Herbal medicine for cancer patients: An evidence based review

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Abstract

Complementary and alternative medicine (CAM) is widely embraced by cancer patients due to largely patient driven demands for integration of herbal therapies into cancer treatment. The value of herbal medicine in cancer patients can only be fully realised when prescription is integrated into conventional cancer management models; a medico rather than patient driven strategy. Integrated medicine is a holistic approach to cancer care, with some herbal medicines showing proven effectiveness as adjuvants to conventional medical treatments. At the present time there is little evidence of a systematic process of evaluation or dialogue between mainstream medicine and herbal medicine practitioners. This review offers an evidence-based perspective of herbal medicine for cancer prevention, cancer treatment, managing cancer survival and palliation.

INTRODUCTION

Complementary and alternative medicine (CAM) is widely embraced by cancer patients both in Australia and internationally (Ernst & Cassileth 1998; Tascilar et al. 2006). In a recent survey, more than half of Australian cancer patients reported using herbal medicine (MacLennan, Wilson & Taylor 2002), although one suspects lack of disclosure might have underestimated actual use. Due to the serious and often terminal nature of cancer, patients are a vulnerable population and may have large financial and psychological investment in herbal therapies (MacLennan, Wilson & Taylor 2002). The largely patient driven demand for integration of herbal therapies into cancer treatment offers an opportunistic window for less than ethical practitioners. The value of herbal medicine in cancer patients can only be fully realised when prescription is integrated into conventional cancer management models; a medico rather than patient driven strategy. An evidence-based approach must be more broadly adopted by qualified herbalists to facilitate an integration of herbal medicine into the traditional cancer care model by conventional oncology specialists. This review offers an evidence-based perspective of herbal medicine for cancer prevention, cancer treatment, managing cancer survival and palliation.

CANCER PREVENTION

An epidemiologic study of 24 European countries using mortality data reported that fish oil is protective against colon and breast cancers while animal fat consumption was carcinogenic (Caygill, Charlett & Hill 1996). The ratio of n-3 to n-6 polyunsaturated fatty acids (PUFAs) has been implicated in modulating cancer incidence and progression (Leitzmann et al. 2004; Weisburger 1997). Chemo-preventative actions demonstrated by n-3 EFAs include suppression of neoplastic transformation, inhibition of cell growth and enhanced apoptosis, and anti-angiogenicity (Rose & Connolly 1999); whilst several studies implicate n-6 PUFAs as stimulators of these reactions (Leitzmann et al. 2004; Weisburger 1997). Recent reviews by Terry et al. (2003) and Terry et al. (2004) found that overall the evidence remains unclear as to whether dietary fish or fish oil consumption exerts a protective effect against the development of breast and prostate cancers. Leitzmann et al. (2004), in a prospective cohort study of 47866 men found an association between alpha-linolenic acid (ALA) and advanced prostate cancer, but an inverse relationship with the ALA metabolites eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The ratios of omega 3:6 appear to be highly influential in conveyed risk (Leitzmann et al. 2004).

In terms of colorectal cancer, both EPA, DHA and fish oil itself have been shown to exert antineoplastic effects (Pons et al. 2003). Theodoratou et al. (2007) undertook a meta-analysis of the effect of high intake of n-3 PUFAs in a combined data set of five case-control studies and found a significant decreased risk of colorectal cancer with n-3

PUFA consumption.

Current evidence, based on in vitro and in vivo studies as well as epidemiological evidence, suggests that some foods have cancer preventative potential (Craig 1997; Ernst 2003). The highest anti-cancer activity is found in garlic, onions, soybeans, ginger and the umbelliferous vegetables (e.g. carrots, celery, parsley and parsnips) (Craig 1997).

