Research and regulatory issues for integrative oncology

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ABSTRACT

Many oncology patients are empowering themselves to self-treat with herbs, nutritional supplements, and mind–body techniques. Other practitioners, such as acupuncturists, are becoming involved in the supportive care of cancer patients. Government research agencies are supporting studies that evaluate complementary therapies. This educational article provides an overview of the challenges in designing appropriate studies of complementary and alternative therapies, evaluating the results, and regulating implementation of useful therapies.

KEY WORDS

Integrative oncology, CAM, research, regulation, acupuncture, natural health products, herbs

1. INTRODUCTION

Public interest in, and research into, complementary and alternative medicine (generally called CAM) are both increasing. However, many medical practitioners would like to eliminate the term "alternative medicine." However, "alternative" is a useful anthropologic term for examining paradigms of practice such as Chinese medicine or Ayurveda.

Complementary therapies are any therapies that are used with mainstream treatments (primarily surgery, drug treatments, chemotherapy, and radiotherapy). Complementary therapies are used in addition to mainstream treatments to improve outcomes. Complementary therapies can reduce side effects in patients and improve quality of life.

"Integrative medicine" is the current term for the evidence-based association of complementary therapies with mainstream medicine. There is great interest in conducting clinical trials to evaluate complementary therapies for use in a program of integrative medicine for cancer patients.

2. PROBLEMS AND APPROACHES IN DESIGNING CLINICAL RESEARCH FOR CAM

"Alternative therapies" are typically promoted as viable treatment options—that is, "alternatives" to so-called mainstream therapies such as chemotherapy, radiation, and surgery. Alternative therapies are unproven, seldom based on a credible scientific rationale, and potentially harmful—especially when patients are led away from effective, proven therapies by the lure of false promises and an emphasis on a lack of adverse side effects as compared with conventional therapies.

In contrast, "complementary therapies" are to be distinguished from alternative therapies. In the context of cancer, complementary therapies are combined with conventional medicine into an "integrative oncology" program. Integrative oncology focuses on the roles of massage and other touch therapies, acupuncture, music therapy, botanicals, meditation and other mind–body approaches, nutrition, and fitness therapies, among others, in a research-orientated program. Treatment programs aim to reduce symptoms and to improve quality of life for cancer patients. Complementary therapies enhance the efficacy of conventional therapies and are evidence-based.

Using modern research techniques, some so-called alternative therapies may be proved effective, at which point they will no longer be called "alternative." For example, in the early 1990s, many practitioners considered acupuncture to be an alternative therapy. Today, some acupuncture regimens are incorporated into conventional standards of practice. The change came about because evaluation of acupuncture began to show definite neurophysiologic effects. Experiments using methodologies such as positron emission tomography and functional magnetic resonance imaging in human beings have showed that certain points in the soft tissues actually activate specific parts of the brain stem that in turn activate the autonomic nervous system.

Thus, specific acupuncture points can produce very subtle psychopharmacologic modulation.

Acupuncture is now being studied in randomized controlled clinical trials (RCTs). It has been shown to be useful for certain—but by no means all—conditions. For example, a recent large well-controlled study showed that acupuncture is very effective for relieving pain and improving function in patients with osteoarthritis [1].

Some alternative therapies turn out not to be helpful; some turn out to be useful. The important focus is the evidence, and the research that provides that evidence. The U.S. government, through the National Center for Complementary and Alternative Medicine (NCCAM), and the National Cancer Institute Office of Complementary and Alternative Medicine (NCI–OCCAM) are funding the evaluation of complementary therapies through a conventional grant process. Standards for the development and reporting of clinical trials of acupuncture have been developed [2].

Many manufacturers of natural health products (NHPs) are now taking the same road as conventional drug developers. Quality-assured products are being developed through the same U.S. Food and Drug Administration (FDA) and Health Canada approval processes that are used for other drugs. Standards for the development and reporting of clinical trials of NHPs have been developed [3]. Many professionals involved in clinical research are currently involved in CAM studies.

Most of the increase in research on CAM has been driven by pressure from the public. Surveys over the past 5 or 6 years have shown that at least 40% of the U.S. population use complementary therapies from time to time. According to some surveys, up to 70% of breast cancer patients and 37% of prostate cancer patients use CAM. The U.S. Congress created NCCAM in response to the increased use of CAM by the public. The agency's annual budget has increased from about $2 million to about $120 million. Steven Strauss, a very well-esteemed conventional physician–researcher initiated the Center and has done a great deal to improve the credibility of CAM research.

3. INCREASED RESEARCH OPPORTUNITIES

A great deal of opportunity to evaluate new CAM therapies now exists. Many of these therapies are outside the standard medical model. For example, studies are being conducted in acupuncture and massage.

Prioritizing research has been a challenge. Funding for clinical trials is limited. Many committees within NCCAM and OCCAM have determined the areas that the public are most interested in and the current research data that show the most promise. Currently, NCCAM has decided to step back and focus more on mechanistic research—that is, to determine how some of these interventions work. Once the neurophysiologic and neuropharmacologic bases for these therapies are known, researchers can be much more logical in how they design clinical trials. They won't have to deal with the plethora of alternative therapies that, despite lacking a scientific basis, are touted to work. This approach will provide some scientific credibility before clinical studies are conducted.

