

# COMPLEMENTARY AND ALTERNATIVE THERAPEUTICS: Rigorous Research is Needed to Support Claims<sup>1</sup>

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■ **Abstract** The establishment of the National Center for Complementary and Alternative Medicine (NCCAM) in 1998 as a part of the National Institutes of Health was catalyzed by the increasing interest and use of complementary and alternative medicine (CAM) modalities by the public. This article presents an overview of CAM, summarizes similarities and differences between the regulatory requirements for drugs and CAM/botanical products, identifies several challenges and opportunities for conducting research to demonstrate the safety and efficacy of CAM therapeutics, and highlights the role of NCCAM in supporting and stimulating research in this area.

## WHAT IS CAM? AN OVERVIEW OF CAM AS THERAPEUTICS

Complementary and alternative medicine (CAM) practices can be described as those not currently considered to be an integral part of conventional medicine. As CAM practices are proven safe and effective, they may become integrated into mainstream medicine. The majority of patients use CAM approaches to complement conventional health care, rather than as an alternative to it (1). CAM practices can be grouped into five major domains (Figure 1).

## MARKET FACTORS

Advances in biomedical science over the past century, coupled with improved sanitation measures and public health practices (2), have led to remarkable gains in the health of the American people and an increase in the life expectancy from

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47 years in 1900 to 77 years today (3). This impressive achievement is due in large part to the development and use of vaccines and antibiotics, which have significantly reduced the number of deaths from acute infectious diseases, such as tuberculosis, influenza, and pneumonia. Nonetheless, new and re-emerging diseases, such as the resurgence of cholera in the Americas after over a century, the emergence of hantavirus in the continental United States, and the westward spread of West Nile fever from the East Coast, remain a serious threat. In addition, the world now faces the menace of bioterrorism.

The predominant challenges for medicine today, however, come increasingly from chronic diseases that are prevalent among the growing numbers of aging Americans. Chronic diseases often resist cure and may coexist with unrelieved pain. As the members of the “baby boomer” generation age, they have hopes of continuing to live free of disease and disability. They are usually well informed and want to participate actively in decisions about their own health care. These factors contribute to an increased interest in CAM. Looking at long-term trends of CAM use in the United States, Kessler et al. (4) found that 68% of adults had used at least one CAM therapy in their lifetime and that lifetime use increased steadily with age.

The elderly are not the only group to be attracted to the use of CAM. Frustrated by the inability of mainstream medicine to treat, prevent, or cure all illnesses, many people have turned to CAM approaches. The expenditures for alternative medicine professional services in the United States are estimated at \$21.2 billion, with the preponderance of costs paid out of pocket. Out-of-pocket expenditures for CAM therapies were estimated at \$27 billion, comparable to out-of-pocket costs for all U.S. physician services (5).

In the United States, the increase in use of CAM since the 1950s (4, 5) has been accelerated in the past few years by a number of factors. With the explosive growth of the Internet, consumers have greater access to an increasing body of information, including advertising and marketing of CAM practices. Consumers, armed with more (though not necessarily more reliable) information, are asking for products and services that they believe to be safe and efficacious. In addition, a number of CAM practices serve as either the first line of medical care or augment conventional medical treatment in both developed and developing countries around the world. The world is becoming a global community, due in part to the enormous volume of international travel, and individuals are exposed to the health practices of peoples who live far away. Finally, racial/ethnic minorities who have immigrated recently to the United States may continue to use the health practices of their countries of origin.

## **INTEGRATION: FROM CAM TO CONVENTIONAL**

In some cases, the existence of a widely used natural product has informed the development of a conventional drug product and its movement into medical practice. The development of aspirin is but one example (Table 1). Therapeutic benefits of the leaves and bark of the willow tree were known by Hippocrates and used by many indigenous peoples, such as Native Americans, to relieve pain and fever. In

**TABLE 1** Aspirin: integration of a botanical product into medicinal practice**400 BC**

The Greek physician Hippocrates prescribes the bark and leaves of the willow tree to prevent pain fever.

**Middle Ages**

Reportedly, demand for wicker furniture takes precedence for use of willow bark and Europeans stop using willow bark remedies.

**1500s–1700s**

A number of ethnic groups, including Native Americans, use various parts of the willow tree for its analgesic properties.

**1763**

In England, Edward Stone used willow tree bark to reduce the fever caused by malaria.

**1832**

A German chemist isolates salicin and synthesizes improved analogs, including acetyl salicylic acid (aspirin).

**1899**

Aspirin becomes the top drug worldwide.

**1915**

Aspirin is moved to over-the-counter status.

**1915–1999**

Various formulations of aspirin (low strength, children's chewable, enteric coated, extra strength, timed release) are manufactured for targeted markets.

**Early 1970s**

Aspirin is determined to act by inhibiting the production of prostaglandins.

1897, a German chemist with the Bayer Company isolated a chemical compound, salicin, from willow bark. Several analogs were successively synthesized to reduce irritating side effects and improve stability. By 1899, one of the synthesized entities, acetyl salicylic acid, commonly known as aspirin, had become the number one drug worldwide. The mechanism of action of aspirin was not known, however, until the 1970s, when scientists discovered its ability to inhibit the production of prostaglandins that are involved in inflammation. Even a century after its development, new uses are still being identified for aspirin. The U.S. Food and Drug Administration (FDA) has approved the use of aspirin to reduce the risk of recurrent myocardial infarction or heart attack, to prevent a first myocardial infarction in patients with unstable angina, to reduce the risk of death during a suspected heart attack, and to prevent a recurrent stroke. Research continues to explore the use of aspirin to prevent selected cancers, such as colon and esophageal. Willow bark-containing products are still in use, although the concentrations of salicylates vary greatly among species of *Salix* (6).