The intake of large quantities of fruits and vegetables, foods that are rich in beta-carotene, is associated with a lower risk of cancer (Cohen, Kristal & Stanford 2000; Cooper 2004; Terry, Terry & Wolk 2001), however, whether beta-carotene has anticancer properties in humans is unclear. Postulated mechanisms include antioxidant activity preventing oxidative damage to deoxyribonucleic acid (DNA) and lipid peroxidation, stimulation of gap junction communication, effects on cell transformation / differentiation, inhibition of cell proliferation and oncogene expression, effects on immune function and inhibition of endogenous formation of carcinogens (Cooper, Eldridge & Peters 1999a). Additional mechanisms may include the metabolic conversion of beta-carotene to retinoids, which then modulate the gene expression of factors linked to differentiation and cell proliferation (PDRHealth 2005). Unfortunately, none of these mechanisms has been conclusively found to contribute to cancer prevention in vivo (Patrick 2000; Cooper, Eldridge & Peters 1999b). The questionable role of beta-carotene is further fuelled by the findings of two large intervention studies, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (Heinonen et al. 1994) and the Carotene and Retinol Efficacy Trial (CARET) (Omenn et al. 1996), which found a significantly increased risk of lung cancer in high-risk subjects who took synthetic beta-carotene. Subsequent studies compound the debate regarding beta-carotene. The Physician's Health Study (22071 males) and the Women's Health Study (39876 women) both showed no harm or benefit from beta-carotene supplementation on the incidence of cancer (Cook et al. 1999; Hennekens et al. 1996; Lee et al. 1999). The outcome is that beta-carotene alone is no longer recommended for cancer prevention, although a diet rich in beta-carotene containing foods is still advocated (Pryor, Stahl & Rock 2000).

Antioxidative vitamins and phenolic phytochemicals in addition to beta-carotene are also proposed to be chemo-preventative (Lee & Lee 2006). Epigallocatechin gallate (EGCG), a polyphenol isolated from green tea is believed to exhibit high chemo-preventative potential. Nakachi, Eguchi and Imai (2003) reported in a prospective cohort study that increased green tea consumption was associated with a delay of cancer onset and death. Hakim et al. (2003) in a phase-II randomised controlled trial found that green tea consumption significantly reduced oxidative DNA damage in 143 heavy smokers. While most evidence shows a positive correlation between green tea and cancer prevention, a prospective study by Nagano et al. (2001) found no association between green tea consumption and cancer incidence.

Resveratrol and Quercetin, also polyphenols, have been shown to have some chemo-preventative action in in vitro and animal models (Lee & Lee 2006). Supporting human clinical trials for resveratrol are lacking (Lee & Lee 2006). The anti-carcinogenic effects of quercetin seen in animal studies (Erlund 2004) alongside epidemiological studies, suggest a chemo-preventative role in colon cancer (Kim et al. 2005; Park et al. 2005), lung cancer (Schwarz, Kisselev & Roots 2005), prostate cancer (Yuan, Pan & Young 2004) and breast cancer (Otake et al. 2000).

Evidence-based data regarding soy as an anticancer agent is limited. In vitro and animal trials suggest several pathways by which isoflavones may reduce the incidence of cancer (Rosenberg Zand, Jenkins & Diamandis 2002). Experimental evidence points to an inhibitory effect of soy bran on prostate cancer growth and isolated lignans on colon cancer (Adlercreutz 2002a; Adlercreutz 2002b); however, there are no positive clinical human intervention studies to support soy as a chemo-preventative agent.

Folic acid may have a chemo-preventative role as suggested by epidemiological, animal and human data. Folate status appears to affect the risk of developing cancers in selected tissues although the exact nature of its action is still unknown (Bollheimer et al. 2005; Powers 2005). Early in the 1990's folate status was thought to be linked to the incidence of colon cancer (Cravo et al. 1992), however in 2005, a major systematic review of in vitro, animal and various clinical and epidemiological studies concluded that high folate intake does not have a chemo-preventative impact on colon carcinogenesis (Bollheimer et al. 2005). The potential role of folate in the prevention of cervical cancer is equivocal and not supported (Henao et al. 2005; Sedjo et al. 2003). According to Choi and Mason (2000; 2002) folate's action still represents a plausible modulator of cancer risk due to its critical role in the production, methylation and repair of DNA, regulation of cell turnover and suppression of excessive proliferation.

