of these efforts has been to increase the likelihood that the research will yield both definitive and reproducible results. NCCAM's Natural Product Integrity Policy (<http://nccam.nih.gov/research/policies/naturalproduct.htm>) has been updated to better link the stringency of requirements for informational detail with the stage of a natural product's investigation along the continuum of exploratory research and targeted development.

Nonetheless, there remain major needs for improved methodology for characterizing and analyzing natural products. Furthermore, it remains true that information about the adult and pediatric safety profiles of most CAM natural products, including their interactions with drugs or other natural products, is limited. Claims that these products have fewer side effects or are "safer" than conventional pharmaceutical alternatives are generally unproven and sometimes erroneous, as well documented by reports of adverse herb-drug or herb-herb interactions, product contamination, or product adulteration.

## Strategies

The primary scientific challenge in studying CAM natural products is bringing the available and emerging tools, technologies, and approaches of the sciences of pharmacology and pharmacognosy to bear on the study of chemically and biologically complicated interventions and approaches. Increasingly, however, researchers are taking advantage of state-of-the-art technologies and systems biology approaches to better understand the biological effects of these products and to more effectively study their potential to contribute to health and well-being.

### **Strategy 2.1: Harness state-of-the-art “omics” and other high-throughput technologies and systems biology approaches of the sciences of pharmacology and pharmacognosy to:**

- Elucidate biological effects, mechanisms of action, and safety profiles of CAM natural products
- Study interactions of components with each other and with host biology
- Build a solid biological foundation for translational research needed to carry out clinical studies.



These tools and technologies offer considerable promise in addressing the need for better methods to qualitatively, quantitatively, and comprehensively capture the chemical diversity of complex CAM natural products. “Omics” and other high-throughput technologies also offer promise for investigating the validity and potential of hypothesized but largely unsubstantiated additive or synergistic effects at the core of many herbal medicine traditions. Greater clarity about the biological activities of individual components should facilitate study of possible synergistic effects. For example, most techniques for standardization and characterization of herbal medicines currently in use focus on the analysis of a limited number of abundant or easily detected and measured “marker” compounds, which may or may not be relevant to biological or clinical effects.

## Studying the Effects of Probiotics on the Human Microbiome



Probiotics, as defined by the World Health Organization, are “live microorganisms which, when administered in adequate amount, confer a health benefit.” They are available to consumers in foods (e.g., yogurt) and as dietary supplements. In theory they introduce deficient or absent microbes (usually bacteria) that are normally present and believed to be beneficial. There is scientific evidence that probiotics are useful in treating some forms of diarrhea, and emerging evidence that they may be helpful in treating a number of other conditions. NCCAM supports a large portfolio of research on probiotics.

At the same time, the trans-NIH Human Microbiome Project is exploring the complex microbial ecology of the body, using new technologies such as high-throughput sequencing and comparative and functional genomics. This work is yielding important insights into the functional significance of many normally present microbial species, including their roles in human health and disease.

NCCAM is closely aligning its probiotic research with the work of the NIH Human Microbiome Project. This collaboration seeks to provide additional insights into the potential applications of probiotics and to provide additional platforms for advancing understanding of the human microbiome. NCCAM is also working closely with other NIH institutes and centers, the Food and Drug Administration, and the U.S. Department of Agriculture to share resources and expertise, harmonize technology standards and translational tools, develop biomarkers, and facilitate progress in research and regulatory policy.



### Strategy 2.2: Support translational research to build a solid biological foundation for research on CAM natural products to:

- Develop and validate sensitive and reliable translational tools to detect and measure mechanistically relevant signatures of biological effect and to measure efficacy and other outcomes
- Conduct preliminary/early phase studies of safety, toxicity, dosing, adherence, control validation, effect/sample sizes, ADME (absorption, distribution, metabolism, and excretion), and pharmacokinetics
- Build upon established and proven product integrity policies and processes.

Clinical intervention studies must be grounded on a solid foundation of information derived from basic and clinical translational research. This work requires multidisciplinary research collaborations between basic and clinical scientists.

Maximally informative studies require careful characterization of the intervention, determination of suitable outcome measures, validation of laboratory measures of biological effect, an understanding of pharmacokinetics and pharmacodynamics, rigorous attention to product integrity, and other steps necessary to ensure that later research is as informative and definitive as it can be.

Specific efforts are needed to explore the adult and pediatric safety profiles of CAM natural products—including their interactions with pharmaceuticals and with other CAM natural products—in widespread, self-care use by the public.

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## Basic Research on CAM Natural Products

For centuries, plant-derived medicines have been a cornerstone of most folk medicine and traditional medical systems. This use is sustained by perceptions of effectiveness, although the benefits and risks of many of these traditional remedies are poorly documented. This experience does, however, provide fertile ground for identifying new treatments for many health problems. Indeed, many of the most important modern drugs have deep roots in traditional medicine.

Curcumin provides a good example. It is a component of turmeric, the spice that gives a golden yellow color to curries, and has been used in Chinese and Ayurvedic medicine to treat a host of health problems, including rheumatism, fever, intestinal disorders, amenorrhea, and topical treatment of wounds. Recent research supported by NCCAM and others has revealed significant effects of curcumin on a number of cell-signaling pathways relevant to disease processes: *in vitro* curcumin can be shown to inhibit NF-K activity, COX-2 and 5-LOX expression, and to reduce the formation of cytokines.

This body of basic research provides information critical to the formulation of hypotheses for disease treatment. It also allows the design of better clinical research since changes in gene expression may provide a biological signature of the effects of this promising compound. It also points toward leads for research to deal with the problem that curcumin, as an isolated compound, has limited bioavailability.

Sorting through the vast global experience to identify other promising compounds for targeted research and development is an enormous strategic challenge. Recent advances in metabolomics, genomics, chemical separation, molecular characterization, and high-throughput screening provide new tools to address this challenge. These state-of-the-art methodologies should also prove helpful in characterizing chemical and biological properties and ultimately in designing better and more informative clinical studies.







**Strategy 2.3: Support targeted large-scale clinical evaluation and intervention studies of carefully selected CAM natural products.**

A successful clinical trial is definitive in addressing its primary goals and also yields as much information as possible, whether or not the hypothesized clinical benefit is observed. This measure of success is especially important for large clinical trials, given their inherent complexity, expense, and risks. To help ensure success, large clinical trials should be based on a strong mechanistic hypothesis supported by basic research and exploratory clinical studies; a sound body of pharmacokinetic/ADME information; and the translational tools (e.g., laboratory measures of biological effect) needed to maximize knowledge gained, including measurement of ancillary biomarkers or other signatures of biological effect. Clinical and laboratory measures of effect must be sensitive enough to detect reasonable and realistic clinical effects or to determine with a high degree of certainty that a negative result is truly negative.

NCCAM’s investment in large clinical trials of CAM natural products should be highly selective and only made when there is ample scientific and public health justification (see Framework for Priority Setting in the Introduction). This work requires a well-defined and transparent process for priority setting and a milestone-driven and transparent approach to oversight of progress in the various steps of clinical evaluation.

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