Similarly, for many centuries, native people in many parts of the world have used extracts of the foxglove (*Digitalis purpurea*) plant as a diuretic, heart tonic,

emetic, and rat poison. In the eighteenth century, British surgeon William Withering conducted experiments to demonstrate the uses and side effects of foxglove and determined that the dried powdered leaf of the plant was more effective than the fresh leaf. Crude extracts of the plant were hard to prepare in a reproducible manner. With the discovery of the active component of foxglove, an analog, digoxin, was synthesized, which has a short half-life in the body. Digoxin has been used as a prescription drug for decades in patients with heart failure and to this day remains a first line therapy for congestive heart failure. Digitalis is no longer recommended for self-medication (7).

## THE REGULATORY ENVIRONMENT

Not all natural products have served as the basis for classical drug discovery and development. Most continue to be used as they have for eons, as complex mixtures that today are regulated in the United States differently from drugs. An overview of the legal framework under which conventional drugs and diverse natural products are regulated in the United States (Table 2) shows the difference between the development of CAM products and conventional drugs, either prescription or over the counter (OTC).

The emphasis in early federal regulatory statutes was on safety. Until the early twentieth century, the Bureau of Chemistry in the Department of Agriculture was responsible for assuring the safety of both foods and medicines. The Biologics Control Act of 1902 (8) ensured the purity and safety of vaccines and the Federal Food and Drugs Act of 1906 (9) prohibited interstate commerce of misbranded or adulterated foods and drugs. The poisoning of more than 100 people, mostly children, with a sulfanilamide elixir containing a component of antifreeze, ethylene glycol, led to the enactment of the Federal Food, Drug, and Cosmetic Act in 1938 (10). This act created the present day FDA in 1940 and required medicines to be demonstrated safe prior to marketing.

Two important amendments to the FDC Act followed. The Durham-Humphrey Amendments in 1951 (11) required certain drugs to be labeled as prescription only; a drug that could be labeled for use without professional supervision was to be available OTC, without a prescription. The thalidomide crisis in 1962 led Congress to enact the Kefauver-Harris Drug Amendments (12), which required manufacturers to prove both product effectiveness and safety in well-controlled studies and also applied certain requirements such as informed consent to clinical studies. In addition, regulations require manufacturers of both prescription and OTC products to follow current Good Manufacturing Practice (cGMP) to assure quality and standardization of their drugs and to list their facilities and products with the FDA.

Later legislation for drug products focused on providing financial incentives to the pharmaceutical industry. The Orphan Drug Act of 1983 (13) stimulated investment in the development of drugs to treat rare diseases or conditions affecting fewer than 200,000 persons in the United States. Manufacturers of orphan drug products enjoy seven years of market exclusivity if the products are not patentable

**TABLE 2** Selected legislation concerning the regulation of drugs and dietary supplements

Year	Legislation	Main provisions
1902	Biologics Control Act	Ensured the purity and safety of vaccines
1906	Pure Food and Drugs Act	Prohibited interstate commerce of misbranded and adulterated foods, drinks, and drugs
1938	Federal Food, Drug, and Cosmetic Act	Required demonstrated safety for medicines (no clear-cut distinction between prescription and OTC drugs)
1951	Durham-Humphrey Amendments	Established specific standards for classification of prescription and nonprescription drugs <sup>a</sup>
1962	Kefauver-Harris Drug Amendments	Required manufacturers to prove both effectiveness and safety for prescription drugs
1983	Orphan Drug Act	Provided financial incentives for investment in therapeutics for rare diseases <sup>b</sup>
1984	Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act)	Allowed FDA to accept abbreviated new drug applications for generic products after patent expiration
1995	Dietary Supplement Health and Education Act	Amended the Federal Food, Drug, and Cosmetic act for dietary supplements

<sup>a</sup>In 1972, the FDA began a comprehensive review of the active ingredients in OTC drug products; some were removed from the market because they were found to be unsafe and/or ineffective.

<sup>b</sup>Rare diseases are defined as affecting fewer than 200,000 individuals in the United States.

and a 50% tax credit for research and development expenses. Sponsors may also apply for a clinical research grant from the FDA. The Drug Price and Patent Term Restoration Act of 1984 (14), commonly called the Waxman-Hatch Act after the congressional sponsors of the bill, authorized the FDA to accept abbreviated new drug applications (ANDAs) from manufacturers of a generic product once the patent on the innovator's product has expired; innovator companies also gained restoration of up to five years of a product's patent life that had been lost during the process of gaining approval from the FDA to market the product.

The regulation of herbal products has been complex. Prior to 1994, these products were marketed either as foods or drugs, depending on their intended use and whether any health claims were made. All of this changed in 1994 when Congress passed the Dietary Supplement Health and Education Act (DSHEA) (15) to protect access by consumers to safe dietary supplements. This law defined a new category of food for regulatory purposes, the dietary supplement (16), which includes herbs, other botanicals, vitamins, and minerals.

DSHEA requires manufacturers to clearly state on the product label that it is not intended to diagnose, treat, cure, or prevent any disease, but rather will be used to supplement the diet. Statements can be made claiming benefits related to a classical nutrient deficiency disease, describing the role of the supplement intended to affect the structure or function, characterizing the documented mechanism by which the supplement maintains structure or function, or describing the general well-being from consuming the supplement. These are generally referred to as structure/function claims. For example, improving cardiovascular health may be such a claim, rather than preventing a heart attack, which would be a specific disease claim that a dietary supplement could not legally make.

Drugs and dietary supplements are subject to different requirements concerning their manufacture and their standards for safety and efficacy (Table 3).