DISEASE PROGRESSION AND PATIENT SURVIVAL

Baical skullcap (Scutellaria baicalensis) is an ingredient in a popular Chinese / Japanese herbal formulation (Minor Bupleurum Combination), known as Xiao Chai Hu Tang (China) or Sho-saiko-to (Japan) which has been used for 3000 years (Bruan & Cohen 2007). Sho-saiko-to was administered over a period of 8 years to 1.5 million patients with chronic liver diseases due to its ability to significantly suppress cancer development in the liver (Yamashiki et al. 1999). The long traditional use of this herb has validated its safe use in pyretic diseases and as an anti-liver cancer agent. As such, it is now a prescription drug approved by the Ministry of Health and Welfare in Japan (Bruan & Cohen 2007).

The immuno-stimulatory effects of Sho-saiko-to are attributed to its ability to stimulate granulocyte colony-stimulating factor (Yamashiki et al. 1992), regulate the cytokine production system (Yamashiki et al. 1997) and improve the production of IL-12 an important cytokine for maintenance of normal systemic defence and bio-regulation (Yamashiki et al. 1999). The anti-cancer effect of Sho-saiko-to is attributed to two of its seven herbal components, baical skullcap and licorice root (Yamashiki et al. 1999).

Baicalein, baicalin and wogonin have been shown to induce apoptosis and inhibit proliferation in various human hepatoma cell lines (Chang, Chen & Lu 2002). Baical skullcap has been shown to be an effective chemotherapeutic agent for head and neck squamous cell carcinoma by selectively and effectively inhibiting cancer cell growth in vitro and in vivo (Zhang et al. 2003). Inhibition of PGE2 synthesis via suppression of COX-2 expression may be responsible for its anticancer activity, with prostate and breast cancer cells particularly sensitive (Ye et al. 2002). In an in vivo study, baical skullcap extract showed significant inhibition of bladder tumour growth (Ikemoto et al. 2000). Baical skullcap is one of the herbs found in PC-SPES, a complex of Chinese herbs that is clinically active against advanced prostate cancer (Hsieh et al. 2002; Oh et al. 2001; Small et al. 2000). Potential roles may exist for baical skullcap as an adjunct to cancer treatment and in the prevention of metastases, however, its role is not currently supported with any strong evidence and further clinical trials are warranted to determine its effectiveness.

The active principals of Ginseng (Panax Ginseng) include saponins, polysaccharides, flavonoids and volatile oils. In cancer therapeutics, the saponins and polysaccarides have been investigated most widely (Helms 2004). Unfortunately, there are no human clinical trials reporting on the anti-cancer properties of ginseng. Several recent in vitro and animal studies have reported the anti-tumour (Helms 2004; Shin et al. 2004), anti-proliferative (Kim et al. 2002; Park et al. 2002), anti-metastatic (Shin et al. 2004; Hasegawa et al. 2002; Shibata 2001) and apoptosis-inducing effects of ginseng (Hwang et al. 2002). Conversely, a recent study by Xie, Zeng & Huang (2001), investigated a group of 131 patients receiving radiotherapy for nasopharyngeal carcinoma; 64 were randomly assigned to receive ginseng polysaccharide injections. Clinical remission rates were similar among the treatment and placebo groups, as were overall survival and rate of disease free survival (Xie, Zeng & Huang 2001).

Overall, in vitro and animal studies point to the ability of ginseng to limit and slow cancer growth as well as to enhance the ability of the immune system and tumour cells to overcome chemo-tolerance and incite apoptosis (Ernst et al. 2007; Helms 2004). Ginseng's ability to increase effectiveness of other chemotherapeutic agents, to act synergistically and to result in lower doses (and therefore side effects), is increasingly documented (Bruan & Cohen 2007; Ernst et al. 2007; Helms 2004). There is a wealth of anecdotal evidence but no randomised controlled trials that ginseng cures any type of cancer (Helms 2004; Block & Mead 2003). Despite this, the use of ginseng for cancer is well accepted in China (Helms 2004).

The wide ranging effects of curcumin (curcuma longa) on tumourigenesis, angiogenesis, apoptosis and signal transduction pathways have been studied in many in vitro and animal models (Gururaj et al. 2002; Mohan et al. 2000; Thaloor et al. 1998). Curcumin is known to inhibit oncogenesis during both the promotion and progression stages of various cancers (Anto et al. 1996; Menon, Kuttan & Kuttan 1999; Sagar Yance & Wong 2006). Recently, curcumin was found to possess chemo-preventative effects against skin cancer, stomach cancer, colon cancer and oral cancer in the murine model (Braun & Cohen 2007). Unfortunately there are no human clinical trials assessing curcumin, and as such, further evidence of its anti-cancer properties is warranted.

