Review

Review of Evidence-Based Clinical and Experimental Research on the Use of Acupuncture and Chinese Herbal Medicine for the Treatment or Adjunct Treatment of Cancer

Huisheng Xie DVM, MS, PhD, Betsy Hershey DVM, DACVIM (Oncology), Aituan Ma DVM, MS, PhD

ABSTRACT

Traditional Chinese Medicine includes acupuncture and herbal medicine. Clinical evidence indicates that acupuncture and herbal medicine can be beneficial in the treatment of cancers in people and animals. Acupuncture reduced pain or discomfort, promoted quality of life, or reduced drug-associated side-effects in cancer patients. Acupuncture also promoted the activities of humoral and cellular immunity as well as natural killer (NK) cell activity. It improved patient survival and quality of life as an adjunct with transcatheter arterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma and unresectable hepatocellular carcinoma, Chinese herbals improved patient survival time, quality of life, alleviation of symptoms, and decreased marrow toxicity. Some herbs together with conventional protocols (chemotherapy or surgery) demonstrated a promising outcome in lymphoma and breast cancer in both humans and dogs. The possible mechanisms of herbal anti-cancer effects include: inhibition of the metabolism of tumor cells, alteration of tumor cell membranes and information conduction, inhibition of tumor cell proliferation, induction of tumor cell apoptosis, enhancement of immune function and anticancer capabilities, inhibition of neovascularization to prevent tumor growth and metastasis, prevention of metastasis through improvement of the physical and chemical properties of blood cells, reversal of drug resistance and enhancement of the effectiveness of chemotherapy.

Key words: Acupuncture; Chinese herbal medicine; traditional Chinese medicine; cancer; clinical application, oncology, evidence based medicine, clinical trials

ABBREVIATIONS

MCT Mast cell tumor
SCC Squamous cell carcinoma
TCM Traditional Chinese medicine
WHO World Health Organization
CRT Chemoradiation therapy (CRT)
HNC Head and neck cancer
PEG Percutaneous endoscopic gastrostomy
BCRL Breast cancer-related lymphedema
NK Natural killer
TACE Trans catheter arterial chemoembolization
UHCC Unresectable hepatocellular carcinoma
CHM Chinese herbal medicine
HCC Hepatocellular carcinoma
QOL Quality of life
MST Mean survival time
PRST Pain-relieving sustained time

From: Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL (Xie), Integrative Veterinary Oncology, 2501 N 32nd Street Phoenix, AZ 85008 (Hershey), College of Traditional Chinese Veterinary Medicine, Agricultural University of Hebei, China (Ma)

Cancer is the most common natural cause of death in dogs and cats in the United States. About 45% of dogs that live to 10 years or older die of cancer.[1-2] The most common cancers in pets are lymphoma, mammary tumors (benign/malignant), mast cell tumor (MCT), hemangiosarcoma, soft tissue sarcomas, melanoma, squamous cell carcinoma (SCC) and osteosarcoma. [3-5] Traditional Chinese Medicine (TCM) has been used for the diagnosis and treatment of tumors since the Warring States Period (475 to 221 BC),

when "*Ling Shu Jing*" (Miraculous Pivot) stated "the tumor was caused by the pathological factors which had stayed in the body over a long time". [6] Clinical evidence indicates that acupuncture and Chinese herbal medicine can be beneficial in the treatment of cancer in dogs and people.[7-13] This paper reviews acupuncture and Chinese herbal medicine for the treatment or adjunct treatment of cancers, and possible mechanisms of action.