- **Manufacturing.** Drug products must meet cGMP requirements. Although the law permits the FDA to develop specific GMPs for dietary supplements, to date such GMPs have not been issued. Currently, companies must follow existing manufacturing requirements for foods.
- **Product characterization.** Sponsors of prescription products must document information about the chemical purity of the active ingredient as well as product formulation and stability. An OTC drug product must meet the OTC monograph standards. DSHEA does not require any chemical characterization or standardization.
- **Safety.** Drug products must be approved by the FDA as safe prior to marketing (prescription) or be contained in one of the OTC monographs. Manufacturers of dietary supplements are responsible for ensuring that their products are safe, but the FDA bears the burden of proof to show that a product is adulterated. For example, in February 2002, the FDA issued a safety alert warning consumers to stop taking the dietary supplement/herbal product PC SPES because the marketed product was found to contain undeclared prescription drug ingredients (17). Although the FDA monitors adverse effects after either drug or dietary supplement products are on the market, newly marketed dietary supplements are not subjected to premarket approval or a specific postmarket surveillance period. In the face of a rapidly expanding market, some observers have expressed concern that the FDA has inadequate resources to monitor the safety of dietary supplements (18).
- **Efficacy.** Although DSHEA requires companies to substantiate claims of benefit for dietary supplements, citation of existing literature is sufficient. In contrast, extensive premarket testing is required for prescription drug products; OTC drug products must meet OTC monograph standards.
- **Claims.** For dietary supplements and for OTC drugs, the FDA has primary responsibility for claims on product labeling, whereas the Federal Trade Commission has primary responsibility for claims in advertising. The FDA has responsibility in both areas for prescription drugs.

TABLE 3 A comparison of requirements for drugs and dietary supplements<sup>a</sup>

	Prescription drug product	Over-the-counter (OTC) drug product	Dietary supplement
Label claim	Intended to treat or prevent disease	Intended to treat or prevent disease	Intended to affect general well-being or to counteract nutrient deficiency
Labeling oversight	Food and Drug Administration (FDA)	FDA	FDA
Product characterization	Must include information about <ul style="list-style-type: none"> <li>■ Chemical purity of active component</li> <li>■ Manufacturing method and facilities</li> <li>■ Product formulation and stability</li> </ul>	Manufacturer must meet OTC monograph standards	None needed
Product review	Final formulation	Active ingredient	None
Data review	Private	Public	None
IND/NDA	Required for new chemical entity or for new indication for existing product	<ul style="list-style-type: none"> <li>■ NDA may be submitted to market a current prescription drug in a new dosage or formulation (e.g., ibuprofen)</li> <li>■ NDA is required for new drug delivery systems or formulations (e.g., sustained release formulation)</li> <li>■ Grants exclusive marketing rights for a number of years</li> </ul>	Not required for commercial marketing

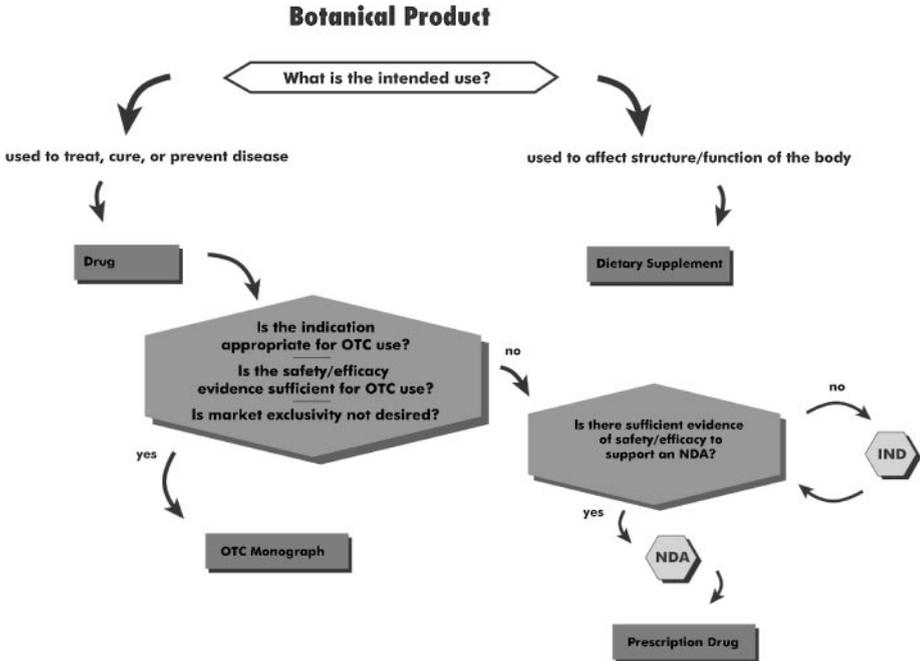
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TABLE 3 (Continued)

	Prescription drug product	Over-the-counter (OTC) drug product	Dietary supplement
Manufacturing requirements	current Good Manufacturing Practices (cGMPs)	cGMPs	cGMPs modeled on food practices
Demonstration of safety	<ul style="list-style-type: none"> <li>■ Premarket approval required</li> <li>■ Testing in animals</li> <li>■ Phase I/II/III clinical trials</li> <li>■ Post marketing surveillance system</li> </ul>	<ul style="list-style-type: none"> <li>■ Manufacturer must meet OTC monograph standards<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Premarketing approval or postmarketing surveillance not required</li> <li>■ Citation of existing literature</li> </ul>
Demonstration of efficacy	<ul style="list-style-type: none"> <li>■ Premarket approval required</li> <li>■ Testing in animals</li> <li>■ Phase I/II/III clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>■ Manufacturer must meet OTC monograph standards</li> </ul>	<ul style="list-style-type: none"> <li>■ Citation of existing literature</li> </ul>
Regulation of advertising claims	FDA	Federal Trade Commission (FTC)	FTC
Financial incentives	<ul style="list-style-type: none"> <li>■ Process patent</li> <li>■ Use patent (e.g., new formulation)</li> <li>■ Market exclusivity (e.g., seven years for rare disease indication)</li> </ul>	<ul style="list-style-type: none"> <li>■ Marketing rights granted for drug product if NDA submitted</li> </ul>	<ul style="list-style-type: none"> <li>■ None</li> </ul>

<sup>a</sup>A dietary supplement is defined by the Dietary Supplement Health and Education Act of 1994 as a product intended to supplement the diet that contains one or more of the following: a vitamin, a mineral, an herb, a botanical, an amino acid, or a dietary substance to supplement the diet.

