

COMPLEMENTARY AND ALTERNATIVE MEDICINE: THE CURRENT SITUATION IN ONCOLOGICAL TREATMENT

Prof. Dr. Erkan Topuz

Institute of Oncology, Istanbul University

Complementary and Alternative Medicine (CAM) defines the series of treatments that is conducted in addition to or in place of conventional basic medical treatments. Alongside spiritual, physical and mental methods of treatment, herbal, vitamin, mineral, metabolic and clinical methods of treatment are also included under this umbrella. While some of these types of treatment have been scientifically proven, some are of little or no benefit. In the last decades, dramatic changes have taken place in the naming of CAM as a part of total patient care in patients, the public sector and emergency services.

Physicians and other health professionals have had difficulties in accepting CAM as a scientific approach. Historians of this discipline have reported on the immense changes that have taken place in this field in the last 30 years (since the times when the scientific community practicing these interventions were called charlatans). Since those times, the defining terminology used by clinicians and researchers have been gradually accepted by the medical community of the West. However, there is still no approach to putting these methods of treatments into a standard of scientific investigation. In modern terms, while complementary medicine has been included in combination with conventional treatments, alternative medicine includes those practices instead of conventional medicine and which is not proven by scientific research.

GENERAL OVERVIEW: CAM

As the National Centre for Complementary and Alternative Medicine (NCCAM) has defined, CAM is currently a series of medical and health care, practice and product which is not seen as a part of conventional medicine. Even though some scientific evidence has been found regarding CAM treatment, there are still some important questions which remain to be answered that have been investigated by well organised

scientific studies. These are questions such as whether the treatment is safe or not, or whether the methods of treatment in question are of benefit to the disease or problem. Included in the field of CAM are alternative medical systems such as homeopathy and naturopathy and traditional Chinese medicine and medical cultural systems such as Ayurveda, body-mind interventions such as yoga, prayer and meditation, biology-based systems such as diet and herbs, manipulative and body-based systems such as massage and chiropractics and energy-based methods of treatment such as Reiki, Qi-gong and magnetism.

CAM is widely used; however, the positive or negative affects of the treatment have not been sufficiently understood by the patients or the practitioners. In the USA, CAM has become a million dollar industry. It was estimated that the cost of CAM treatment and products was \$27-34 billion USD in 1998. These costs are met by the individuals themselves because this type of treatment is not included in the scope of medical treatment covered by health insurance. In addition, there is also the risk of consumers using these products without proper observation. Cancer patients are among the major consumers of CAM treatment. Estimates show that 88% of those diagnosed with cancer are users of CAM. The CAM modalities most often used in high percentages by cancer patients are prayer and use of exercise. However, the use of these in basic practices is a source of discussion. In a study, it was found that (with the exception of prayer), the CAM treatments most frequently preferred are, in order of highest frequency, vitamins and herbal medicines (63%), movement and physical treatments such as exercises, massage and chiropractic manipulation (60%), psychotherapy (41%), mind/body techniques (49%), special diets (33%) and other therapies (11%). The expectation of cancer patients from CAM are alleviation of symptoms, better life quality, ensuring support for the immune system and some patients' use CAM as a hope that the illness progression will recede or be a potential cure. Although the frequent use of CAM therapies by cancer patients are especially relational to illness and its severity, it is also closely connected to the persons belief system and cultural or ethnic background.

CAM RELATED PATIENT-PHYSICIAN COMMUNICATION

In spite of the high CAM usage by patients, there is often little to no communication or understanding between the patients and the physician in regards to CAM. Some patients are not aware of some treatments which may be beneficial to them and sometimes patients are used for observing potential benefits. Medical literature has well documented the lack of routine communication between patients and their physician

regarding the use of CAM. In a study it was found that 63-72% of cancer patients using CAM non-specifically and simultaneously with conventional treatment did not inform their physicians. In this study, the most frequent responses to why they did not inform their physicians was that their physicians would not find it important that they were using CAM (60%) and the belief that it was not the physicians responsibility (20%). Of the total of responses, only 14% reported that the physician would not accept it or approve of it. There are disproportionate beliefs about CAM by oncologists and cancer patients in regards to the gaps in communication.

Other studies have supported the perception that patients and physicians are not aware of CAM methods, such as herbal treatment for instance. In a study regarding the use of dietary supplements by patients, 44% of consumers of over-the-counter products claimed that they believed their physician had only little knowledge of these products. In addition, although it has been scientifically proven that 72% of these are ineffective, studies show that there is sufficiently strong evidence that these supplements have potential benefits. Nevertheless, these patients were in favour of government regulations to be affective in safety and no misleading information to be given in advertisements for the products.