ACUPUNCTURE AND CANCER TREATMENT

Clinical Trials

There are 3 clinical trials that met inclusion criteria for this review that evaluated acupuncture treatment of cancer in human patients. In the first trial, cancer patients were divided into groups based on severity of pain (mild, moderate, severe) and then randomized into acupuncture group vs. medication group. The acupuncture group patients were treated with dry needling techniques at 3-5 severe *A-shi* or other related acupoints; for example, BL-20, BL-21 and CV-12 were used for stomach cancer. Medication groups were treated with aspirin (mild pain), codeine (moderate pain) and morphine (severe pain) based on the World Health Organization (WHO) 3 step administration principle. Efficacy of pain relief of acupuncture was 94.1% compared to the medicine group of 87.5% ($P<0.05$).[7] In another randomized controlled clinical trial, it was shown that acupuncture treatment significantly promoted quality of life and reduced drug-associated side-effects of breast cancer patients medicated with anti-estrogens as compared with the sham acupuncture treatment.[8]

Dysphagia is a common side effect following chemoradiation therapy (CRT) in patients with head and neck cancer (HNC). After dry needle at acupoints including ST-7, ST-36, LI-2, LI-11 and CV-23; a total of 9 of 10 HNC patients (90%) post CRT reported an improvement in swallowing functions, xerostomia, pain, and fatigue levels. In addition, 6 of 7 (86%) percutaneous endoscopic gastrostomy (PEG) tube-dependent patients had their feeding tubes removed after acupuncture, with a median duration of 114 days (range 49 to 368 days) post chemoradiation therapy versus PEG tube duration (without acupuncture) with a median duration of 150 days (range 178 to 365 days). [9]

In a study to evaluate the safety and potential efficacy of acupuncture on upper-limb edema, 37 women with a clinical diagnosis of breast cancer-related lymphedema (BCRL) for 0.5-5 years were enrolled. The affected arm had a circumference ≥2 cm larger than the unaffected arm. Patients received dry needle acupuncture at TH-14, LI-4, LI-15, LU-5, ST-36, SP-6, CV-3 and CV-12 twice weekly for 30 minutes over 4 consecutive weeks. The mean reduction in arm circumference difference was 0.90 cm (95% CI, 0.72-1.07; $P<0.0005$). Eleven patients (33%) exhibited a reduction of ≥30% circumference after acupuncture treatment. There were no serious adverse events and no infections or severe exacerbations after 255 treatment sessions and 6 months of follow-up interviews. The authors concluded acupuncture for BCRL appears safe and may reduce arm circumference.[14]

Basic Research Studies on Immune Modulation Associated with Acupuncture

Five research studies that evaluated effects of acupuncture on the immune system met inclusion criteria. In the first study, Johnson et al reviewed 110 publications and concluded that acupuncture is associated with changes in natural killer (NK) cells, which secrete cytokines that inhibit or kill cancer cells.[15] The use of acupuncture increased NK cell quantity and function in both humans and animals. It also could be used to promote the induction and secretion of NK-cell activating cytokines that engage specific NK cell receptors that endogenously enhance anticancer immune function. Three of the most commonly used acupoints in these studies were ST-36, PC-6 and LI-4. [15]

The quantitative and qualitative effects of acupuncture on the immune system was evaluated by collecting blood from 17 healthy human volunteers aged 21-51 years old both before and after acupuncture treatment. The activity of T cells, B cells, macrophages and NK cells was assessed by using flow cytometry to measure CD-positive cell counts and cytokine expression levels. As compared with the control group, a statistically significant increase in the number of CD2(+), CD4(+), CD8(+), CD11b(+), CD16(+), CD19(+), CD56(+) cells as well as IL-4, IL-1beta and IFN-gamma levels in the cells were found in the acupuncture group after dry-needling stimulation at BL-18, BL-20, BL-23 and ST-36. These observations indicate that acupuncture may regulate the immune system and promote the activities of humoral and cellular immunity as well as NK cell activity.[16]

Tests were done on T cell subpopulations, NK activity, humoral immunity and leukocyte count in patients undergoing chemotherapy and acupuncture. Cell levels were measured both before acupuncture treatment and after 4 courses of electro-acupuncture was added at acupoints including ST-36, SP-6, CV-12 and PC- 6. Patients undergoing combined acupuncture and chemotherapy showed significantly higher leukocyte counts than that of the control group ($P < 0.01$).[17] The authors conclude electro-acupuncture may limit the immunologic damage associated with chemotherapy and can thus be used as auxiliary therapy for patients undergoing chemotherapy.[17] T lymphocyte subsets were also evaluated in another study where human patients with malignant tumors were treated in 30 minute sessions daily for 10 days with dry needle acupuncture at PC-6, LI-4, CV-4 + local acupoints. Results of this study showed increases in T lymphocyte subsets, and beta-endorphin as well as decreased concentrations of soluble interleukin 2 receptor.[18]