The main domains outlined by NCCAM for research are traditional systems, particularly Chinese medicine and Ayurveda, naturopathy and homeopathy. The remedies used in homeopathy are controversial, but some merit may lie in the therapeutic relationship and the non-specific effects of the homeopathic system [4]. Chinese medicine has been particularly fruitful [5,6]. One of the components of Chinese medicine is acupuncture, which has already been shown to be a useful modality for symptom control. Chinese medicine also includes a vast pharmacopeia of herbal therapies that has been built for more than 3000 years. Some very important herbal derivatives may be useful in cancer treatment. The Chinese government and Chinese universities have been extremely cooperative in sharing their knowledge about Chinese medicine.

In 2006, the NCI held a symposium to discuss the future of research in Chinese medicine with participants from Canada, the United States, and China. The Chinese attitude toward research was very qualitative, and their research methodology was not rigorous. Researchers in North America, on the other hand, lack the knowledge of herbs that Chinese researchers have, but they have the rigorous knowledge and infrastructure for conducting quantitative research studies. Bringing the two perspectives together has been very important for developing new studies.

Table I outlines the varieties of complementary medicine as classified by Pietroni [7]. The basic categories are psychological approaches and self-help exercises, specific therapeutic methods, complete systems of healing, and diagnostic methods. Common themes in the philosophies of CAM also exist:

- Vitalistic philosophy (underlying energy or vital force)
- Self-healing nature of the body
- General, all-encompassing theory of disease
- Interdependence of mental and physical health: prevention and positive health

The CAM models of medicine are different from the simplistic, reductionist, and mechanistic conventional models. They involve complex systems and synergistic interactions that are sometimes called "holistic."

The pharmaceutical model for clinical trials is relatively straightforward. A quality-assured product, usually a single chemical, is compared with a placebo or the next best treatment, in a RCT. The trial completely differentiates the human healing factors from the drug. In other words, when all of the studies are complete and the drug is given outside of a therapeutic relationship, it is expected to have the effect described on the data sheet.

TABLE I The varieties of complementary medicine

Pietroni (1990) [7] classification	Psychological approaches and self-help exercises: relaxation techniques, meditation, expressive diaries
	Specific therapeutic methods: massage, reflexology, yoga, aromatherapy, spiritual healing
	Complete systems of healing: Traditional Chinese Medicine, Ayurveda, homeopathy, naturopathy

Complementary therapies, on the other hand, often involve the participation of a human being in a healing relationship at the same time as the therapy is given. The human factor may also exist in the pharmaceutical therapies, but to a much lesser extent. Thus, when conducting a new study, whether on a complementary therapy or a drug, researchers must look at validity.

Validity includes internal validity and external validity. Internal validity is the likelihood that the effect of the intervention is a result of the intervention itself. Studies are controlled to ensure that the intervention is causing the outcome affect. External validity is the likelihood that the intervention will have the same effect in the general population. For example, if a antidepressant drug is effective in a clinical trial of patients who are hospitalized for major depression, it may not be as effective in patients who are not hospitalized. It is most unlikely that the patient population using a therapy will be exactly the same as the controlled population in the study.

In CAM model validity, the likelihood that the study accurately reflects the system under investigation is important. "Acupoint selection" has been the major criticism of acupuncture studies, because acupuncturists select acupuncture points based on the Chinese method of taking a history and understanding the patient's constitution. Thus, a standard set of acupuncture points is not being used for all patients.

Report validity, the likelihood that the report about the study accurately reflects the study results, is another consideration. For example, a recent well-publicized study on *Echinacea* for cold prevention reported that *Echinacea* does not work at all [8]. However, the researchers used a particular species of *Echinacea* that is not generally used for cold prevention (*E. angustifolia* instead of *E. purpurea*), at a dose below the standard dose. It is not possible to generalize the results of one form of a herb to other forms. Researchers must be very careful in describing results and specifying the particular product that was studied. This need for specificity is elaborated in more detail by the CONSORT (Consolidated Standards of Reporting Trials) group's standards of reporting research on NHPs.

The only way to build up the "big picture" in science is to study it at various levels and in various contexts. That study starts with basic science to determine the mechanism of action. Next comes clinical research to determine, through RCTs, whether patients show improved outcomes. Policymakers and regulators want meta-analyses to determine whether something works for the population as a whole rather than for specific individuals.

Patients often do not necessarily care whether the outcome is objectively positive. Many are more concerned with whether they feel better and with the personal effect of the particular intervention. Toxic side effects must also be considered, and costs may be weighed, especially if the patient is not paying for the therapy.

Practitioners simply want to be able to find out if their patients will get better. In prescribing interventions for patients, they must constantly juggle basic science, clinical trials, health policy, and affordability of treatment in their health care setting. Decisions must also be made about the interventions that are to be used in the health care system—that is, health services research.

Thus, complementary medicine research has as many components, if not more, as are found with other types of research.

Most complementary medicine research originally came from observational data. An initial research activity is the systematic review of the literature, especially with regard to safety issues. If the data are promising, then researchers can proceed to phase I, II, and III studies. The NCI has proposed a best-case review for complementary therapies for cancer. For example, if physicians give high-dose vitamin C to 30 patients with advanced pancreatic cancer, and the cancer disappears without any further treatment in 5 patients, the NCI wants to know about it.

