



Published in final edited form as:

Eur J Cancer. 2011 March ; 47(4): 508–514. doi:10.1016/j.ejca.2010.11.018.

HERBAL THERAPY USE BY CANCER PATIENTS: A LITERATURE REVIEW ON CASE REPORTS

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Abstract

Complementary and alternative medicine use is common among cancer patients. In many surveys, herbal medicines are among the most commonly used group of treatments. Herbal remedies are believed by the general public to be safe, cause less side effects and less likely to cause dependency.

The authors performed a literature review to assess which herbal approaches have had associated cancer case reports and determine which of these have been studied in prospective research. Eighteen case reports of patients having apparent antitumour effects from herbal therapy and 21 case reports of toxic effects of herbs used by cancer patients were identified. Clinicaltrials.gov and MEDLINE (via PubMed) were searched for each of the herbal products identified in these reports. Clinical trials in cancer populations were identified for green tea extracts or compounds (n = 34), phytoestrogens (n=27), mistletoe (n =8), Ganoderma lucidum (n=1), Noni (n = 1) and Silymarin (n = 1). Daikenchuto, PC-SPES, Nyoshinsan/TJ and Saw palmetto have also been studied prospectively.

In conclusion, some of the herbs with promising case report findings have undergone prospective clinical investigations but many others have either not yet been explored or the results have not been reported in English. Unconventional therapies, such as herbs and minerals, used in ancient medical traditions have led to the identification of active anticancer agents. Mechanisms to support prospective research with such approaches are discussed.

Keywords

herbs; complementary and alternative medicine; cancer; treatment; toxicity

Complementary and alternative medicine use is common among cancer patients. A population based study conducted by Gansler et al in the United States found that the complementary methods (CM) most frequently reported used by cancer survivors were prayer/spiritual practice (61.4%), relaxation (44.3%), faith/spiritual healing (42.4%),

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The authors do not have any financial disclosures

Conflict of Interest Statement: None declared

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nutritional supplements/vitamins (40.1%), meditation (15%), religious counseling (11.3%), massage (11.2%), and support groups (9.7%).¹ A multinational survey found that 35.9% of cancer patients were either past or present users of complementary and alternative medicine (CAM). Herbal medicines were by far the most commonly used group of treatments, escalating in use from 5.3% before the diagnosis of cancer to 13.9% after the diagnosis of cancer.² Many individuals use certain CAM approaches with expectation or hope for therapeutic effects on the tumour which might improve their survival.³ Herbal remedies are believed by the general public to be safe, cause less side effects and less likely to cause dependency.⁴ Relatively little English language clinical research literature about the use of CAM approaches in cancer has addressed studies of anticancer treatments.

We performed a literature review to assess which herbal approaches have had associated cancer case reports and determine which of these have been studied in prospective research.

Methods

We conducted a search for all English language articles in MEDLINE via PubMed with publication dates from January 1960 to March 2009. The search included the following terms and Boolean operators: Neoplasms/diet therapy OR Neoplasms/drug therapy OR Neoplasms/therapy AND Case Reports NOT vincristine NOT vinblastine NOT taxol NOT irinotecan NOT etoposide NOT leucovorin NOT warts NOT fibroid. The search was also limited to articles in the Complementary Medicine subset of MEDLINE and to articles about humans. This search yielded 1162 articles which were individually reviewed yielding 374 case reports.

We also searched EMBASE using the following text words and Boolean operators: Alternative medicine OR phytotherapy OR traditional medicine OR herbs/herbal AND neoplasms AND case reports. The search yielded 432 case reports. The EMBASE search covered articles published from 1950 through 2008.

We sought case reports of the use of herbal compounds by cancer patients. Case reports were classified as to whether the report described an apparent therapeutic benefit (i.e. anti-tumour response or symptomatic improvement) or rather an adverse effect following consumption of an herbal preparation.

We searched MEDLINE via PubMed for reports of clinical trials using the names of the herbal interventions described in the case reports. Clinicaltrials.gov was searched to identify active or recently completed trials of the same interventions

Results

Forty-three articles describing 71 individual case reports were identified that met the above criteria for inclusion. There were 18 case reports of patients having apparent anti-tumor effects from herbal therapy. (Table 1) Of these, 5 cases involved prostate cancer, 3 cases of lung cancer and 5 cases of lymphoma. Other cancers/tumours represented were described as intracranial tumour, hepatocellular cancer, gastric cancer, malignant melanoma and Barrett's adenocarcinoma. Most of the cases involving prostate cancer were associated with the use of the herbal supplement PC-SPES.

There were 21 case reports of toxic effects of herbs used by cancer patients. (Table 2) Of these 6 were associated with Traditional Chinese Medicine, 6 with mixtures of herbs, 2 with the use of PC-SPES, 2 with mistletoe and 5 with various other herbs.