CHINESE HERBAL MEDICINE AND CANCER TREATMENT

Chinese Herbal Medicine for the Treatment of Liver Cancer-Clinical Trials

A systematic review and meta-analysis of 37 randomized controlled clinical trials involving 2,653 patients was conducted to compare the efficacy and safety of Traditional Chinese Medicine (TCM) plus trans catheter arterial chemoembolization (TACE) with that of TACE alone in treating unresectable hepatocellular carcinoma (UHCC). The results showed that TCM+TACE compared with TACE alone, improved patient survival, quality of life, alleviation of symptoms, and tumor response. No serious adverse events from TCM were reported and study results concluded the addition of TCM to TACE was therapeutically beneficial. [19]

In one retrospective study, 85 patients of 165 patients with UHCC received TACE alone as the control group. Another 80 patients (TACE + Chinese Herbal Medicine (CHM) group) received combined therapy consisting of TACE and a long-term oral herbal treatment with *Jiedu* Formula granule (JDF). This CHM formula was composed of 4 ingredients: root of Actinidia valvata (*Mao Ren Shen*)**,** root of Salvia chinensis (*Shi Jian Chuan*), bulb of Cremastra appendiculata (*Du Juan Lan*) and gizzard membrane of Gallus gallus domesticus (*Ji Nei Jin*). The median overall survival (9.2 months) in the TACE+CHM group was significantly longer than in the control group (5.87 months). The authors concluded that Chinese herbal medicine could improve the prognosis of patients with UHCC and prolong their survival.[20]

In a case-controlled clinical trial, a total of 120 patients with hepatocellular carcinoma (HCC) were randomized into two groups: transcatheter arterial chemoembolization (TACE) group, (n=60) and TACE + CHM group (n=60). In TACE +CHM group, patients were given JDF and cinobufacini injection which was extracted from the skin of *Bufo bufo gargarizans Cantor*.[21] There was a significant difference in survival rate between the two groups (P<0.01). The mean survival time (MST) of patients in the TACE+CHM group was 49.53 months versus 39.90 months for the TACE alone group. The 1-, 2-, 3-, 4- and 5-year survival rates were 90%, 82%, 80%, 70% and 63%, respectively, in the TACE+CHM group, and 79%, 70%, 60%, 60% and 36%, respectively, in the TACE alone group. A significant difference was demonstrated in survival time between the two groups (P=0.045) with Chinese herbal medicine able to postpone tumor recurrence and metastasis, prolong the survival time and increase the survival rate of post-surgical patients with HCC. [21]