The next step is to evaluate the data and decide whether studies should be conducted. Important deficiencies, such as lack of pathology data, or concomitant treatments with other therapies, will be noted. The NCI has been extremely cooperative and open-minded about evaluating initial data and facilitating research on complementary therapies.

In clinical research, RCTs are the "gold standard." There are some methodology challenges, however. In surgical research, randomization and double-blinding is very difficult. The study of complementary therapies faces similar challenges (Table II). For example, in evaluating acupuncture, how does one produce a sham acupuncture needle? Early randomized studies with acupuncture tried to create sham acupuncture by inserting the needle 3 mm instead of 5 mm, or to the side of the site of the actual acupuncture point by 3 mm or 4 mm. Unfortunately, even those interventions seemed to have a partial specific effect. Some studies now use sham acupuncture needles in which a sheath hides the needle, which is a blunt peg that slightly presses

against the skin. The validity has been found to be quite good, and some controlled studies have shown that subjects cannot always differentiate between the real and the sham needle.

Rigorous controls are necessary in studies of complementary therapies to separate out the component of expectation or non-specific effects (the so-called placebo) and regression to the mean over a period of time. On the other hand, some practitioners wish to amplify the non-specific effects, considering them to produce synergistic beneficence for outcome.

The effect of any health care may be influenced by many factors besides the main intervention. Often, patients improve naturally. Confounding factors, such as lifestyle changes, can influence the patient's outcome. Chance can have an effect. Patients on placebo may improve. The RCTs try to specify the effect of the actual intervention. The healing relationship and the mind–body belief system (as shown by the placebo effect) *is* powerful and can be used to the patient's advantage if part of the informed consent. Investigation into patterns of care and the interventions of complex systems that can include pragmatic research will be a necessary part of an integrative oncology program.

Table III outlines problems specific to CAM research. The first problem is the alternative theoretical framework of CAM. It is important that future research focus on scientific mechanisms. The entire framework cannot always be incorporated into the research study. Often, CAM is a complex intervention.

To illustrate the difficulty of conducting a CAM study, consider an intervention for bronchitis. In conventional terms, the condition under study can be subdivided into asthma, bronchitis, and emphysema. However, in a Chinese medicine acupuncture study, these subdivisions would be irrelevant. Chinese medical

TABLE II Problems with clinical research design for complementary and alternative medicine

- Difficulties may arise similar to those in any randomized controlled trial.
- Treatment groups may discuss treatment with each other.
- Appropriate placebo may not be available.
- Participation in study context may affect outcomes.
- Trial subjects are self-selected.
- Compliance may be reduced because of placebo possibility.
- Standardized treatments may not be relevant in CAM practice.
- Analysis may ignore individual variations in response.
- Clinician may create selection bias.
- Outcome measures may not be relevant to patients.
- Important psychological variables may be neglected.

TABLE III Problems specific to research in complementary and alternative medicine (CAM)

Alternative theoretical framework:	Mode of action in some CAM systems cannot be conceived in scientific terms.
	Whole framework cannot be incorporated into the research study (for example, acupuncture and Chinese medicine, trials of non-specific effects).
Different diagnostic systems:	Need to recruit "homogenous" groups.
	Diagnostic criteria and techniques are different in CAM than in orthodox medicine.
	Eligible patients may have to be selected twice to achieve homogeneity: once for biomedicine, followed by sub-selection for CAM categories (that is, need to screen more patients).
Single- or double-blind trials:	Interactions between healers and patients cannot be completely blinded in some CAMs (for example, acupuncture or massage).
	Some CAMs need continuous treatment adjustment (for example, herbalism, acupuncture).
Individual or standardized treatment:	Emphasis in CAM is on individualized treatment, multi-modalities approach.
	The practice of CAM can be quite variable; it is crucial to specify exactly what is to be done in a trial for reproducibility.
Individual response to treatment:	Individual response can be lost in analysis.
	Individual response must be detailed; multiple study endpoints may be needed.
Outcome measures in CAM:	Subjective symptoms or signs of improvements are important (for example, pulse diagnosis, patient's energy level).
	A primary endpoint measure as a sign of improvement with multiple secondary endpoint measures may be necessary.

practitioners would categorize the problem into constitutional terminology derived from the patient's history, which they would divide into various elements such as "Earth, Water, Metal, Fire, and Wood." One patient may have more Water, and another may have more Fire. The acupuncture treatments for these patients would be different, depending on each patient's constitution. Thus, in true Chinese medicine, it would be necessary to categorize patients with asthma, bronchitis, and emphysema by their Chinese diagnosis before randomizing them into an acupuncture study.

Another problem specific to CAM is that interactions between healers and patients cannot be completely blinded. There are some ways to handle this problem, such as the sham acupuncture technique mentioned earlier. Also, the practitioner should not evaluate the data from the intervention. Data evaluation should be conducted by an independent observer. Some CAM treatments require treatment adjustments over time—more so than in conventional medicine. For example, a conventional acupuncturist will observe the results of using various acupuncture points for the first 2 weeks and will then change the acupuncture points to improve results. The same methods are used with herbal medicine. These variations add a great deal of complexity to CAM studies.