Mistletoe (Viscum album) or iscador (a derivative), is a popular cancer remedy in Europe where it is available in many mainstream oncology clinics (Cassileth 1999). In vitro studies show that it is anti-angiogenic by down-regulation of

vascular endothelial growth factor and it also induces apoptosis of cancer cells (Sagar, Yance & Wong 2006). In a murine model, lung metastases were reduced and survival was increased (Zarkovic et al. 2001). A poorly controlled clinical study in human subjects showed an increase in survival in a variety of cancers, but no definitive conclusions could be drawn (Grossarth-Maticek et al. 2001). A recent phase III trial on the effect of an adjuvant mistletoe treatment in 477 patients with head and neck squamous cell carcinoma showed that 5-year survival of the mistletoe group was the same as the control group. In addition, no stimulation of the immune system or improvement in the quality of life could be detected (Steuer-Vogt 2001).

Most studies of mistletoe provide insufficient evidence to recommend it outside of clinical trials (Linde et al. 2001); although a recent rigorous trial of 689 women with breast cancer provided provocative evidence for further testing for fatigue during cancer treatment. A total of 219 women received mistletoe as an adjuvant to their standard treatment. Patients taking the lectin-standardised mistletoe extract had a lower incidence of nausea, gastrointestinal tract symptoms, fatigue and depression compared to controls (Sood et al. 2007). A recent systematic review of prospective trials on anthroposophic mistletoe extracts defined it as a therapy for improvement of quality of life and reduction of side effects of chemo- and radiotherapy (Kienle & Kiene 2007). Survival benefit was shown and tumour remissions were described in cohort studies (Kienle & Kiene 2007). Further properly designed clinical trials are required to investigate clinical efficacy and its possible dependency on the mode of application (Kienle & Kiene 2007). Likewise, debate over mistletoe preparations and their standardisation requires more evaluation (Horneber et al. 2001).

Slippery elm is a key ingredient in Essiac tea which is one of the most popular herbal cancer alternatives in North America (Cassileth 1999). It is used during radio- and chemotherapy for reduction in symptoms associated with cancer treatment and as a possible adjunctive treatment (Cheung, Lim & Tai 2005). Recent in vitro tests with Essiac have identified anti-cancer activity, however, its effects in vivo are controversial and evidence of efficacy is anecdotal (Leonard et al. 2006). No clinical trial using Essiac in humans has been reported in a peer-reviewed, scientific journal.

Licorice (Glycyrrhiza glabra), garlic (Allium sativum), and grapeseed extract (Vitis Vinifera) are all potential anti-cancer agents (Ray, Parikh & Bagchi 2005; Tanaka et al. 2006; Wang & Nixon 2001; Zhang et al. 2005). A 2001 review indicates that licorice and its derivatives may protect against carcinogen-induced DNA damage and that glycyrrhetinic acid is an inhibitor of lipo-oxygenase and cyclo-oxygenase, inhibits protein kinase C, and down regulates the epidermal growth regulator factor (Wang & Nixon 2001). Tanaka et al. (2006), reported promising results in a preliminary double-blind, randomised clinical trial in patients with colorectal adenomas, with the use of high-dose aged garlic extracts (AGE 2.4 mL/day). AGE significantly suppressed both the size and the number of colon adenomas in 51 patients after 1 year of treatment ($p=0.04$) (Tanaka et al. 2006). Proanthocyanidins from grapeseeds exerted antitumour properties in several animal models (Ray, Parikh & Bagchi 2005; Zhang et al. 2005).