In the last 10 years, CAM practices have increasingly captured the interest of biomedical research groups. The National Institute of Health (NIH) established an Alternative Medicine Office for the first time in 1992 and allocated a first annual budget of \$2million USD. In 1998, the Alternative Medicine Office expanded and became the NCCAM, with an annual budget of \$50million USD. One aspect of the Oncology Centre for Complementary and Alternative Medicine (OCCAM) and the National Institute of Cancer is to fund and support CAM related cancer research. The Federal support received, assisted in increasing the knowledge of medical professionals with research findings and provided education regarding these modalities. Furthermore, this progress helped to establish the legality of CAM and supported progress gained by further cooperation amongst CAM practitioners. In Turkey, an Alternative and Complementary Medicine Advisory Board has been recently established within the Cancer Advisory Board and is becoming institutionalised.

ETHICAL AND THERAPEUTIC APPROACHES

Questions which may arise concerning CAM should be answered by physicians. The use of CAM by the public is aimed at preventing malignancies, preventing the adverse effects of chemotherapy and radiotherapy and/or rehabilitation and to provide support for the patient after

treatment. The most important problems are safety, standardisation and access, which in a hospital environment increase the trust to CAM practice and the accessibility to CAM services. Among the safety concerns are: the direct toxic effects of products and herbs, interaction of CAM therapies with conventional chemotherapy or other prescribed medication and reduction of the effects of conventional treatment due to metabolic interactions. For example, patients may use herbs that reduce some of the symptoms of cancer but unknown intrinsic effects caused by chemical substances in the products may occur or adverse effects of contaminated substances may be observed. In addition to the well-known interactions with medicine, there may be herbs and antioxidants which may interact with medication and interrupt the effectiveness of the chemotherapy or radiotherapy treatment.

There are methods of treatment which should not be recommended or should not be accepted. Besides this, there are therapies which are directly amplified by laetrile or hydrazine sulphate. Some CAM treatments can reduce the effectiveness of conventional treatment and can interact with other medication to show serious and life threatening side effects. Sometimes the practice of CAM treatments prevents the patient with serious underlying problems such as malignancy from receiving the common and effective treatment. A product called St. John's Wort is used to treat the symptoms of depression. However, the most recent random controlled studies have shown that it has no more than a placebo effect. Besides this, St. John's Wort may reduce the affectivity of medication such as cyclophosphamide and cyclosporine. Findings show that St. John's Wort, garlic, ginkgo, Echinacea and kava modulate the cytochrome p450 isoenzymes and may reduce the level of cyclophosphamide in many important antieoplastic medications (Table 1). There are medication-herb interactions that may increase toxic levels. For example, the use of garlic, ginkgo and ginseng together with anti-thrombosis agents can increase the instance of bleeding. The physicians of the cancer patients must inform them about herbal or botanical agents taken in addition to conventional treatment in response to the unexpected adverse affects of chemotherapy which a known agent is not effective. Similarly, clinicians should question herbs/supplement products in cases where allergy to medication symptoms is present. Antioxidants are among over-the-counter products that are often used for the prevention of chronic diseases and cancer; however, the guidelines for usage of these products during chemotherapy and radiotherapy are still being discussed.

Table 1. Medication-herb interactions

<u>Herb</u>	<u>Medication</u>	<u>Effect</u>
Echinacea	Cyclophosphamide; vinca alkaloids	CYP3A4 inductions
Essiac	Anthraquinones; others	Inhibition of CYP3A causes synergism with chemotherapy
Garlic	Warfarin	Interaction, reduced effect
Gingko	Cyclophosphamide; vinca alkaloids	CYP3A4 and CYP2C19 inhibition
Ginseng	Cyclophosphamide	CYP3A4 inhibition
Milk thistle	Doxorubicin	Inhibition of P450, leading to reduction of metabolism of doxorubicin
St. John's Wort	Cyclosporine; irinotecane; taxanes; Imatinib	Sub-therapeutic levels of chemotherapeutic agents are metabolised by CYP3A4.