<sup>b</sup><http://www.fda.gov/cder/otc/index.htm>



**Figure 2** Dietary supplements proceed through the approval process depending on the claims that are made for the product (a more detailed process flow chart can be found at <http://www.fda.gov/cder/guidance/1221dft.pdf>, attachments A and B, pp. 39–40).

Again, when sold as dietary supplements, CAM products cannot claim to treat or prevent a disease. CAM therapies that are intended to treat or prevent disease would have to proceed through the drug approval pathway (Figure 2). These therapeutic products are subject to the same requirements as are other drugs, such as purity, stability, safety, and efficacy, and must adhere to stringent manufacturing requirements. For example, edetate, or EDTA, was approved by the FDA half a century ago to treat heavy metal poisoning through its action of forming chelates with divalent and trivalent metals. More recently, chelation therapy has been used for off-label purposes to ameliorate angina pectoris and to reduce the symptoms of peripheral vascular disease, coronary artery disease, and cerebrovascular disease (19). There are little data from controlled clinical trials regarding the efficacy of chelation for these indications. For manufacturers to make claims regarding EDTA-containing solutions for these indications, but more importantly, for public health purposes, rigorous studies are required. To this end, the National Center for Complementary and Alternative Medicine (NCCAM), in collaboration with the National Heart, Lung, and Blood Institute, has launched a \$30 M, five-year, multisite, randomized, double-blinded, placebo-controlled trial to investigate the

safety and efficacy of EDTA chelation therapy in individuals who are suffering from coronary artery diseases (the Request for Applications announcement can be found at <http://www.nccam.nih.gov>).

A drug product that contains the same active constituent as a botanical product would be regulated according to different paths, as long as they are marketed with different intent. The combination of caffeine with any other stimulant, such as ephedrine alkaloids<sup>2</sup>, may not be sold as an OTC drug product (20). However, dietary supplement products that contain ma huang (a source of ephedrine) and natural product stimulants such as kola nut (50% caffeine) are permitted on the market under DSHEA.

## FEWER FINANCIAL INCENTIVES FOR BOTANICAL PRODUCTS

Manufacturers and producers of CAM products intended to treat or prevent disease and that will be marketed directly to consumers might not enjoy the same financial incentives, such as market exclusivity and patent protection as do drugs. For example, a drug that is approved by the FDA for prescription use is eligible for any protection that remains under an existing patent. A pharmaceutical manufacturer may extend product exclusivity by obtaining a new patent for a revised formulation, such as a sustained release product that alters the bioavailability profile of the active component, or for a new indication.

Market exclusivity is awarded for certain uses for a drug product, such as to treat or prevent orphan diseases. In this case, the most powerful incentive for a company to develop a product with a small target population is the Orphan Drug Act's market exclusivity clause.

Under certain circumstances, manufacturers may submit a new drug application (NDA) for an OTC drug product, which grants market exclusivity for a certain number of years. An NDA may be submitted for a current prescription drug to be marketed in a new formulation or dosage. A manufacturer of a product for which an OTC monograph exists is required to submit an NDA for a new drug delivery formulation, such as a sustained release product.

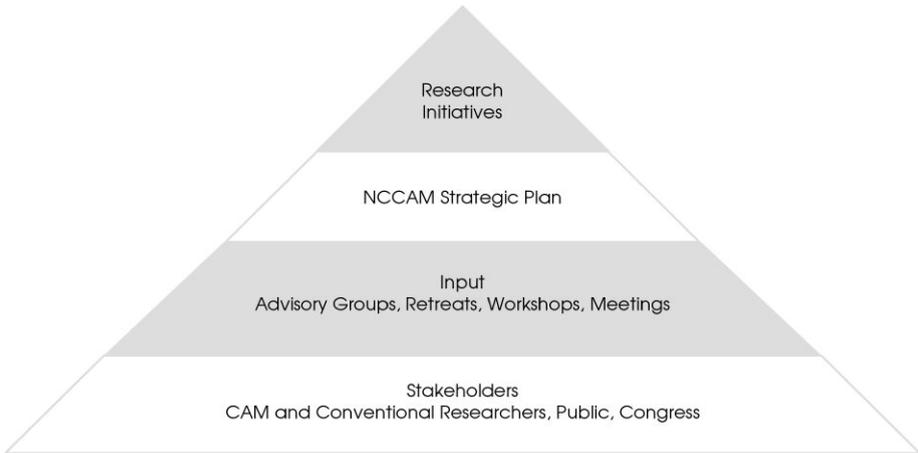
## THE RESEARCH ENTERPRISE

### Prioritizing Research Needs and Opportunities

Given the widespread use of CAM practices and products and the lack of private sector investment to prove their safety and efficacy, the responsibility to do so fell to the National Institutes of Health (NIH). In 1998, the NCCAM was created by Congress as a component of the NIH to conduct basic and applied research

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<sup>2</sup>Ephedrine alkaloids include ephedrine, pseudoephedrine, and norephedrine (phenylpropanolamine, PPA).



**Figure 3** NCCAM's planning process solicits input from a broad base of constituents to develop research plans and initiatives.