The emphasis in CAM on individualizing therapies is another problem. Practitioners of CAM do not like to put patients into one group (as occurs in conventional studies), because the treatment cannot be individualized. Results achieved by standardizing patients may not always be valid in Chinese medicine or in other complementary therapy systems.

No overall consensus has been reached about how best to design CAM studies. Table IV outlines possible design approaches. When planning CAM studies, RCTs should always be considered; the methodology should be adjusted as needed. However, the CAM study design should be innovative and flexible.

Systems ("pragmatic") research is becoming more important. For example, instead of evaluating specific acupuncture points, a study evaluates the acupuncture practitioner against a Western physician to compare the two systems and determine which system produces the better outcome. This comparison approach is one way forward that is being considered for clinical research in CAM.

In conducting CAM research, it is important to bring the complementary therapy under study back to the cultural context in which it is used. Chinese medicine is a whole system that includes combinations of herbs, acupuncture, lifestyle, and diet. The holistic approach presents a major challenge, but it is a challenge that can be met.

4. REGULATION

Regulation of CAM is inconsistent, and standards vary. Some specialties, such as acupuncture and therapeutic massage, have relatively narrow definitions of practice; others, such as naturopathy, contain an enormous scope of practice without obvious boundaries except for the restriction against prescribing drugs. Most CAM specialists do not require a significant evidence base to practice their therapies. Credible practitioners are willing to open their practice to close scrutiny; they support evaluation through good research methodology.

4.1 Acupuncture

Acupuncture should be administered by a certified practitioner, preferably licensed by a regulatory body, who

TABLE IV Possible design approaches for studies in complementary and alternative medicine (CAM)

Prospective observational studies:	"Best case series"
	Details of interventional method
	Toxicities
	Relevant endpoints
	Essential data for designing future randomized trials
Randomized whole-systems approach:	Individualized treatment
	Validated, relevant endpoints
	Intent-to-treat analysis
Randomized specific-modality approach:	Specific modality adapted from traditional system
	Randomized to controls without therapy and groups with "ineffective" therapy approach
	"Double-blind" by having diagnosis, treatment, and evaluation carried out separately by independent investigators
	Intent-to-treat analysis
Randomized single intervention approach:	Single intervention compared with placebo or conventional therapy (or both)

carries insurance and, if treating cancer patients, is preferably further trained and accredited by a cancer care institution. It is important that acupuncturists who treat cancer patients have received further training in the standards of oncology practice.

In Canada, regulation varies between the provinces. Some provinces, for example British Columbia and Quebec, have colleges of Traditional Chinese Medicine. In others, Chinese medicine may be regulated by the bodies governing individual health care professions (for example, the College of Physicians). Currently, regulation is inconsistent and confusing, leading to varying standards.

In the United States, acupuncture training, certification, and licensing varies from state to state, but regulation is generally more consistent and reaches a higher standard than is seen in Canada. At the very least, the acupuncturist should have attended a school accredited by the Accreditation Commission for Colleges of Acupuncture and Oriental Medicine, passed the National Certification Commission for Acupuncture and Oriental Medicine examination, and be licensed through a state regulatory agency recognized by the Federation of Acupuncture and Oriental Medicine Regulatory Agencies. Physicians practicing so-called medical or anatomic acupuncture may come under different regulations and representative bodies (for example, The American Association of Medical Acupuncture).

4.2 Massage Therapies

The required training and licensing laws for massage therapists vary between states in the United States and between provinces in Canada [9]. Education, experience, certification, and licensing are all important credentials. Philosophy and education vary, with some massage therapists holding the mistaken belief that cancer is a contraindication for massage. The Commission on Massage Therapy Accreditation in the United States considers a minimum of 500 hours of training a basic requirement. If a therapist is licensed in the United States, the initials LMT (Licensed Massage Therapist) or LMP (Licensed Massage Practitioner) are used after the therapist's name. In non-licensing states, a therapist should have CMT (Certified Massage Therapist) as a minimum qualification. The initials NCTMB indicate that the therapist has voluntarily taken and passed an examination given by the National Certification Board of Therapeutic Massage and Bodywork.

In Canada, the "gold standard" for massage therapy education, as set out by the Canadian Massage Therapists Alliance, is a minimum of 2200 hours. However, considerable diversity can be found in the hours of education, the curricula, and the types of educational institutions that teach massage therapy across the country. Some educational institutions have articulation agreements with universities for degree completion in science at the baccalaureate level. Increasingly, massage therapy education in Canada is embracing an evidence-informed, outcomes-based model for curricula.

Massage therapy is currently a regulated health profession in Ontario, British Columbia, and Newfoundland and Labrador. In the regulated provinces, students must successfully complete written and practical entry-to-practice examinations based on standards of practice set by the regulatory body. Through this process, successful applicants are eligible to use the designation Massage Therapist (MT) or Registered Massage Therapist (RMT) and to qualify for third-party insurance coverage for services. In many unregulated provinces and territories, well-organized professional associations impose educational standards similar to those in the regulated provinces. Membership in these provincial associations may also include title designation and access to third-party insurance coverage for services.