In order to be able to make recommendations to his patients, the oncologist must know which complementary treatment to recommend, which are acceptable and which are not. To be able to make recommendations, the schema to be used should be proven and be effectiveness-based. All treatments which are recommended must have evidence of effectiveness and safety (e.g. acupuncture). In a study conducted regarding acupuncture, only 43 minor adverse cases were found and no serious adverse cases were observed. Among the minor cases were slight local discomfort and some local bleeding in the place of the needle. Acupuncture is a treatment well tolerated by cancer patients. This treatment can be administered to those patients who have had anticoagulation treatment and who have appropriate laboratory values and modification of standard techniques. In regards to effectiveness, positive results were seen in several random studies conducted for nausea caused by chemotherapy and nausea and vomit control with acupuncture and agreement has been ensured with the NIH. There are acceptable methods of treatment lying between the two extreme ends of the scale. Although there is no hard evidence of effectiveness, the safety of the treatment is supported. Examples of complimentary treatment in this category for symptoms of pain management, dryness of mouth due to radiation and fatigue or sleeplessness and anxiety for post-chemotherapeutic treatments is acupuncture and massage for nausea, anxiety and stress due to autologous transplantation of bone marrow.

DEVELOPMENT OF CAM IN INTEGRATIVE MEDICINE

Integrative medicine (ET) has begun to be used recently in the West with the realisation that there are many beneficial components of complementary medicine. As defined by NCCAM, ET combines scientifically proven, high quality, effective and safe CAM treatments with basic medical treatments. In relation to its use in oncology, the focus is on the complementary aspects of ET (such as acupuncture, meditation, music therapy) on conventional methods of treatment such as surgery, chemotherapy and radio-therapy. In the beginning, CAM was initiated by the patients themselves and as previously mentioned, there has been a lack of communication between patients and their physician regarding the matter even though such methods were attractive to and were frequently practiced by the patients. These kinds of treatments should be a part of the patient-physician dialogue because these treatments positively or negatively affect the treatment decisions, medical aspects and general well-being of the patient. Integration requires patients, their physicians and CAM practitioners to work in close contact with each other. In most cases, the oncologist administering the treatment is the primary coordinator and implementer of the treatment and must be aware of all treatments that the patient is undergoing. The primary physician overseeing the patient's treatment supports all requirements of the patient to improve the well-being and life style by combining complementary treatments and conventional treatments effectively. Entrenching other types of treatments in the general therapy plan can only be possible with evidence-based complementary treatment options. These treatment options must have satisfactory risk-benefit ratios and must be proven to be effective and safe. Physician must explain to their patients that integrative treatments provide support to conventional medicine and are categorised as preventive medicine and that they should not be seen as an alternative to conventional medicine. As one patient states, "integrative medicine is like building bridges between patients and their physicians". Combining conventional treatment with complementary treatment within the scope of a therapeutic and empathic patient-physician relationship helps to ensure a complete treatment for the patient.

Whether it be in a hospital, under ambulatory conditions or in group practice, policies and procedures should be in place and implemented for the establishment of ET centres. For successful ET programs to be established and sustained, questions concerning trust of CAM practitioners, selection of recommended complimentary treatments, when to recommend the treatments and person responsible if any adverse affects are experienced should be answered. How can a suitably priced ET program be provided to all who request such services without discrimination of income of persons? This is an important issue because many complementary treatments are not included in the scope of health

insurance and payment per treatment is requested. These are but a few of the ethical and legal problems which need to be resolved in the scope of oncology.

EDUCATIONAL RESOURCES

There are a few reliable databases from which physician can obtain information about the benefits and adverse effects of herbal and botanical products. These databases contain information about medication-medication and medication-herb interactions. The education of physicians are stimulated by the widespread use of herbal and botanical medication by patients, their unfamiliarity and lack of training regarding these products and their concerns about the safety of their patients. In a newly conducted study of 20 physicians at a centre for cancer found that 50% of these physicians rarely asked their patients questions about the use of CAM treatments and, in comparison, 60% of their patients frequently asked them about CAM. Physicians reported that their biggest problem was that they were not familiar with the services and the deficiency of evidential data. There are training courses at national meetings, opportunities for training and workshops available for interested physicians and other health professionals. Furthermore, many faculties of medicine and health care academies have included CAM education and practices to their curriculum. In some programs, medical students and pharmacy and nursing students have begun studying complementary treatments in conjunction with conventional treatment in clinical case studies. However, these materials have yet to be included in the curriculum of many post-graduate programs. In spite of this, this kind of knowledge and approach concerning treatment of patients will be important in the training of future generations of physicians and other health professionals.