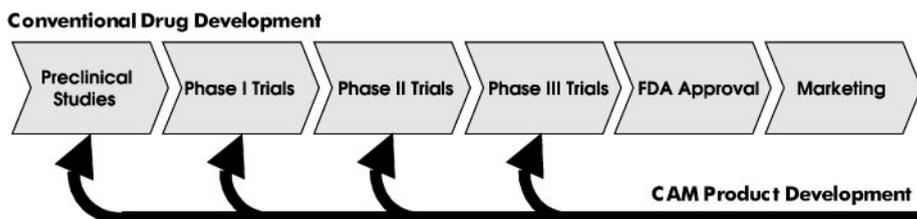
(intramural and extramural) and research training, disseminate health information, and other programs with respect to identifying, investigating, and validating CAM treatments, diagnostic and prevention modalities, disciplines, and systems. With the funds appropriated by Congress to the Center each year, NCCAM provides support for research that is initiated by research investigators as well as for research in targeted areas. These areas of need and opportunity are identified through NCCAM's planning process (Figure 3). NCCAM relies on input from its advisory groups (e.g., the National Advisory Council for Complementary and Alternative Medicine), researchers in the CAM and conventional communities, the public, and Congress to develop and select initiatives that solicit research applications in specific areas. Factors that are considered to determine the highest priority initiatives include the extent of credible preliminary data, use by the U.S. public, significance from a public health point of view, availability of appropriate scientific expertise to conduct the research, and, for clinical trials, the availability of a patient population to study. Semiannual planning retreats provide a forum for NCCAM staff to identify and discuss gaps in the research portfolio, propose approaches/initiatives to respond to the identified opportunities and needs, prioritize initiatives within the budgetary framework, and make decisions about activities to be initiated in future years.

In 2000, NCCAM developed a strategic plan, *Expanding Horizons of Healthcare* (<http://nccam.nih.gov/strategic>), that delineates four key areas as part of the Center's mission: investing in high quality research, training CAM investigators, expanding outreach activities, and facilitating integration of CAM and conventional medicine. The strategic plan, developed with input from a broad range of stakeholders, outlines the Center's research agenda and will guide the development of initiatives and activities for the coming five years.

## Research on CAM Therapeutics

With the support that has been provided since its creation, NCCAM has invested in a broad array of scientific research projects that span the spectrum from basic research, such as interactions between botanical products and conventional drugs, to the conduct of clinical trials to study the safety and efficacy of CAM modalities. The NCCAM portfolio also includes support for research training and education grants. In addition, the Center disseminates information through the NCCAM Clearinghouse ([info@nccam.nih.gov](mailto:info@nccam.nih.gov)) and the NCCAM website (<http://www.nccam.nih.gov>).

Because CAM interventions are already being used, clinical research is NCCAM's highest research priority and serves as one entry point for a product into the research pipeline. Thus, the study of CAM products differs from the model of conventional drug development (Figure 4), where basic research serves as the foundation for drug development. Scientific advances help to identify potential strategies for further testing in animal model systems and clinical trials in humans. In an idealized drug development model, single, defined chemical entities are synthesized or extracted, purified and characterized, and preclinical studies are conducted to determine activity in *in vitro* test systems. Promising compounds progress to studies in animals to study physiological and pharmacological effects, bioactivity, mechanisms of action, adverse effects, and toxicology. The most promising entities with respect to safety and efficacy move forward to small clinical



**Figure 4** Stages in development of conventional drugs and CAM products. The conventional model of drug development proceeds in a sequential fashion. The process begins with the conduct of preclinical studies in which single, defined molecular entities are synthesized, purified, and characterized, and animal studies are conducted to determine bioactivity, mechanisms of action, and adverse effects. Promising compounds are then evaluated in Phase I human trials for safety, in Phase II trials for clinical activity and dose ranging, and in larger Phase III trials to determine efficacy. Marketing approval is granted by the FDA on the basis of successful demonstration of safety and efficacy. The NCCAM model for the development of CAM products operates in reverse. Phase I, II, and even Phase III trials of natural products are undertaken based on their history of presumed safe use, the extent of public use, the public health opportunities, and the existing level of evidence about them. Investigators then “back-fill” the knowledge base by conducting preclinical studies. (Reprinted with permission from *Nature Reviews Drug Discovery* “Stages in the Development of Conventional Drugs and CAM Products.” Copyright 2002 Macmillan Magazines Ltd.)

trials in humans to evaluate tolerability (Phase I), controlled trials to assess clinical activity and determine dose range for study (Phase II), and larger controlled trials to establish clinical efficacy (Phase III). Thousands of compounds may be screened before a successful new drug is identified. Postmarketing surveillance studies and reporting of adverse events to the FDA provide an umbrella to identify those products that may show higher-than-anticipated problems when introduced into the larger population.

Because many CAM therapeutics are already being used by the public, research is conducted on products that are already on the market. Phase II and even Phase III trials of CAM products are undertaken based on their history of presumed safe use, the extent of public use, the public health opportunities, and the existing level of evidence about them. Investigators then add to the knowledge base by further evaluating dose response, obtaining physiological and pharmacological data, and determining bioactivity, mechanisms of action, and adverse effects (21).

NCCAM also relies on reviews of the current literature to help identify areas for clinical investigations. For CAM products, the information ranges from anecdotes and case studies to uncontrolled trials and small randomized controlled trials. In striving to elevate CAM research to a higher standard, NCCAM views randomized, double-blind controlled trials as the “gold standard,” and designs of clinical trials supported by NCCAM are the most rigorous possible. Of course, not all CAM approaches, like many conventional practices such as surgical interventions, can be well blinded or placebo controlled, but one must still depend on designs that incorporate adequate sample sizes and validated endpoints.

## RESEARCH ON BOTANICAL PRODUCTS: CHALLENGES AND OPPORTUNITIES

The lack of consistent and reliable botanical products represents a formidable challenge to conducting clinical trials, as well as basic research. Although many botanicals are widely used, 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 the clinical trial material require special attention, for example, (a) use of different parts of the plants (e.g., roots, seeds, aerial parts, whole plant), (b) use of different cultivars and species, (c) optimal growing and harvesting conditions, (d) use of the whole extract or a specific fraction, (e) the method of extraction (e.g., alcoholic, tea, pressed juice), (f) chemical standardization of the product, (g) bioavailability of the formulation (e.g., extract, tablet, capsule), and (h) the dose and length of administration.