MANAGEMENT OF CANCER THERAPY SIDE EFFECTS

Herbal agents are increasingly being investigated to address the debilitating side effects from conventional cancer treatment. Ginger (Zingiber officinale) may be effective in treating chemotherapy-induced nausea and vomiting (Manusirivithaya et al. 2004; Sontakke, Thawani & Naik 2003). Ginkgo (Ginkgo biloba), has been used to reduce the toxic side effects of some chemotherapeutic drugs. Evidence from in vivo studies show protective effects against nephrotoxicity induced by cisplatin and cardiotoxicity induced by doxorubicin (Ozturk et al. 2004; Naidu et al. 2002). While clinical trials are not yet available to determine its effectiveness in practice, this aspect of herbal medicine in cancer patients represents large and diverse opportunities for positive integration into oncology patient management.

Astragalus (Astragalus membranaceus) has been used in cancer therapy to not only reduce the associated side effects but also to enhance the effectiveness of chemotherapy (Block & Mead 2003). A Cochrane systematic review of Chinese herbs for chemotherapy induced side-effects in colorectal patients analysed the results of four trials that used a formulation containing astragalus (huang-qi) (Taixiang, Munro & Guanjian 2005). Despite study limitations, it was concluded that formulations of astragalus may stimulate immuno-competent cells and decrease side effects in patients treated with chemotherapy (Taixiang, Munro & Guanjian 2005).

One of the more problematic side effects of radiation therapy is the incidental damage to normal tissues. Damage to normal tissues, in some cases, can be sufficiently severe to stop radiation treatment. For example, acute radiation skin

toxicity (Wheat, Currie & Coulter 2007) can cause such debilitating skin breakdown that the full course of radiation therapy can not be completed. Wheatgrass extract has been shown to decrease the time to onset of the most severe grading of acute radiation skin toxicity, improving treatment compliance (Wheat, Currie & Coulter 2007). There are other potential side effects, short and long term, that result from cancer treatment that might benefit from herbal medicine. While there is a lack of empirical evidence for support, the following might find a place in cancer management: analgesics (pain/palliation), antidepressant (compliance/recovery), antidiarrhoeal (abdominal radiotherapy), antiecchymotic (chemotherapy), antiemetric (chemotherapy, gut radiotherapy), antifibrotic (radiation damage), antioedematous (surgical or radiation damage), antioxidant (free radicals from radiotherapy), cathartic (constipation), collagen stabilising (radiation damage) and hypnotics (rest).

ADVERSE REACTIONS AND INTERACTIONS

Relatively little herb-drug interaction research has been conducted to date (Braun & Cohen 2007). Cytotoxic drugs for cancer treatment are among the strongest drugs available and tend to have a complex pharmacological profile, narrow therapeutic index, steep dose-toxicity curve and many pharmacokinetic and pharmacodynamic differences both within and between patients (Beijnen & Schellens 2004). Theoretically, antioxidant supplements have the potential to reduce treatment effectiveness, especially if oxidative mechanisms are required for cytotoxicity such as with alkylating agents (i.e. anthracyclines, mitomycin, bleomycin and podophyllum agents) (Labriola & Livingston 1999). Currently, there is very little evidence supporting this theory (Labriola & Livingston 1999). Recent reviews of human studies involving oxidating agents and antioxidant supplements have reported that none of the studies showed a decrease in therapeutic efficacy or increase in cancer drug toxicity (Block 2004). It is worthwhile noting that hormonal anti-cancer agents, biological agents, anti-metabolites and some plant-derived agents are not highly dependent on creating reactive oxygen species (Labriola & Livingston 1999).

Long term side effects of cisplatin, an important chemotherapy drug, are due to the formation of free radicals that lead to oxidative organ damage (Braun & Cohen 2007). Herbal and nutritional antioxidants have been investigated in both animals and humans and several studies have shown improvement or prevention of some side effects and possibly increased treatment effectiveness (Ali & Moundhri 2006; Lamson & Brignall 1999; Seifried et al. 2003). Vitamin E and selenium have ameliorated experimental cisplatin nephrotoxicity in several studies (Ali & Moundhri 2006; Pace et al. 2003), as has the antioxidant lycopene (Atessahin et al. 2005). Alternatively, combination therapy with vitamins C and E and selenium failed to show any protective effects against cisplatin-induced nephrotoxicity (Weijl et al. 2004). Poor patient compliance, small patient numbers and insufficient doses of the antioxidants were limitations in this study. Currently the evidence does not support the view that antioxidant supplements reduce drug effectives and further research is warranted.