The Complementary Medicine Department was established in 2001 within the Institute of Oncology of the Istanbul University and a proposal has been presented by the Executive Committee of the Institute of Oncology to the Istanbul University Senate for this department to become a major department.

RESEARCH

As clinical researchers, what we want to know is whether complementary therapy is actually clinically effective and if so, what is the mechanism of effectiveness. The NCI and NCCAM now finance piloting studies and well-organised research activities concerning CAM. Until 16.01.2005, the NIH allocation of budget for ET research has shown a significant increase. The OCCAM office of the NCI has been

established to receive the comments of the CAM practitioners and decide whether the data for Desire for Practice is sufficient or not. CAM practitioners have been requested to provide the OCCAM with their clinical data, pathology slides and treatment and result data for control purposes. In organisations such as the Dana-Farber Cancer Institute, piloting activities are conducted as feasibility studies for conducting of clinical research in ET. Well-designed, random, placebo controlled studies will be conducted according to the results of the piloting activities. The 3 studies approved by the Local Ethics Board of the Institute of Oncology of the Istanbul University are still being conducted despite all difficulties. If the major department is established, a multidisciplinary structure will be present and a wider research field will be possible.

TRENDS FOR THE FUTURE

A new society has been established to attempt to scientifically resolve the questions and problems of CAM and the developing discipline of ET. The Society for Integrative Oncology (SIO) is an international organisation comprising of oncology professionals who use effective complementary treatments and try to integrate these with other treatments. Although the SIO is in the establishment stage, they have conducted 2 consecutive annual conferences. The aim of these conferences was “to provide education for oncologists and other health professionals interested in integrative treatment”. These conferences provided supportive data for complementary treatment and their effectiveness in oncology practices (especially evidence-based practices) (www.integrativeonc.org). Participants in the conferences were informed about important international work being conducted in the developing integrative cancer centres. The general sessions and research studies concentrated on non-pharmacological approaches (e.g. acupuncture) and use of botanical products, phyto-oestrogens and anti-oxidants in the treatment of cancer.

The SIO can work towards becoming a forum where scientific data concerning complementary treatments can be presented and at the same time, the importance of developing infrastructure which can assist in the development of ET principles and practices can be emphasised. The overall objective should be to develop multi-disciplinary experience and to create a therapeutic synergy between conventional and complementary treatment.

As the head of the Alternative and Complementary Medicine Advisory Board, to which I assisted in developing the infrastructure, established within the Cancer Advisory Board of Ministry of Health in Turkey, I provide 7-8 conferences per year for physicians and I try to raise the awareness of the public. In addition, I am the author of the book titled “Kanserde Alternatif ve Tamamlayıcı Tıp (Bilimsel Yaklaşım)

[Alternative and Complementary Medicine (Scientific Approach)]” which I present for the betterment of Turkish medical science.

Additionally, RTÜK [Radio and Television High Council] was informed of the approach of the media towards charlatans. A legal decree is attempted to be passed on this matter. By doing so, non-scientific broadcasts will be prevented and thousands of patients will be protected as a result.

RELEVANT END POINTS AND DEFINING CONCLUSIVE SOLUTIONS

Some CAM approaches such as mind-body therapy including guided affirmations or meditation are beneficial to quality of life. The use of these approaches in cancer centres are gradually increasing. In addition, group support activities have shown to be beneficial for survival. Therefore, these need to be included in definitions of clinical indexes for quality of life and basic end point activities. Prevention of 12 effects of chemotherapy such as fatigue, menopausal symptoms and neuropathy are being tested in terms of botanical agents. These models should be directed to studies with uniform designs, to studies having a quality of life end point with definite and acceptable effectiveness dimensions and lastly to sufficiently strong control studies. Researchers in this field of CAM must develop protocols with sufficient detail and uniform end point and quality of life end point adaptations of practice in relation to mind-body therapies, meditative therapy and group support.

Table 2. Difficulties and obstacles in integrative oncological research

- Variability, inconsistency and personalised nature of integrative models
 - Points which are not well defined and are subjective (especially for supporting treatments)
 - Insufficient pre-clinic models
 - Placebos and controls not well designed
 - Difficulties in blinding and random selection
 - Insufficiencies in protection of intellectual rights or patenting and limited private sector investments
 - Lack of funding and cross-disciplinary education for researchers and insufficient qualified controllers in financial support and publications
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DIFFICULTIES IN TESTING BOTANICAL / HERBAL AGENTS

Studies related to botanical agents have their own specific problems and each need to be resolved during the establishment of the research strategy.