Unlike conventional drugs, herbal products are not regulated for purity and potency. Some of the adverse effects and drug interactions reported for herbal

products could be caused by impurities, unnamed adulterants, or batch-to-batch variability. The chemical characterization (or fingerprint analysis) and standardization of botanical products would facilitate their evaluation in basic research and clinical studies. A study (22) supported by NCCAM compared the labeled amount and type of ginseng in 25 commercial products with the actual content. The study showed that, although each product was appropriately labeled for the type of ginseng contained within, the concentrations of ginseng, as determined by analysis of marker compounds, differed widely from that stated on the label.

## Preparation of Standardized Products

Given the popularity of botanical products, NCCAM has taken several steps to ensure the development of well-defined products to conduct conclusive clinical trials. With the great need for standardized botanical products, industry involvement is critical. NCCAM is working with industrial and academic partners through several mechanisms; echinacea is illustrative of these interactions (Table 4). One investigator is attempting to identify the best source of crude echinacea (*Echinacea angustifolia*), an herb used for treatment of common respiratory infections. The investigator is biochemically profiling “marker” compounds in the plant to determine the optimal conditions for cultivation relative to the yield of potentially medicinal components. Later work will focus on the isolation and characterization of the most biologically active components. Another investigator is examining the correlation between composition and bioactivity of echinacea and is using an *in vitro* model to determine the circumstances under which the liver activates specific echinacea components possessing the kinds of immunostimulating effects that are thought to help speed the resolution of infections.

In addition, NCCAM plans to support a contract for the development and production of research grade cranberry (*Vaccinium macrocarpon*) products and placebos for use in clinical studies. There is evidence from small clinical trials suggesting that cranberry may relieve symptoms of urinary tract infection (UTI) and may reduce the need for antibiotics in treating such infections (23). The products developed under the contract will be evaluated in basic and clinical research studies on the role of cranberry in the prevention and treatment of UTIs and other conditions for which there is credible evidence of efficacy.

A critical step in ensuring that NCCAM can secure sufficient standardized botanical products is to build collaborative relationships with industry. In May 2001, NCCAM and the NIH Office of Dietary Supplements (ODS) convened a colloquium to begin a dialogue regarding how NCCAM, ODS, and industry can work together to definitively evaluate CAM therapeutic products for composition, safety, and efficacy (24). The meeting involved two key groups: industrial stakeholders that supply raw materials and manufacture and market CAM therapeutics (e.g., dietary supplements), and organizations that develop and apply standards to determine the identity, quality, and safety of these products. Industry representatives

**TABLE 4** NCCAM-supported research on echinacea<sup>a</sup>

Stage of study	NIH grant mechanism <sup>b</sup>	Principal investigator/ institution	Study summary
Standardization of echinacea	R44	Xiping Wang/Gaia Herbs, Inc.	<ul style="list-style-type: none"> <li>■ Prepare raw material and collect data on plant identity</li> <li>■ Prepare marker compounds and testing methods</li> <li>■ Test marker compounds to identify promising end products using different extraction methods</li> <li>■ Evaluate optimum delivery presentation and product stability</li> </ul>
In vitro studies	K01	Cynthia Wenner/ Bastyr University	<ul style="list-style-type: none"> <li>■ Investigate the correlation between formulation composition and bioactivity of echinacea</li> <li>■ Study herb/drug interactions by examining echinacea's effects on drug-induced inhibition of Cytochrome P450 isoenzymes involved in drug metabolism</li> </ul>
Phase II trials	P50	Fayez Ghishan/ University of Arizona	<ul style="list-style-type: none"> <li>■ Determine the efficacy of herbal therapy and craniosacral manipulation to prevent acute otitis media in children with recurrent otitis media infection</li> </ul>
Phase III trials	R01	Ronald Turner/ University of Virginia	<ul style="list-style-type: none"> <li>■ Evaluate the effect of different echinacea constituents on rhinovirus infection and rhinovirus-induced illness (experimental common cold model)</li> </ul>
Phase III trials	R01	James Taylor/ University of Washington	<ul style="list-style-type: none"> <li>■ Study echinacea for the treatment of upper respiratory infection</li> </ul>
Phase III trials	K23	Bruce Barrett/ University of Wisconsin	<ul style="list-style-type: none"> <li>■ Test the efficacy of echinacea as early treatment for upper respiratory infection: explore dose dependency, compare specific preparations, investigate mechanisms of action</li> </ul>

<sup>a</sup>Echinacea is a widely used herbal remedy for the common cold. NCCAM supports a broad array of studies on echinacea. Investigators supported by NCCAM are using crude preparations of echinacea in clinical trials in order to determine if the herb is effective in preventing and/or treating upper respiratory and middle ear infections. The studies differ in the type of echinacea preparation used, product form, duration of administration, patient population type and size, and outcome measurements. Together, however, these studies may demonstrate some applicability to these conditions, providing information about the best opportunities for conducting conclusive clinical trials employing a highly characterized and standardized product.

<sup>b</sup>R44: Small Business Innovation Business Research (SBIR) Grant; K01: Mentored Scientist Award; P50: Center Grant; R01: Research Project Grant; K23: Mentored Patient-Oriented Research Career Development Award.

are increasingly involved in self-regulation with respect to product standardization and quality assurance. Because there are few financial incentives for industry, NIH plays an important role in supporting basic research on mechanism of action and modeling studies and clinical trials to determine safety and efficacy. Based on the understanding gained of the common interests and the complementary roles each group can play, a foundation has been laid for pursuing opportunities to develop future collaborations.