Specialized education and experience in working with cancer patients is essential. Programs for advanced training in massage care of the patient with cancer are integrated into undergraduate curricula in the regulated provinces in Canada and are available in continuing education programs in both Canada and the United States (for example, at the Memorial Sloan–Kettering Cancer Center). Important elements include safety, communication with oncologists, and record-keeping. Massage therapists are also urged to participate in clinical trials, and courses on research methodology are encouraged.

5. REGULATION AND RESEARCH ISSUES IN BRINGING NHPS INTO CLINICAL PRACTICE

In the next few years, research on NHPS is likely to increase dramatically. Many NHPS have deservedly received a bad reputation because they were not well validated, and they were sold with nonexistent or falsely constructed evidence. Surveys of contents of NHPS have shown great variability. For example, in surveys of *Ginseng* preparations, several products were found to contain little *Ginseng*. Other products have been found to be surreptitiously laced with conventional pharmaceuticals. Examples include PC-SPES [a herbal product for prostate cancer (Botanic Labs, Brea, CA, U.S.A.)], which was laced with diethylstilbestrol (DES), coumadin, and alprazolam; and various erectile herbal preparations, which were laced with sildenafil.

New leadership in the NHP industry is working to set standards for others to follow. In the future, it is expected that many NHPS will go through pathways similar to those for standard drugs [10]. This approach will be more challenging, because NHPS are usually mixtures of chemical extracts.

The NHPS are important because, worldwide, many more people consume botanicals than consume drugs. According to the World Health Organization (WHO), more than 4 billion people use herbal medicine regularly. In the United States, about $18 billion was spent

on the NHP market in 2003. About 120 standard drugs are derived or synthesized from a NHP. The difference between a drug and a NHP is that a drug is a highly purified single chemical preparation used at a relatively high dose; in contrast, a botanical is a complex mixture of chemicals usually used at lower doses. Herbal medicine is a major component of all traditional medicine. Research on the safety and efficacy of NHPs is increasing rapidly. Many laboratory studies of herbal derivatives, especially in cancer, have been published or are underway. Studies are showing that various herbs have major anticancer activity in the laboratory.

5.1 Regulation of NHPs

Regulation of NHPs varies by country. In the United States, the *Dietary Supplement Health and Education Act* (DHSEA) of 1994 was developed with good intentions (Table V). The public wanted to have over-the-counter access to herbs and vitamins. Unfortunately, the DHSEA has been abused, leading to a great deal of misleading marketing and branding, and in turn, to a bad reputation for herbal products as a whole. That reputation is undeserved, because some herbal products, when authenticated, quality-assured, and put through the appropriate clinical trials, will be extremely important for treatment of disease and for health maintenance. Clinical trials are already proving some claims—but also rooting out the ineffective ones.

The DHSEA defines a "dietary supplement" as any product (other than tobacco) that is intended to supplement the diet and that contains one or any combination of these ingredients: vitamins, minerals, herbs, other botanicals, or amino acids. Dietary supplements are intended to be used in a form such as a tablet, capsule, pill, or gelcap. Dietary supplements are meant to enhance health, but they are neither conventional foods nor conventional drugs, which makes them very difficult to control.

The regulations require very specific labelling for dietary supplements:

- The identity, which is usually non-specific, must be identified (for example, *Ginseng*, of which there are many varieties).
- The quantity must be listed (for example, 60 capsules).
- The structure–function claim can be made in a very broad sense. The label cannot say that the dietary supplement will cure a particular condition; however, it can use a non-specific term, such as "increasing vitality." (Although the claim phrase means very little from a scientific viewpoint, people are impressed by such claims and buy the product.)
- The words "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" must also be included. They are usually printed in very small letters at the bottom of the label.
- Directions for use (for example, "Take one capsule daily") are another mandatory component. However, manufacturers do not often know the quantity that consumers should be taking, because dosage has usually not been evaluated in scientific studies or with pharmacokinetics.
- The supplement facts panel lists the serving size, amount, and active ingredients. Often, evidence is lacking about the active ingredients. Some manufacturers may fabricate the active ingredients for labelling purposes.
- The name and place of business of the manufacturer, packer, or distributor must also be supplied. This information is meaningless, because some of these products are coming from other countries without good manufacturing practices, and the product has not been tested after import.

TABLE V *Dietary Supplement Health and Education Act* of 1994

A dietary supplement must meet all of the following conditions:
• A product (other than tobacco) intended to supplement the diet, which contains one or any combination of vitamins, minerals, herbs or other botanicals, or amino acids
• Intended to be taken in tablet, capsule, powder, softgel, gelcap, or liquid form
• Not represented for use as a conventional food or as a sole item of a meal or the diet
• No claim to treat a specific disease

Some terrible tragedies have resulted from certain Chinese herbs and Ayurvedic products that contained contaminants and heavy metals. The example of PC-SPES, which was deliberately and covertly contaminated to increase clinical activity, is noteworthy. A promising product when evaluated in the laboratory, PC-SPES was sold as a complex mixture of herbs, mainly derived from Traditional Chinese Medicine, with activity against prostate cancer. Phase III randomized controlled trials were planned under the sponsorship of the NCI. Before the trials started, the NCI required laboratory quality control tests to be conducted. Researchers found that the herbs had been contaminated. An anti–prostate cancer hormone (DES) had been added, as had alprazolam (a sedative) and coumadin (intended to stop the DES from causing blood clots). The factory in China manufactured all of those drugs, as well as the herbs. Thus, the public can be misled by the labels of dietary supplements. When studies of herbal products are conducted, careful quality assurance of the particular product and batch is necessary.