Pre-Clinical Models for Integrative Medicine

Many integrative approaches (such as those including mind-body approaches) cannot be modeled before being clinically tested. This does not provide the opportunity to establish a strategy for privatising these frequently used types of treatments. Herbal/botanical therapies are becoming more and more attractive with previous and latest success of natural products and their derivatives in modern pharmacopoenia. Some of these agents' estimated biological activities can be tested by using appropriate in-vitro and in-vivo systems. However, many assumed effects (such as immune stimulation) and anti-angiogenic and other stromal-tumour interactions cannot be assessed by using tissue culture models. Some herbs being used for many years in the treatment of breast cancer are showing its anti-proliferate effects on human cell strings in in-vitro and in-vivo. This single agent could specifically be used in combination treatments. Among the specific effects of frequently used herbs is modulation of growth factor receptors, apoptosis, mitochondrial function, immune activation, control of cell cycle, inflammation and steroid hormones. As a result of multi-active agents, new high-speed gene expressions and proteomics techniques can be used to collect plant extras in one place even though their active mechanisms may be complex and these could even lead to the identification of the main compounds which are responsible for anti-proliferate activity.

Table 3. Nutritional sources of bioactive compounds

Nutrient	Compound
Fibrous vegetables	Isothiocyanates, indole-3- carbinol
Turmeric	Curcumin
Soya	Isoflavons
Pineapple	Bromelain
Grapes	Rezveratrol
Green Tea	Catechins
Ginger	Gingerols
Cayenne pepper	Capsaicin
Various foods	Querciten
Citrus fruits	Limonene
Strawberries	Anthocyanidins
Garlic	Organo-sulphur compounds

A visual practice of botanical agents which can be demonstrated in laboratory conditions are hot flushes and treatment of other oestrogen deficiency symptoms. Herbal compounds have a small amount of oestrogenic activity and an amount of these are found in herbs which are frequently used in treatment of menopausal symptoms. In addition to this, some oestrogenic herbs and Soya (known collectively as phyto-oestrogens) bind to the oestrogen receptor, ER-beta, selectively. In estradiol pre-clinical models, it binds to the ER-alpha and the ER-beta and activates these transcriptionally and induces the development of hormone-sensitive breast cancer cells. The selective stimulation of ER-beta does not stimulate the development of breast growth but inhibits the genes which affect the bone metabolism, which suggests that together with less risk than the risk of the potential of progress of the breast cancer by oestrogen, potential bone protection effect and other menopausal consequences stem from this. This has become the justification for testing of such herbal agents in women who have menopausal symptoms and who can not use oestrogen due to breast cancer diagnosis. This type of herbal formulas used in traditional Chinese medicine shows ER-beta selectivity and is used in clinical tests for hot flushes (together with an assessment of oestrogenic activity in a few target tissue samples).

Herbal products which are bio-active agents have potentially harmful effects. They may cause renal and hepatic toxicity. As with other types of medication, botanical agents may cause pharmacological and pharmacodynamic interactions. Many botanical agents and their compounds may affect the metabolism and its enzymes; however, only very few have been formally investigated. Many of these interactions can be estimated in in-vitro and in-vivo pre-clinic model systems. Herbal components can interrupt the activity of anti-cancer medication. Therefore, their combination with standard cancer therapy practices should be carefully investigated. Increasing and inhibiting the effects of chemotherapy and radio-therapy and related effects can be shown in laboratory models, however, the conflicting results of the model used shows that the model is a simple one and that clinical results may not be determinant. The effects of herbal agents on metabolism enzymes must be carefully investigated in the future. Enhanced research should be conducted to identify the reduction or increase of the effects of clinical interactions on standard treatment of chemotherapy and radio-therapy.

Issues Concerning Consistency, Purity, Manufacturing and Regulation

Without purifying a single compound or ensuring the implementation of strong quality control practices, the botanical products used as nature

provides them exhibits diversity. Herbs consumed can show variations in terms of the herbal compounds, the parts of the herb used and the conditions in which it developed. Furthermore, it has been documented that foreign substances are added consciously to medication such as steroids, diuretics and hormones. PC-SPES, a seven herb compound used as a possible sure for prostate cancer, has been taken off the market due to contaminants in the herbal formula. This had lead to the abandonment of several random studies. It is still not clear whether the contaminants in the formulas are explanatory of the effects in in-vitro or clinical studies. A general compound analysis is necessary to test the toxicity and safety of some active compounds in consistency of manufacturing to develop methods which can prove the relative amounts by using chromatography or mass spectroscopy.