## Bioavailability/Bioequivalence Issues

Manufacturers of both prescription and OTC drug products must demonstrate not only that the product contains the amount of drug that is stated on the label, but that the active component is bioavailable. For prescription drug products, manufacturers measure the blood level concentrations of the drug over a time interval. A generic product is shown to be comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Generic applicants must demonstrate that their product is bioequivalent to the innovator drug by measuring the concentrations of both products in blood or plasma in 24 to 36 healthy volunteers (25). OTC drug products must meet specifications identified in the drug monograph, such as dissolution and disintegration test standards. Various forms of a botanical product are available on the market—dried forms, which may be milled to different particle sizes, tinctures, extracts, capsules, and tablets—yet the bioavailability and comparability of these different products has not been well studied. Likewise, the bioequivalence of products from different manufacturers has not been demonstrated. Such studies will prove increasingly important to advance the CAM research field.

## CAM-Drug Interactions

Each year a number of deaths occur when patients take a drug that interacts with other medications in their regimen or incites reactions that might not have been predicted from the studies that permitted the drug's licensure. A small number of drugs are withdrawn each year as a result of harmful or fatal adverse drug reactions and interactions. Even though the safety of new drugs is determined through extensive premarket clinical testing, certain patient populations not adequately represented in the clinical trial stage may react more strongly. In addition, the younger, healthier patient who participates in many clinical trials is not always representative of the individuals who will be taking the drug. It may take months or years of actual use before problems are discovered.

The causes and significance of drug interactions are multifaceted and can affect the processes by which pharmacologically active entities are absorbed, distributed, metabolized, and excreted (26). An enhanced or diminished modulation of the pharmacologic properties of a drug by another entity may be harmful (administration of tetracycline with an antacid that contains divalent or trivalent

metallic ions results in formation of poorly soluble chelates and reduction in antibiotic absorption) or beneficial (because probenecid competes with penicillin for renal excretion, administration of the two drugs together increases serum levels of penicillin and prolongs its half life).

Because of widespread use, often for centuries, and because the products are “natural,” many people assume complementary and alternative medicines to be inert or at least innocuous. Yet interactions between these products and drugs do occur and may have profound clinical consequences. For example, the active ingredients in Ginkgo biloba extract, a leading herbal supplement in the United States (27), are reported to have antioxidant properties and to inhibit platelet aggregation (28). This herbal supplement is promoted for use in improving cognitive function and blood flow (29). Several reports have been published on the increased bleeding associated with the use of Ginkgo biloba alone or in combination with other drugs that have anticoagulant or antiplatelet effects, such as warfarin and aspirin. Of note is information from a national survey showing that fewer than 40% of patients disclose the use of CAM therapies to their physician (30).

St. John's wort (*Hypericum perforatum*) is another leading herbal supplement sold in the United States (31), taken most often to treat various forms of depression. Reported cases of interactions with drugs together with pharmacokinetic data strongly suggest that St. John's wort is an inducer of a broad range of enzymes that metabolize drugs (32); a recent article suggests applying knowledge about the role of two hormone receptors that may regulate cytochrome P450 expression to the development of toxicological screens in the drug discovery process (33). In this regard, St. John's wort has been shown to interact with a number of drugs that serve as substrates for the cytochrome P450 CYP 3A enzymes responsible for metabolism of approximately 60% of current pharmaceutical agents. Substrates for the CYP 3A subfamily include cyclosporin, oral contraceptives, indinavir, sertraline, estrogen, and progesterone (34). A study conducted at the NIH (35) found that St. John's wort, when taken together with the HIV protease-inhibitor drug, indinavir, significantly reduced the plasma concentrations and approximately halved the area under the curve for orally administered indinavir. Inadequate plasma concentrations of protease inhibitors are a cause of antiretroviral resistance and treatment failure. Preliminary evidence indicates that St. John's wort also lowers the therapeutic activity of some types of oral contraceptives (36). Heart transplant rejection was reported as soon as three weeks after St. John's wort was added to the drug regimen of heart transplant patients on cyclosporin therapy (37) to prevent transplant rejection. Finally, the results of recent study suggest that St. John's wort may compromise the effects of certain cancer treatments, such as irinotecan (38). The FDA has issued a public health advisory warning physicians of potential adverse interactions with St. John's wort and advising them to alert their patients (39).

NCCAM supports a number of studies investigating the mechanism of action of CAM therapies and interactions with other drugs. In 2001, NCCAM issued a

**TABLE 5** Selected NCCAM-funded studies on mechanism of action of CAM therapies and interactions with other drugs

Principal investigator/ institution	Study aim	Type of study
B. Timmermann/U. of Arizona	<p>Curcuma longa rhizome (turmeric), Zingiber Officinale Rhizome (ginger), Boswellia serrata (boswellin)</p> <ul style="list-style-type: none"> <li>■ Determine the active components and their ability to regulate inflammation</li> <li>■ Characterize the disposition, gastrointestinal absorption kinetics, and bioavailability</li> <li>■ Assess the pharmacokinetic and pharmacodynamic characteristics</li> </ul>	<p>In vitro</p> <p>Animals</p> <p>Phase I trial</p>
G. Henderson/U. of California	Investigate the pharmacologic interactions between herbal products and asthma medications	In vitro
A. Hurwitz/U. of Kansas Medical Center	Investigate interactions of ginseng and ginkgo with various drugs	In vitro
S. Liao/U. of Chicago	Determine if green tea extracts, a complex herbal known as PCSPES, and extracts of individual PCSPES components affect the chemotherapeutic effect of growth of a drug used for prostate cancer	In vitro
D. Shen/Fred Hutchinson Cancer Research Center	Investigate whether significant interactions occur between two widely used opioid analgesics, oxycodone and fentanyl, and St. John's wort	Phase I
J. Markowitz/Medical University of South Carolina	Evaluate 10 commonly used herbs for inhibition/induction of enzymes that metabolize drugs (e.g., CYP3A4, 2136)	In vitro
P. Murphy/Columbia University	Evaluate the effects of St. John's wort on oral contraceptives	Phase I/II

request for applications to further stimulate research in this area. A list of selected studies is shown in Table 5.