In another prospective randomized controlled design clinical trial, 97 patients with the middle/late stage of HCC were assigned to the CHM group (49 cases) treated with Chinese herbal medicine therapy alone and the control group (48 cases) which were treated with chemotherapeutic agents combining iodized oil chemo-embolization and analgesics.[22] The immediate and long-term efficacy, adverse reaction, pain-relief initial time (PRIT) and pain-relieving sustained time (PRST) of the treatment, as well as the change in improvement of patients' quality of life (QOL) were observed. The CHM therapy group included using Oleum fructus bruceas (*Ya Dan Zi You*) intervention combined with oral intake of *Gan Ji Tang* and external application of *Ai Li Tong*. *Gan Ji Tang* ingredients included Codonopsis (*Dang Shen*), Atractylodes (*Bai Zhu*), Bupleurum (*Chai Hu*), Paeonia (*Chi Shao Yao*), Curcuma (*E Zhu*), Eupolyphaga sinensis (*Tu Bie Chong*), Hedyotis Herb (*Bai Hua She She Cao*), Hirudo (*Shui Zhi*) and Ostrea (*Mu Li*). *Ai Li Tong* contained Venenum Bfonis (*Chan Su*), Strychni (*Ma Qian Zi*), Cynanchi Paniculati (*Xu Chang Qing*), Moschus (*She Xiang*) and Borneolum syntheticum (*Bing Pian*). There was no statistical difference (P>0.05) between the two groups when disease control was evaluated, however, adverse reaction occurrence rate was significantly less in the CHM group when compared to the control group (P<0.05). The pain-relief initial time (PRIT) was significantly superior in the herbal group when compared to the control group (10.37±2.18 h vs 7.78±1.95 h, P<0.01). After treatment, the CHM group patients' somatic activity, symptoms and quality of life (QOL) were significantly improved when compared to those in the control group (P<0.05). The survival rate in the two groups was similar at the 3rd month after treatment, but the CHM group was superior in terms of half- and 1-year survival rate (65.9% vs 42.5% and 38.6% vs 18.1%, respectively, P<0.05). The median survival time in the CHM test group was 8.9 months and that in the control group was 5.3 months.[22, 23]

Zhu reported that in a controlled study, 80 patients with primary middle and advanced stage liver cancer were randomly assigned to the TACE group (40 cases) and to TACE plus herbal group (40 cases). Results showed that Kanglaite injection, extracted from herbal Coix seed oil (*Yi Yi Ren*), combined with TACE was significantly superior to TACE group alone in improving symptoms and Karnofsky scores with effects such as decreasing tumor growth and reducing marrow toxicity for patients with advanced stage HCC.[24]

Chinese Herbal Medicine for the Treatment of Lymphoma-Clinical Trials

Lymphoma is the most common hematologic neoplasm in dogs. It is highly chemo-sensitive with complete remission rates ranging from 65 to 90% and median survival times of 26 to 51 weeks.[25,26] There is general consensus that combination protocols based on doxorubicin (e.g., in combination with cyclophosphamide, vincristine, and prednisone--CHOP) are associated with the longest disease-free interval and survival times.[26] Reported side effects of the CHOP protocol, however, include sterile hemorrhagic cystitis, myelosuppression,

and gastrointestinal toxicity.[26] While the treatment for lymphoma is efficacious with well-established outcomes (survival time, time to complete or partial remission, and disease-free interval), clients and oncologists equally emphasize the importance of a good quality of life (QOL) in cancer bearing dogs when selecting treatment options.[27] The Acupuncture Service at University of Florida Small Animal Hospital treated 10 canine patients with lymphoma from 1999 to 2012. The final outcome was determined in 7 of the 10 cases with 3 cases undetermined due to loss of contact with the client. The overall QOL including activity level, mental stimulation, social relations, appetite and stool were generally better after acupuncture and herbal medicine treatment in all 7 cases with a complete medical record. A combination of CHOP and acupuncture/Chinese herbal medicine was used in 5 cases while acupuncture/herbal medicine alone was used in 2 cases. The survival time of 5 lymphoma dogs which received both chemotherapy and acupuncture/herbal medicine ranged from 8 to 56 months (average of 25.2 months) while the survival time of 2 dogs receiving only acupuncture/herbal was 7 and 8 months. The three primary Chinese herbal medicines used in these cases were Wei Qi Booster[a] (modified *Si Jun Zi Tang*), Stasis Breaker[a] (Modified *Nei Xiao Wan*) and Max's Formula[a] (*Nei Xiao Luo Li San*). The ingredients and indications for these Chinese herbal medications have been published.[28]