Under the DHSEA, herbal products can be marketed in the United States only as food supplements. A NHP manufacturer can make no health claims without FDA approval. A herbal manufacturer can get FDA approval if the product goes through all of the standard processes of a drug approval and if the evidence eventually shows

that the herb is effective and can be used for treating a specific condition. The process starts with a clinical trials application. However, the process takes a long time and a great deal of money. Most manufacturers are not prepared to proceed through the approval process because they are not required to do so by law.

The regulations are, unfortunately, very hospitable toward the marketing of natural remedies, but not toward evidence of their content and efficacy. Safety data are often lacking. Marketing authorization follows the WHO guidelines, which state that a substance's historical use is a valid way to document safety and efficacy in the absence of scientific evidence to the contrary. These guidelines may not be appropriate for the so-called developed nations. The risk–benefit ratio may favour herbs in some developing countries, but it is not suitable for NHPs in most North American or European populations. The WHO means well in principle, but in practice there are major difficulties with its guidelines.

In Canada, the Natural Health Products Directorate of Health Canada has compromised with a middle way, in which the foundation is assurance of quality and safety of NHPs, along with the opportunity to state traditional indications on the packaging (if the NHP has been used traditionally for more than 30 years or so). However, manufacturers are encouraged to evaluate these products through clinical trials so that they can state specific medical indications, if evidence-based. Health Canada's Federal Office of Natural Health Products or Natural Health Products Directorate was developed between 1999 and 2004. Its purpose is to ensure that Canadians have access to NHPs that are safe, effective, and of high quality, while respecting freedom of choice and philosophical and cultural diversity.

5.2 Research on NHPs

Scientists and physicians have regarded NHPs with suspicion. Clinical research has been of poor quality, resulting in diverse and inconclusive results. False negatives resulting from the use of inappropriate products or poor quality products (not authenticated) and a lack of statistical power further confuse the issue. The CONSORT organization works to standardize the way in which clinical trials are conducted, including the way in which results are reported. The organization recently published *Reporting Randomized, Controlled Trials of Herbal Interventions: An Elaborated CONSORT Statement* [3]. This important paper emphasizes the need for authentication of the product to be used in a clinical trial before that trial is started. Knowing the constituents of the product, being assured of batch-to-batch quality, and demonstration of lack of contamination are all essential steps.

In clinical trials of NHPs, researchers propose a hypothesis based on traditional observations that a particular herbal product *may be* effective. It is necessary to authenticate the product (including the particular species), where it is grown, and the conditions under which it is grown. The herbal product must be analyzed chemically. Then translational research in the laboratory is undertaken to determine whether the herbal product has mechanistic value and is likely to be effective in the clinic. Dose optimization using simple extracts and complex mixtures alike is necessary to determine how much of the herb is needed to produce the effect. Phase I pharmacokinetic studies follow. Safety and efficacy are both paramount. Thus, it is likely to take 10 to 15 years of research before phase II–III studies of a herbal product can be conducted.

The major challenge in research on NHPs is scientific authentication of the product (Table VI). There is no point in starting a clinical trial unless researchers know exactly what they are studying. Once clinical trial results are available, researchers want to be able to reproduce the agent with the exact constitution of chemicals evaluated in the clinical trial. Traditionally, in Chinese medicine or herbalism in Europe or North America, the herbalist is a specialist in agriculture—knowing, for example, where the particular herb grows best, from which direction the sunlight should be coming, how much sun and water the herb needs to grow optimally, and in which season the herb should be harvested. In addition, knowing the exact part of the plant to be used is imperative.

The same standards apply today. Researchers are conducting a large clinical trial for a herbal derivative to treat arthritis in the United States (Thunder God Vine). Before starting the study, they visited China where the herb is grown and used the expertise of the local population to ensure that the botanical would always be farmed in standardized conditions. When they received the product, they also evaluated it chemically in the laboratory to ensure that the constituents were the same. They then transferred the exact growing conditions to an agricultural plant in North America where they could reproduce the climatic conditions of the location in China. This approach is very different from designing and creating a drug using molecular biology that involves manipulating chemical structures in the laboratory. With herbal products, researchers are actually manipulating the chemicals in the field using agricultural techniques, and then bringing them back to the laboratory for study.

TABLE VI The major challenge in natural health products research: scientific authentication

Simple versus complex mixtures:	Phytochemical spectrum
	Good agricultural practice
	Good manufacturing practice
Combinations and derivatives:	Synergistic
	Redundant
	Second-generation derivatives

Good agriculture practice and good manufacturing practice are necessary for a consistent phytochemical spectrum. Combinations of chemicals can be synergistic or redundant. The complex mixture of chemicals in herbs may be synergistic or suboptimal. Herbalists generally believe that the chemical combinations are synergistic. In our opinion, the product should be optimized and any harmful constituent removed, especially if redundant. Developing second-generation derivatives, in which one potent chemical is synthesized is an option. However, that method may not be the only appropriate one. Technology is available for maintaining combinations of chemicals, which may have advantages in terms of synergy and reduced toxicity.