## Safety and Efficacy

Although participants at the NIH-Industry Colloquium mentioned earlier agreed that studies on the safety and efficacy of biologically based products are important, they disagreed on the level of evidence that is needed. Some advocates of herbal medicines are satisfied with the existing evidence that these products are safe and

effective. Because there are currently no regulatory requirements or guidelines for what constitutes adequate studies, the private and public sectors must continue to work together to provide the public and health professionals with reliable research data.

Compelling data are now beginning to emerge from NCCAM-funded research studies. A report in *The British Medical Journal* (40) showed that St. John's wort is more effective than placebo in treatment of depression, and perhaps as effective as an older generation antidepressant drug, imipramine. Because of the intense interest in the use of St. John's wort, NCCAM and its research partners are collaborating on several studies of the safety and effectiveness of St. John's wort in treating depression. One study compared St. John's wort with placebo and sertraline, currently one of the most commonly used antidepressants. The results of the study show that St. John's wort is no more effective for treating major depression of moderate severity than placebo (41). Other studies on St. John's wort are under way.

NCCAM's research interests are broad, encompassing virtually all branches of medicine and health conditions across the lifespan. Data from basic and early clinical research studies are used as the basis for launching major clinical trials. In addition to the study of St. John's wort, NCCAM is conducting the largest and most definitive Phase III clinical trials ever undertaken for a range of CAM therapies, and thousands of research subjects have been enrolled. In collaboration with research partners at NIH, NCCAM is sponsoring several large clinical trials to address a variety of popular CAM modalities for important public health issues such as depression, arthritis, heart disease, and dementia (Table 6).

**TABLE 6** NCCAM is conducting the largest and most definitive multicenter, Phase III clinical trials ever undertaken for a range of CAM therapies (as of September 1, 2002)

Condition	Therapy	NIH Cosponsor <sup>a</sup>
Dementia	Ginkgo biloba	NIA, NHLBI, NINDS
Osteoarthritis	Accupuncture	NIAMS
Osteoarthritis	Glucosamine/chondroitin	NIAMS
Lung cancer	Shark cartilage	NCI
Prostate cancer	Vitamin E/selenium	NCI
Minor depression	St. John's wort	NIMH, ODS
Coronary artery disease	EDTA chelation therapy	NHLBI
Benign prostatic hypertrophy	Saw palmetto/African plum	NIDDK, ODS

<sup>a</sup>NIA: National Institute on Aging; NHLBI: National Heart, Lung, and Blood Institute; NINDS: National Institute of Neurological Disorders and Stroke; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NCI: National Cancer Institute; NIMH: National Institute of Mental Health; ODS: Office of Dietary Supplements; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases.

## CONCLUSIONS

The examples cited illustrate both the promise and challenges presented by CAM therapies. Through rigorous research, we will be able to determine not only to what extent each therapy is safe or effective, but also under what circumstances an effective CAM modality may be contraindicated. As the recent studies with St. John's wort show, a widely used botanical drug may impart unexpected adverse consequences when taken together with drugs that are part of the contemporary pharmaceutical arsenal. It is critical that untested but widely used CAM treatments be rigorously evaluated both for safety and efficacy. In the current regulatory climate, maintaining a strong research effort is critical and the NIH has stepped into the void left by the private sector. Studies on the underlying mechanisms of action, safety, efficacy, and purity of products will provide answers regarding which are suitable to be incorporated into medical practice. Only when providers and consumers have reliable information can they make well-informed decisions about which products and practices are appropriate and which should be rejected.

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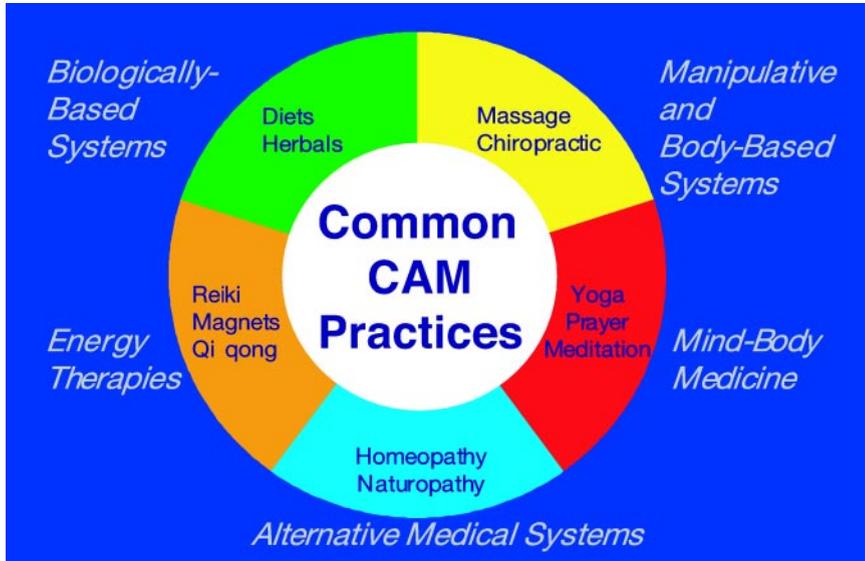
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**Figure 1** Five major CAM domains. NCCAM defines complementary and alternative medicine (CAM) practices as those not presently considered an integral part of conventional medicine. As CAM modalities are proven safe and effective, they may become adopted into mainstream medical practice. The five areas shown in the schematic represent but one way to array CAM approaches. Examples in each area are provided below (see NCCAM strategic plan at <http://www.nccam.nih.gov> for more details):

- Alternative medical systems—traditional oriental medicine, homeopathy, Ayurveda.
- Mind-body interventions—meditation, prayer, biofeedback.
- Biologically-based therapies—botanicals, herbs, special diet therapies.
- Manipulative and body-based methods—chiropractic, massage.
- Energy therapies—Qi gong, Reiki, magnets.