The complications reported in cases involving PC-SPES include pulmonary embolism and disseminated intravascular coagulation.^{23,24} Mistletoe was reported to have caused delayed type hypersensitivity and hypereosinophilia in the treatment of breast and pancreatic cancer respectively.^{25, 26} Aristolochic acid containing herbs from Traditional Chinese Medicine (TCM) resulted in renal failure, nephropathy and pre-operative hepatitis^{27,28,29,30,31}. A Chinese herbal remedy used in conjunction with radiotherapy for lung cancer treatment resulted in radiation pneumonitis.³² Various herbal mixtures resulted in prostate cancer growth stimulatory activity, delayed type hypersensitivity, hypokalemia, hypokalemic hypochloremic metabolic alkalosis, hyponatremia and drug interaction.^{33,34,35,36,37,38} Other reported adverse events included: development of male breast cancer after prolonged consumption of a phytoestrogen³⁹, intraoperative haemorrhage following consumption of saw palmetto⁴⁰ and severe bone marrow suppression associated with consumption of *Selaginella doederleinii*⁴¹ and *Cantharanthus roseus*⁴²

Four case reports described patients using herbs for symptom management. (Table 3) Two cases involved the use of Kampo herbal medicines by patients in Japan for the treatment of menopausal symptoms following chemotherapy and radiation induced enteritis. Silymarin was used in association with antimetabolites to reduce the lipoperoxidative damage and the subsequent liver function alterations induced by these drugs while mistletoe was used to improve quality of life in five patients with various types of cancers.

We sought to find out if there were any clinical trials assessing these herbs as potential anticancer agents. There were eight clinical studies in Clinicaltrials.gov assessing the effect of mistletoe on several types of cancer. Two of the studies were complete, five were open but not recruiting and one was recruiting.⁴⁸ Forty-two studies were listed assessing the potential of green tea extracts, or polyphenol mixtures (e.g. Polyphenon E), alone or in combination with other compounds for the prevention or treatment of various cancers or premalignant conditions. Of these, three were terminated and nine are complete.⁴⁹ A phase 1 clinical trial of the Polynesian herbal noni was initiated 2001 at the Cancer Research Center of Hawaii, Honolulu. The trial was completed in June 2006 but no published article summarizing the findings was identified.

Discussion

Little is known of the impact of case reports and case series on the initiation of prospective preclinical or clinical research that are eventually substantiated by controlled clinical trials.⁵⁰

To obtain the various approvals necessary to initiate a clinical trial there must be preliminary evidence on which to base the hypothesis that a treatment may be efficacious. Case reports and small uncontrolled case series are frequently this first line of evidence⁵¹ but they are not often cited as the primary supporting evidence justifying a subsequent trial.

Observations from the historical use of a compound have proven useful in the identification of some modern drugs. Arsenic has been used as a therapeutic agent for more than 2,400 years.⁵² In the 15th century, William Withering who discovered digitalis was a strong proponent of arsenic-based therapies. Arsenic trioxide was recorded in the Compendium of Materia Medica by Li Shi-Zhen (1518–1593).⁵³ Pharmacology texts of the 1880s describe the use of arsenical pastes for cancers of the skin and breast.⁵⁴ In the 18th century, Thomas Fowler compounded a potassium bicarbonate-based solution of arsenic trioxide (As₂O₃) that would bear his name. Fowler's solution was used empirically to treat a variety of diseases into the early 20th century.⁵⁵

In 1878, a report from Boston City Hospital described the effect of Fowler's solution on the reduction of white cell counts in two normal people and one patient with "leucocythemia".^{56,57} Arsenic compounds were administered as antileukaemic agents until they were replaced by radiation therapy.⁵⁷ The hematological use of arsenic experienced a resurgence in popularity in the 1930s when its efficacy was reported in patients with chronic myelogenous leukaemia (CML).⁵⁷ In the early 1990's, reports from China described the induction of clinical and hematological responses by arsenic trioxide in patients with de novo and relapsed acute promyelocytic leukaemia (APL).⁵⁸⁻⁶⁰ The results of these observational studies were then confirmed in randomized clinical trials in the U.S.^{61,62} Consequently, arsenic trioxide (TrisenoxTM) was approved for the treatment of relapsed or refractory APL by the U.S. Food and Drug Administration in September 2000.