Table 4. Special factors in testing botanical agents

- Inability of pre-clinical models to evaluate host interactions
- Variability in the consistency and purity of botanical agents
- Difficulties concerning regulation and manufacturing
- Adverse cases including medication interaction and renal/hepatic toxicity
- The problematic interpretation of formula treatment results

Well-Designed Control and Placebos and Difficulties in Random Selection

Appropriate controls in random studies concerning integrative treatment are often a problem. In the example of acupuncture, optimal control is still under debate because sham acupuncture, where the needle is administered at the surface, still provides a clinical effect. In one study, it was found that it was possible to significantly reduce nausea caused by chemotherapy in comparison to minimal needle control with electro-acupuncture at the p6 point (wrist). Besides this, appropriate controls were not used in many studies found in the literature and there are not enough treatments to compare with sham studies. Alongside botanical agents, if it is possible that last point subjective and placebos are effective, then placebos have a crucial role.

It is known that random selection of patients subjects in clinical studies are self-defining. This is generally the case for the field of the oncology and especially current studies for integrative oncology treatment or other sources. Some academic centres provide massage therapy or acupuncture for all patients. Therefore, it is understandable that only a small number of appropriate patients randomly selected wish to be a part of the studies concerning placebo controlled or sham controlled research.

Inadequacy of Sponsors, Experienced Researchers and Infrastructure

Sponsorship for CAM studies are almost always supplied by governments or non-profit organisations. Although funds for CAM research are gradually being allocated by National Health Institutions, these funds are still quite low when compared with pharmaceutical and biotechnology sectors. The first generation of wide scale random studies conducted in the field of botanical agents and micronutrients for supporting of cancer prevention and treatment or support of treatment is conducted by the Complementary and Alternative Medicine Office of the National Cancer Institutes. At present, 140 cancer prevention and treatment projects and 30 projects for symptom relief is being funded. Many of these are behavioural or acupuncture based. However some are testing nutritional and botanical approaches.

Many phase I and II studies are being conducted and are increasing in number. This is partly due to the new demands of practice supported by the National Centre for Complementary and Alternative Medicine (NCCAM). The mission of the NCCAM is to invest in research, training CAM researchers, increase access and facilitate the integration of proven models in clinical practices. The most urgent objective is for the stimulation of high quality and relevant research. However, other activities coordinated by the NCCAM are training, publications, organisation of knowledge transfer and standardisation of finding parameters.

Although there is an increase in the number of well-designed clinical studies, there is no clear path for the development of patenting of many integrative approaches. New compounds or synthetic analogues are appropriate for patenting; however, the intervention to isolate the probable active compound leads to a loss in the pharmacological qualities or tolerability in the botanical agents. Therefore, the general investment in the discovery stage of herbal or botanical agents and for integrative medicine in general is limited. A few new or established organisations have begun efforts to sponsor the research and development of botanical and natural products. Governmental agents also have mechanisms to be able to share the costs of development and regulation of hopeful developments in integrative cancer and prevention treatments.

The most important and easiest to overcome hurdles for integrative oncology studies is to further develop experience in this field. The number of research methods, CAM practices and researchers cross-trained in oncology are too few. However, more support for young researchers and guidance providers are apparent and most of these are

conducted within the scope of the National Health Institutes. Providers of scholarships are working to identify the value of, not only the fields of study and specialist fields such as journal editing, but also of publications which are often recommended. Underlying hypotheses and aims and methods and scientific design are traditionally a criteria in assessing the value of a new proposal for research. Besides this, the most commonly used to method of accepting or rejecting a model is relevancy. The issue of relevancy is critical however it is often overlooked in the compiling process.

In spite of many obstacles, the future for integrative oncology and especially research for botanical/herbal products looks bright. However, progress will be gradual. The areas of focus and priority need to be well defined. CAM methods should be standardised as much as possible and should be creative in terms of study design to comply with individualised interventions. The reason is that biological categorisation and regulated treatment must properly be conducted due to the heterogeneous nature of cancer and implementation of biologically focused treatment based on biotechnology. Pre-clinic models should be developed and refined where possible. Cooperative teams must be established to produce studies and to be able to train future generations of researchers. The overseeing aim should be to develop a collection of knowledge which is definitely integrative and to show care in ensuring the quality of specific models that consider the rules of scientific investigation.

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