Hormonal agents are used when a cancer is sensitive to hormonal growth controls (Braun & Cohen 2007). Many key constituents in herbal preparations can theoretically stimulate or inhibit tumour growth or interact with hormonal treatments (Braun & Cohen 2007). Flavonoids have a wide range of biochemical and pharmacological actions and have been the focus of much research, especially in regards to their cancer protective activities, which are attributed to free radical scavenging, modification of enzymes that activate or detoxify carcinogens, and inhibiting the induction of the transcription factor activator protein-1 activity by tumour promoters (Moon, Wang & Morris 2006). The following compounds have been found to decrease oestrogen biosynthesis: chrysin and baicalin, naringenin, genistein and biochanin A (Moon, Wang & Morris 2006). They achieve this by inhibiting activity of aromatase (cytochrome P19) and could theoretically have a use in breast and prostate cancer (Kao et al. 1998). Soy isoflavones can bind to oestrogen receptors and might slow down cell proliferation as a consequence (Wood et al. 2006).

Considerable debate surrounds the use of dietary soy isoflavones as potential cancer protective agents and current data is contradictory as to their effects (Braun & Cohen 2007). Recent research has focused on the potential for soy isoflavones to either enhance or antagonise the effects of anti-cancer agents such as tamoxifen (Constantinou et al. 2005). Some studies have raised the possibility that genistein could compete with tamoxifen for oestrogen receptors and thereby decrease the drugs efficacy, an observation reported in two experimental models (Constantinou et al. 2005; Ju et al. 2002). Alternatively, research conducted with daidzein has produced positive results, enhancing the effect of tamoxifen against breast carcinogenesis in the rat model (Constantinou et al. 2005). Taken together, these results

appear to indicate that genistein may have a deleterious effect when combined with tamoxifen, but the use of soybeans in combination with tamoxifen may in fact be beneficial.

Pharmacokinetic interactions often involve metabolising enzymes (cytochrome enzymes) or drug transporters that affect the bioavailability of many oral chemotherapy agents and can induce multi-drug resistance (Braun & Cohen 2007). Examples of anti-cancer medicines that are P-gp substrates are: daunorubicin, docetaxel, doxorubicin, paclitaxel, taxol, tacrolimus, vinblastine and vincristine (Braun & Cohen 2007). The influence of herbal medicines on P-gp expression is currently receiving much attention. Besides St. John's wort, the isoflavone genistein inhibits P-gp mediated drug transport (Castro & Altenberg 1997). Alternatively, rosemary extract (Rosmarinarus officinalis) acts as a P-gp inducer, increasing intracellular concentration of doxorubicin and vinblastine (Plouzek et al. 1999).

Many chemotherapeutic agents undergo metabolism by the CYP450 system during phase I metabolism (Mills & Bone 2005). Although there are over 50 enzymes in the CYP system, the most important for drug metabolism are CYP1A2, 2D6 and 3A4; with the latter involved in the metabolism of many anti-cancer medicines (Beijnen & Schellens 2004). In terms of herbal medicines, most research has been conducted on St. John's wort which significantly induces CYP enzymes, particularly CYP3A4 with long term administration (Durr et al. 2000; Roby et al. 2000; Ruschitzka et al. 2000). Silymarin has also been investigated for effects on CYP isoenzymes and transporter proteins, and was found to significantly decrease CYP3A4 activity in primary cultures of human hepatocytes (Gurley et al. 2004). Several other herbal medicines have the potential to affect drug absorption and / or metabolism, but further in vivo investigation is required before an interaction prediction can be made (Braun & Cohen 2007). Clinically, the impact of herbal medicines that affect CYP enzymes could be deleterious; serum levels of those medicines that are CYP3A4 substrates will be reduced, potentially reducing drug effectiveness and resulting in therapeutic failure (Moore et al. 2000).

CONCLUSION

Integrated medicine is a holistic approach to cancer care, with some herbal medicines showing proven effectiveness as adjuvants to conventional medical treatments. At the present time there is little evidence of a systematic process of evaluation or dialogue between mainstream medicine and herbal medicine practitioners. Collaboration, guidance and support for relevant research in herbal medicines for cancer patients are needed.

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