Complex mixtures of herbs could be important. In Traditional Chinese Medicine, a complex mixture could be composed of 10 different herbs. This scenario is a nightmare for the reductionist researcher. At the moment, research needs to focus on single herbs, which already contain multiple chemicals. New molecular biology and genomic techniques may permit the concomitant analysis of thousands of chemicals together, and the way is now paved for complex analyses.

An oncology research group from Yale University, which has now become a private company called Phytoceutica, has used modern chemical, genomic, and biologic assays to do a great deal of research on herbal products. One of the group's projects is a combination of Chinese herbs called PHY906 (*Scutellaria, Glycyrrhiza, Ziziphus,* and *Paeonia*). These researchers have developed a system to evaluate the various chemical components using spectrographic techniques. They can extract the various components and reconstitute them in various combinations. They use a computer software system to pinpoint the effects of removing and adding back the chemical constituents, thus optimizing the product's efficacy. Phytoceutica is analyzing thousands of different chemicals contained in these herbs. The researchers have found that the combination traditionally used affects the pharmacokinetics of the other herbs in the combination. For example, some of their botanicals prevent the development of resistance to anticancer agents through effects on enzymes that influence drug absorption, metabolism, and pharmacokinetics. Some of the herbs stabilize the other herbs and increase their solubility. Thus, the combination of these herbs may be synergistic. The researchers are also finding a polypharmacy advantage with this combination of herbs—that is, the various chemicals act on different receptors and have a greater therapeutic effect and fewer side effects than does a single refined component.

There are critical guidelines for NHPs. Standardization is the most important step. Quality control and quality assurance are next, followed by good clinical trial design and appropriate reporting of the results. The identification and quality assurance of herbal products is extremely complex and involves many different approaches to collect data on computers. Worldwide standardization of herbal profiles is necessary. The template for translational research on NHPs must start with chemical content and biologic activity.

There are various ways to measure the activity of herbs. Single chemical analyses are not always adequate. Biologic assays are sometimes necessary. For example, an immunogenic herb might be injected into an animal to observe the number of lymphocytes produced and whether the effect is consistent from batch to batch. Checking the purity of NHPs is another step. Pesticides and heavy metals, which are found in many NHPs, must be removed. Other areas to be studied are consistency and stability, preclinical efficacy and mechanistic knowledge (the subject of a great deal of current research), safety and interactions (tests in animal models), and then clinical efficacy.

New biologic methods for evaluating herbs use cells to detect chemical content. After exposing the cells to the herb, the new protein array chips that are now commonly available can be used to measure the varying degree of proteins induced by the herb's DNA. Thus, researchers can use various techniques to build a comprehensive picture of the exact components of a complex large chemical or mixture of chemicals. Researchers can build chemical profiles of the constituents of herbal products. These chemical profiles can then be used in a standardized library so that every laboratory is working with the same product. However, deriving chemical profiles for these products is complicated and expensive. It is likely that chemical profiles will be patented to protect investment before they are introduced into clinical studies.

Questions need to be answered about the activity of phytochemicals. Where do the constituents interact? Once phytochemicals are in the body, which sites do they act on? What are their biologic functions?

Some work is being done to answer these questions using magnetic resonance spectroscopic techniques and positron-emission tomography. Clinical trials can be conducted after this intensive research and authentication is complete. Phytoceuticals (botanical drugs) are authenticated through standardization. The basis for standardization is the identification of multiple chemical, genomic, and biologic fingerprints; potency and strength; purity; consistency (both qualitatively and quantitatively); stability; and effectiveness.

Establishing research networks is crucial. Linking isolated laboratories to improve scientific communication is necessary to advance research on NHPs. Although research is being published, no one is collating the data. Also, the work is very specialized, and various units may be conducting the analysis in different ways. To move forward more rapidly, data must be networked, libraries of chemical constituents must be developed, and sources of quality-assured constituents for research must be identified. The NHP industry will then start to gain credibility, and applied clinical research can be initiated.

A combination of players—industry, universities, government—is necessary to move NHP development forward (Table VII). Industry will bring in new products to improve health. Although industry's interest is clearly commercial, industry also has an ethical responsibility. Evidence-based research provides assurance of the efficacy and safety of the product that the company is selling. Universities have laboratories that can validate new products, but to operate those laboratories, they require income, part of which comes from commercial enterprises. To a varying extent, the government regulates NHPs and provides a structure for safety and efficacy. Government may provide research funding. These players need to come together into a network of communication. Such a network will result in a synthesis of NHP research and the emergence of useful products for patients.

The new phytoceutical industry will be manufacturing products that are evidence-based either for self-prescription (over the counter) or by prescription. Over-the-counter phytoceuticals will be evidence-based for the particular indicated health promotion. A prescription will not be necessary because the products will be relatively safe. Manufacturers can seek marketing approval from the FDA; if granted, this approval would allow for statements of the relative safety of the product and of the evidence-based indications and contraindications. Botanical-based products will also be developed for the treatment of specific diseases and would require a prescription because of their specific indication, increasing adverse effects, and so forth.