Twenty-seven patients with malignant lymphoma (14 Hodgkin's disease, 9 histiocytosarcoma, 2 plasmacytoma, 2 lympholeucosarcoma) were treated with a combination of western medicine (Ailin-injection) and Chinese herbal medicine. The latter's composition and dose varied depending on the clinical manifestations. All patients had stage III and IV lesions. The total remission rate was 70.37% (complete remission 13 patients, partial remission 6 patients, no remission 8 patients). In addition, in cell line studies, the suppressive effect of Ailin on transplanted tumor in vivo (S-180) was studied. Three repetitions of the treatment yielded suppression rates of 36.09%, 48.80%, 32.67% with an average of 39.18% ($P < 0.002$). The same treatment using S37 cells and Ehrlich ascites tumor cells yielded suppression rates of 37.25%, 35.29% (average of 36.27%; $P < 0.005$) and 46.53%, 44.56%, 51.35%, 45.95% (average of 47.09% ; $P < 0.001$), respectively. The clinical and experimental studies suggest that Ailin-1 had no serious side effects and was well tolerated by patients with malignant lymphoma at moderate or advanced stages with no toxic reactions observed at clinical dose. In the above combination therapy (Ailin plus CHM), the addition of the Chinese herbal medicine had a beneficial supplementary effect on the treatment of patients' cachexia and immuno-suppression along with improved remission rates in humans (70%) versus tumor suppression in cells lines with Ailin only (36.27% and 47.09%).[29]

Basic Research Studies on Development of New Anticancer Chinese Herbal Medicines and Lymphoma

Wogonin (5,7-dihydroxy-8-methoxyflavone), isolated from the roots of the traditional Chinese herb *Scutellaria baicalensis* Georgi (*Huang Qin*), has been recently recognized as a new anticancer drug that possesses a cytotoxic effect against a large panel of human cancer cell lines by inducing apoptosis in vitro. It was demonstrated that the application of drug-coated magnetic nanoparticles (MNPs) could strengthen wogonin-induced cell inhibition, apoptosis, and cell cycle arrest in Raji cells. This was documented by methylthiazol tetrazolium assay, flow cytometer assay, and nuclear 4′,6-diamidino-2-phenylindole staining. The molecular mechanisms of these phenomena were further explored by western blot, in which the protein levels of caspase 8 and caspase 3 were increased significantly while those of survivin and cyclin E were decreased significantly in wogonin-MNPs group. These findings suggest that the combination of wogonin and MNPs provides a promising strategy for lymphoma therapy.[30]

Chinese Herbal Medicine for the Treatment of Mammary Tumors

Ninety-six Chinese herbal medical formulae have been used for the treatment of breast cancer (1990 - 2010) in China with the most commonly used herbs including Astragali (*Huang Qi*), Atractylodis Macrocephalae (*Bai Zhu*), Poriae Cocos (*Fu Ling*), Pseudobulbus Shancigu (*Shan Ci Gu*), Angelicae Sinensis (*Dang Gui*), Coix (*Yi Yi Ren*), Herba Hedyotidis Diffusae (*Bai Hua She She Cao*), and Curcuma Phaeocaulis (*E Zhu*). [31] Other herbals for the treatment of breast cancer included Rabdosia rubescens (*Dong Ling Cao*), Sanguisorba officinalis L (*Di Yu*) and Cornus officinalis (*Shan Zhu Yu*).[32-33]

Eight dogs with histologically confirmed mammary adenocarcinoma had surgical excision of their cancer and no evidence of metastasis on thoracic radiographs. All dogs were administered 0.022 mg/kg Mammosol[b], a proprietary blend of 28 herbal ingredients, mainly including Bubali (*Niu Jiao*), Olibanum (*Ru Xiang*), Myrrh (*Mo Yao*), Astragalus (*Huang Qi*), etc., twice daily for 2 years and monitored with thoracic radiographs and physical examinations at 3, 6, 9, 12, 18 and 24 months post-surgery. Serum biochemical tests for liver and kidney function were evaluated during the study period to monitor for unexpected toxicity. In this study, 7 of the 8 dogs lived greater than 2 years. The dogs that lived less than 2 years only received half the dose of herbs due to improper caretaker compliance. Survival rates were significantly increased in the dogs that had surgical excision and Mammosol as compared to previously published results of dogs that had surgery alone ($P<0.001$) and dogs with surgery and chemotherapy ($P<0.05$) using the discrete Bonferroni method.[34]