Another example of the potential benefits, but also the pitfall of using case reports of unconventional approaches to justify the initiation of prospective cancer clinical trials is the PC-SPES story. PC-SPES is a proprietary formulation that was marketed as a dietary supplement by Botanic Lab (Brea, CA) from 1996 through 2002.⁶³ PC-SPES apparently came to the attention of cancer researchers through reports of use by prostate cancer patients.⁶⁴ Several articles published between 1999 and 2003 described the results of observational studies and clinical trials conducted before adulteration with warfarin, indomethacin and diethylstilbestrol was identified in several PC-SPES lots.⁶⁵ These findings led the National Center for Complementary and Alternative Medicine in 2002 to place a hold on ongoing studies of PC-SPES and a moratorium on further research with the compound.⁶⁶ After several years, two recent reports indicate the reemergence of research with mixtures of the extracts of the herbs from the PC-SPES formula, hopefully, without the adulterants.^{67,68}

Since many herbal medicines have undergone little or no research, often there is little objective information about the potential risks and benefits of their use. Despite the popular notion of herbs as safe, a variety of adverse events associated with their use alone or in combination with conventional anticancer therapy has been reported including occurrence of severe bone marrow depression. Oncologists and medical practitioners should be aware of the adverse effects associated with these herbs, and be sure to obtain a thorough history of the use of such compounds from their patients.

It is generally not possible to ascertain from a published case report whether or not a patient's tumour regression was the result of the herbal medicine. Spontaneous remissions have been reported to occur for a variety of malignancies.⁶⁹ However, given the history of the serendipitous finding of useful therapeutics, well documented cases of cancer regressions with an herbal medicine warrant some consideration for the initiation of prospective research.

The NCI Best Case Series (BCS) program is a process of evaluating case report information from health care practitioners that involves the same rigorous scientific methods used to evaluate treatment responses with conventional medicine.⁷⁰ The program is an opportunity for CAM practitioners to share their well documented cancer cases with the goal of assessing whether sufficient evidence is available for NCI-initiated prospective research.

When surveyed, a majority of both CAM practitioners treating cancer patients and cancer researchers interested in CAM expressed a willingness to participate in collaborative research.^{70,71} The same surveys identified a lack of awareness of appropriate funding resources as a major obstacle to such research. OCCAM has developed funding opportunity announcements (FOAs) to support research in areas with little or no research evidence for particular interventions. One of the FOAs (PA-09-168) encourages research of approaches

for which case report information may be the primary, or only available supporting information.⁷²

Some of the barriers to performing research on herbal therapies include the availability and development of herbal products for research studies. There are also significant difficulties in developing herbal placebos. Crude herbs have bulk, colour, aroma and taste that are difficult to mimic with therapeutically inert ingredients. Another barrier is the estimation of the effect of a single component (e.g., a component herb or diet), or the interaction between two or more components present in an intervention.⁷³

In conclusion, this review identified published cases of cancer patients treated with herbs and that reportedly experienced significant clinical benefit or toxicity. Many of the herbs with positive outcomes apparently have not yet been explored with prospective clinical research. Useful therapeutics have been identified via observations of patients treated with what were once considered unconventional approaches. We propose that the research community should endeavor to conduct prospective research when credible evidence is available suggesting potential benefit to cancer patients from herbal or other unconventional approaches.

Acknowledgments

We thank Mary Ryan for her help in the literature search.

Role of funding source: Funding for this manuscript was provided by the National Cancer Institute. The National Cancer Institute did not participate in the design, analysis, interpretation of data and writing of the manuscript.

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Table 1

Herbs used as cancer treatments

Herb name	Cancer type	Reported outcome	Prospective research*	Source
Essiac	Prostate	Decrease PSA levels from 87.19 to 0.12 ng/ml	No	Al-Sukhni W ⁵
PC-SPES	Prostate	Less than 50% decrease in PSA level	Yes	Urakami S ⁶
PC-SPES	Prostate	Decrease PSA levels from 100 to 24 ng/ml and 386 to 114 ng/ml	Yes	De la Taille A ⁷
PC-SPES	Prostate	Decrease PSA levels from 8.8 to 0.1 ng/ml	Yes	Moyad MA ⁸
PC-SPES	Prostate	Increase serum PSA levels ranging from 345% to 880% after discontinuation of PC-SPES	Yes	Oh WK ⁹
Chinese herbal medicine [#]	Lung	Complete Regression	No	Liang HL ¹⁰
Oriental herbal medicine and <i>Lyophyllum decates</i> sing	Lung	Partial response	No	Kato S ¹¹
Ninjin yoei To (Traditional Chinese Medicine herbal medicine)	Lung	Decreased tumor marker levels CEA: 14.6 to 11.3 ng/ml; CA19-9: 55 to 39.2 U/ml	No	Kamei T ¹²
Chinese herbal extract (specific herbal component not identified)	CLL	Complete Remission	No	Battle TE ¹³
<i>Ganoderma lucidum</i>	Gastric large B-cell Lymphoma	Complete regression	Yes	Cheuk W ¹⁴
Green Tea	CLL	Partial response	Yes	Shanafelt TD ¹⁵
Mixture of 36 herbs	Intracranial tumor (teratoid/rhabdoid tumor)	Complete response	No	Howes TL ¹⁶
Hochu-ekki-to	Lymphoma (Mycosis fungoides)	Partial improvement of skin eruption	No	Tokura Y ¹⁷
Mistletoe	Malignant melanoma	Complete remission of liver metastasis	Yes	Kirsch A ¹⁸
Mistletoe	CD 30+ cutaneous lymphoproliferative lymphoma	Complete regression	Yes	Seifert G ¹⁹
<i>Morinda citrifolia</i> (noni)	Gastric Cancer	Tumour suppression	Yes	Wong DK ²⁰
Peruvian herbal tea	Barrett's adenocarcinoma	Seven year survival	No	Mason GR ²¹
Mixture of 9 herbs	Hepatocellular	Complete regression	No	Cheng HM ²²