The phytoceutical industry is moving more toward a drug evaluation model. Examples of commercial development from university-based authentication exist. For example, a Canadian company called CV Technologies, which grew out of the University of Alberta, took an interest in a phytoceutical product derived from North American ginseng (*Panax quinquefolium*), which contains a combination of polysaccharides. CV Technologies fingerprinted the product to ensure its consistency, purity, and reproducibility from batch to batch when manufactured. According to Traditional Chinese Medicine, *Panax quinquefolium* improves immunity. Researchers at CV Technologies found a biologic effect during laboratory analysis. They then proceeded to conduct three clinical RCTs. The results of those studies were published in peer-reviewed journals between 2004 and 2006, and showed that *Panax quinquefolium* reduced the length of cold and influenza symptoms [11].

TABLE VII Key players in natural health product development

Industry	New products to improve health
	Commercial
University	Scientific validity of new products
	Academic
	Income
Government	Regulation
	Safety
	Efficacy and effectiveness
All	Network
	Communication
	Synthesis
	Emergence

Another example is the previously discussed Phytoceutica, based at Yale University in the United States. Researchers at Phytoceutica proposed that some combinations of Chinese herbs would be effective for cancer treatment, when used in combination with conventional chemotherapy drugs. After a literature review, they developed a product called PHY906, which is an authenticated formula of Chinese herbs that appears to increase the effectiveness and decrease the side effects of chemotherapy drugs. A methodology to define the chemical constituents was developed, the product was fingerprinted, and a genomic profile was obtained. In preclinical studies, researchers found that the PHY906 combination of Chinese herbs enhances the antitumour activity of conventional chemotherapy with capecitabine, irinotecan, or 5-fluorouracil, by enhancing the cytotoxic effects of those agents. Phytoceutica is currently conducting phase I and II studies in colorectal, hepatocellular, and pancreatic cancers [5,6].

5.3 Conclusions About Herbal Therapies and Clinical Trials

Table VIII outlines conclusions about herbal therapies and clinical trials. Standardization and quality control are mandatory before clinical trials are initiated. Herbal products used in clinical trials must be authenticated before study initiation. Institutional review board members reviewing studies must ask themselves whether the product to be studied is a drug or a NHP. If it is an NHP, it must be adequately authenticated and reviewed for safety. Expert contribution to the institutional review board is necessary.

In vivo preclinical studies are necessary to establish the herbal product's schedule, efficacy, and safety profile. Phase I and II human studies are necessary to determine dosing, adverse effects, and outcome effects sizes and variances. Knowing the effect size and variance is necessary for designing a phase III RCT, to determine the number of patients required to give the study adequate statistical power.

Expert design is necessary in authenticating herbal products and conducting clinical trials. A placebo-controlled or general comparator-controlled RCT is the capstone for these studies. Patients must be appropriately selected so that the patients that will benefit most from a particular product can be determined. Researchers must educate clinical trial participants to avoid using additional herbal medicines or supplements while on any trial (whether the product being studied is a

TABLE VIII Conclusions: herbal therapies and clinical trials

Standardization and quality control are mandatory before clinical trials are initiated.
In vivo preclinical studies are necessary to establish the schedule, efficacy, and safety profile of the therapy.
Phase I–II studies are necessary for dosing, adverse effects, variances, and outcome effect sizes.
Expert design of clinical trials is necessary to determine primary and secondary outcomes; a placebo-controlled (or suitable comparator) randomized clinical trial should be the capstone study.
Appropriate patient selection and stratification are necessary.
Education of subjects to avoid use of herbal medicines or supplements while on trial is necessary.

herb or a drug). Many herbs interact with drugs and can change their efficacy or toxicity [10].

6. THE SOCIETY FOR INTEGRATIVE ONCOLOGY

In North America, integrative oncology has evolved into a pragmatic and scientific discipline that is improving outcome for cancer patients, and is contributing to prevention, supportive care, rehabilitation, survivorship and palliative care [11]. The Society for Integrative Oncology (SIO) was founded in 2003, and its inaugural annual conference was held in New York City in December 2004. The conference was sponsored by multiple cancer organizations, including the American Cancer Society, the American Society of Clinical Oncology, and the American Society for Therapeutic Radiology and Oncology.

A non-profit, multidisciplinary organization, SIO attracts health professionals committed to the study and application of complementary therapies and botanicals for cancer patients. Many members come from major international academic cancer centers. These professionals are dedicated to studying and facilitating the cancer treatment and recovery process by using integrated evidence-based complementary therapies.

The mission of the SIO is to educate oncology professionals, patients, caregivers, and relevant others about state-of-the-art integrative therapies, including scientific validity, clinical benefits, toxicities, and limitations. The forum that SIO provides encourages presentation, discussion, and peer review of evidence-based research and treatment modalities in the discipline known as integrative medicine. Because a constantly growing number of cancer patients throughout the world are turning both to alternative and to complementary therapies as part of their cancer treatment, oncologists must have ready access to information about research, existing treatment programs, and the benefits and the dangers of the wide range of complementary therapies available today.

Members of SIO are individuals and organizations dedicated to optimizing cancer treatment. The organization itself promotes the scientific evaluation of complementary therapies, shares results, and encourages symptom control using therapies found to be beneficial. More information can be found at the SIO Web site, www.integrativeonc.org.

7. REFERENCES

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