Chinese Herbal Medicine for Treatment of Melanoma and Acanthomatous Epulis

A combination of *Wei Qi* Booster[a] (*Si Jun Zi Tang*), Stasis Breaker[a] (*Nei Xiao Wan*) and Max's Formula[a] (modified *Nei Xiao Luo Li San*) was used for the treatment of an equine case of unresectable melanoma in a horse and a canine case of acanthomatous epulis along with acupoints including BL-20, BL-21, LI-4, ST-36 and ST-40. [35-36] The unresectable amelanotic melanoma mass (11 x 7 x 4 cm^3), located on the ramus of the right mandible in a 7-year-old intact female Arabian horse, completely resolved 4 months after treatment with Chinese herbal medicine and acupuncture treatments.[35] It has remained in remission for 9 yrs, when the paper on this case was published, at the age of 16 years old. A maxillary acanthomatous epulis mass was present in a 5-year-old male Chihuahua. It was located on the right side of the maxilla over the incisors and canine tooth with a median diameter of 2.4 cm. Three months after therapy with Chinese herbal medicine and acupuncture, the mass began to shrink and was almost completely resolved 12 months after the start of treatment.[36] It remained in remission for 6 years, at which time the dog died of an unrelated event (congestive heart failure). Preliminary data on the basic composition of these Chinese herbal products have been recently published.[37]

Based on anticancer in-vivo and in-vitro studies (inducing apoptosis in cancer cells), individual Chinese herbs that showed promise included Sparganii Stoloniferi (*San Leng*),[38] *Curcuma phaeocaulis* (*E Zhu*)[39] and Panax notoginseng (*San Qi*) extracts.[40] Both Sparganii Stoloniferi (*San Leng*) and *Curcuma phaeocaulis* (*E Zhu*) could purge the interior, break Blood stasis and clear masses. These Chinese herbs have been widely used for any tumor in traditional Chinese medicine. Their anti-neoplastic effects also have been confirmed by modern pharmacological experiments and clinical studies.[38,39] Panax notoginseng (*San Qi*) can stop hemorrhage and resolve Stagnation, exerting beneficial effects on any hemorrhage and stasis conditions. One study demonstrated that Panax notoginseng extracts had significant apoptosis-promoting effect on MNNG-transformed GES-1 cells.[40]

RESEARCH STUDIES ON MECHANISM OF ACTION OF CHINESE HERBAL MEDICINE ANTI-CANCER EFFECTS

Inhibition of the metabolism of tumor cells

Da Huang (Rhubarb) affects numerous elements of cancer cell metabolism and can cause inhibition of respiration, oxidation and dehydrogenation of amino acids and glucose metabolism. It can also decrease DNA, RNA and protein biosynthesis of tumor cells and inhibit tumor cell proliferation with no significant impact on normal cells. *Da Huang* (Rhubarb) can also significantly improve the efficacy of cellular immunity in mice and can promote lymphocyte proliferation and IL-2 synthesis, which play an indirect anti-neoplastic effect. [41]

Alteration of tumor cell membranes and information conduction

In a controlled study, 48 mice were randomly assigned to 3 groups, untreated control group, experimental model group and model with herbal group. Results showed the herbal mixture of *Sheng Di* (Rehmannia), *Ban Lan Gen* (Isatis), and *Bai Hua She She Cao* (Oldenlandia) can significantly reduce the level of cGMP in a HepA hepatoma mouse model and increase the cAMP/cGMP ratio.[42] This study suggested that the anti-tumor mechanism of these herbs is related to a change in the mobility (fluidity) of the cell membrane and regulation of information along the cell signal conduction pathway of tumor cells.