* Indicates whether or not there was at least one trial of the herb as a potential cancer therapeutic listed in Clinicaltrials.gov or reported in MEDLINE.

PSA (Prostate Specific Antigen)

[#] Components of Chinese herbal medicine: *Herba Hedyotis diffusa*, *Maidong Radix ophiopogonis*, *Pugongying Herba taraxaci*, *Sanqi Radix notoginseng*, *Shancigu Pseudobulbus*, *Cremastrae seupleiones*, *Xiyangshen Radix Panacis quinquefolii*, *Yuxingcao Herba houttuyniae*, *Zhebeimu Bulbus Fritillariae thunbergii*, *Zhibanxia Rhizoma Pinelliae preparata*

Table 2

Adverse events associated with herbs and herb-derived compounds used by cancer patients

Herb name	Cancer type	Reported Toxicity	Source
PC-SPEs	Prostate	Pulmonary embolus, Disseminated intravascular coagulation	Schiff JD ²³ , Lock M ²⁴
Mistletoe	Breast, Pancreas	Delayed type hypersensitivity, Hyperesinophilia	Shaw HS ²⁵ , Huber R ²⁶
Traditional Chinese Medicine containing aristolochic acid	Genitourinary, Cervix	Renal failure, Nephropathy, Pre-operative hepatitis	Lord GM ²⁷ , Nortier JL ²⁸ , Cosyns JP ²⁹ , Vanherweghem JL ³⁰ , Critchley LA ³¹
Chinese Herbal medicine (specific herbal component not identified)	Lung	Radiation pneumonitis	Taylor CW ³²
Mixture of Herbs (e.g. Chaparral, flaxseed, alfalfa, red clover, licorice, ginkgo, ginseng, huang qi)	Prostate, Breast, Cervix	Delayed hypersensitivity Reaction, Hypokalemia, Hypokalemic hypochloremic metabolic alkalosis, Hyponatremia	Shariat SF ³³ , Cheng CJ ³⁴ , Lehmann D ³⁵ , Norred CL ³⁶ , Von Gruenigen VE ³⁷
Mixture of herbs (ginseng, Fomes fomentarius, Inonotus obliquus, Phellinus linteus and selenium)	Lung	Drug interaction	Hwang SW ³⁸
Phytoestrogen (Soy, Ginkgo biloba, Salvia officinalis, Salvia pratensis, Licorice root, Lentils)	Breast	Male Breast Cancer	Dimitrakakis C ³⁹
Saw Palmetto	Meningioma	Intraoperative haemorrhage	Cheema P ⁴⁰
Selaginella doederleinii	Cholangiocarcinoma	Severe reversible bone marrow suppression	Pan KY ⁴¹
Catharanthus roseus	Hepatoma	Severe bone marrow	Wu ML ⁴²
Sanguinaria canadensis	Basal cell carcinoma	Bone metastasis	Laub DR ⁴³

Table 3

Herbs and herb-derived compounds used for symptom relief.

Herb Name	Cancer Type	Symptom/Side Effect	Prospective Research*	Source
Daikenchuto	Squamous cell carcinoma of the cervix	Radiation induced enteritis	Yes	Takeda T ⁴⁴
Nyoshinsan/TJ 67	Breast cancer	Menopausal symptoms	Yes	Kogure T ⁴⁵
Mistletoe	Multiple sites	Increased quality of life	Yes	Legnani W ⁴⁶
Silymarin	Promyelocytic leukaemia	Inhibition of liver damage associated with chemotherapy	Yes	Invernizzi R ⁴⁷

* Indicates whether or not there was at least one clinical trial of the herb as a potential cancer therapeutic listed in Clinicaltrials.gov or reported in MEDLINE.