Inhibition of tumor cell proliferation

The inhibition of tumor cell proliferation is another important area of onco-molecular biological research. A randomized controlled study by Qin SY et al. demonstrated that extracts of Chinese fan palm seed (*Pu Kui Zi*) and Pyrola (*Lu Ti Cao*) had a clear dose-dependent and significant anti-tumor activity on a HeLa cell line (cells derived from human cervical carcinoma), with IC50 (95.51 and 95.40 mg·L-1), respectively. Chinese fan palm seed has also been shown to have an inhibitory effect on Bel-7402 tumor cell lines, with IC50 (122.84 mg·L-1).[43]

Induction of tumor cell apoptosis

The apoptotic effects on tumor cells of matrine and oxymatrine, two major alkaloid components extracted mainly from Sophora japonica (*Ku Shen*), Sophora subprostrata (*Shan Dou Gen*) and Sophora alopecuroides (*Ku Gan Cao*), have been studied by Si KW et al.[44] Matrine induced apoptosis of HepG2 cells (a human hepatic carcinoma cell line) was demonstrated by morphologic changes, increased DNA breakdown using a TUNEL assay in-situ, observing apoptosis peaks with flow cytometry and detection of early stage apoptosis using an AnnexinV-FITC/PI double labeled assay.[45] The mechanism of action of matrine to induce HepG2 cell apoptosis was to up-regulate the expression of apoptotic genes wp53 and box and down-regulate the expression of anti-apoptotic genes bcl-2, which eventually led to cell apoptosis.

Enhancement of immune function and anticancer capabilities

Most tumor cells are destroyed by host NK cells, macrophages and neutrophils. In previous studies only 1% of tumor cells survived after 24 hours when injected intravenously into animals and 0.1% of cells could form pulmonary metastasis.[45] There are many opportunities for tumor cells to be destroyed in the blood stream. Traditional Chinese medicines enhance immune function and significantly improve the activity of the natural killer (NK)

cells, macrophages and neutrophils which remove tumor cells. PSK (Kreston) is a protein-bound polysaccharide obtained from cultured mycelia of Coriolus versicolor basidiomycetes mushrooms (*Yun Zhi*) and is a biological response modifier with diverse actions, one of which includes anticancer properties. PSK has been shown to suppress pulmonary metastasis of methylcholanthrene induced sarcomas, human prostate cancer cells (DU145M cell line) lymphatic metastasis of mouse leukemia cancer cells (P388 cell line) and prolong the survival period in spontaneous metastasis models.[46] The effects of oral PSK were also examined in CDF1 mice with liver metastases of Colon 26 adenocarcinoma. The survival of tumor-bearing mice was prolonged and both metastatic foci and liver weight were decreased.

Di Huang (Rehmannia) and *Liu Wei Di Huang Tang* (Rehmannia 6) can enhance proliferation of spleen T-lymphocytes and secretion of interleukin-2 in S180 tumor-bearing mice causing an immune-mediated anti-tumor effect.[47] The Chinese herbal formula *Jian Pi Yi Shen* preparation for infusion, composed of *Dang Shen* (Codonopsis), *Bai Zhu* (Atractylodes), *Gou Qi Zi* (Lycium), *Nv Zhen Zi* (Ligustrum) and others, can increase the capacity of macrophage phagocytosis and the overall number of T lymphocytes in the peripheral blood and inhibit Lewis lung cancer metastasis and U14 lymphatic metastasis via the blood stream.[48] One review paper summarized the status of the anti-leukemia effects of Traditional Chinese Medicine and naturally occurring drugs. It stated that Polysaccharides from *Niu Xi* (Achyranthes), *Di Huang* (Rehmannia) and *Fu Ling* (Poria) have been shown to enhance immune function. The Chinese herbs *Ren Shen* (Ginseng), *Huang Qi* (Astragalus), *Dang Shen* (Codonopsis), *Bai Zhu* (Atractylodes), *Dang Gui* Angelica), *Dan Shen* (Salvia), *E Zhu* (Zedoaria) and others strengthen the immune system as well.[49]

Inhibition of neovascularization to prevent tumor growth and metastasis

Tumor cells obtain nutritional support and send malignant cells out to the host through blood vessels, which results in enhanced tumor growth and metastasis respectively. An important antitumor strategy is to inhibit neovascularization in order to "shut off the lifeline" of the tumor cells. The search for effective angiogenesis inhibiting factors (AIF) has evoked a strong interest in traditional Chinese medicines. Some traditional Chinese medicines like *Shi Quan Da Bu Tang* (Ten Large Tonification), *Xiao Chai Hu Tang* (Minor Bupleurum Decoction), *Yun Zhi Duo Tang* (Coriolan), *Xiang Gu Duo Tang* (Lentinan), *Dang Gui* (Angelica), *Chuan Shao* (Sichuan peony), *Gui Zhi* (Cinnamomum) or extracted components like *Dong Chong Xia Cao* (Cordyceps) polysaccharide and others can induce tumor necrosis factor (TNF).[49-50]

Prevention of metastasis through improvement of the physical and chemical properties of blood cells

Blood viscosity is closely related to tumor metastasis and there have been studies that have shown that increased blood viscosity can promote tumor metastasis and adhesion of tumor cells under certain conditions.[51-53] In the invasive stage of tumors, plasma viscosity increases and microthrombi containing cancer cells form. Adhesion between cancer cell and capillary endothelium develops in these hypercoagulative states. The Chinese herbal formula *Huo Xue Hua Yu* and traditional Chinese medicines *Dan Shen* (Salvia), *Yi Mu Cao* (Leonurus), *Da Huang* (Rhubarb), *Chi Shao* (Paeonia), *Hong Hua* (Carthamus), *Jiang Huang* (Curcuma), *Su Mu* (Sappan), *Shui Zhi* (Leech), *Chuan Xiong* (Ligusticum), *San Leng* (Sparganium), *E Zhu* (Zedoaria), *Ban Mao* (Blister bug), *Hu Zhang* (Polygonum) and others activate blood circulation and dissipate Blood Stasis to reduce hypercoagulation of the blood and tumor metastasis.[54] A study by Cui W et al. showed that the Chinese herbal formula *Huo Xue Hua Yu* (Activating Blood Circulation to Dissipate Blood Stasis) and one of its herbal ingredients *Ji Xue Teng* (Millettia) significantly inhibited platelet aggregation of tumor cells ($P<0.001$), suggesting these as another potential Chinese medicine to inhibit hematogenous tumor metastasis.[55]

Reversal of drug resistance and enhancement of the effectiveness of chemotherapy

One of the main reasons that conventional chemotherapy fails is because multi-drug resistance (MDR) develops as the tumor cells become tolerant to various agents. P-glycoprotein (P-gp) is a polymorphic efflux transporter located on cell membranes. In human tumors, the MDR phenotype is associated with an over-expression of the P-gp encoded by the multi-drug resistance 1 (MDR1) gene and an increase in the ATP-binding membrane protein 190 kDa encoded by a MRP gene (multidrug resistance-associated protein (MRP)), which results in lower intracellular drug concentrations. When MDR occurs there is an overproduction of Pgp, an increase in the activity of the glutathione (GSH) detoxication enzyme system and alteration of the DNA topoisomerase enzyme activity which improves DNA repair.[56]

The effects of andrographolide extracted, from *Chuan Xin Lian (*Andrographis), to reduce the development of MDR was studied by Han Y et al.[57] Different concentrations of andrographolide reversed the MDR effect of large intestine carcinoma cells (HCT-8/5-FU cell line) as determined by a standard MTT assay.[57] From their studies, they concluded that andrographolide could not only increase the tumor toxicity of chemotherapy drugs, but to some degree reverse drug-resistantance of cell lines. The Chinese herbal formula *Fu Fang San Gen* is composed of *Hu Zhang Gen* (Polygoni cuspidate root), *Teng Li Gen* (Yangtao Actinidia root) and *Shui Yang Mei Gen* (Thin leaf adina root). Xie CS et al. used an MTT

assay to determine the ability of the *Fu Fang San Gen* to reverse MDR effects in two multi-drug resistant cell lines, K562/ADR and K562/VC (2 types of MDR human erythroleukemia cells).[58] *Fu Fang San Gen* partially reversed the resistance of K562/ADR and K562/VCR cells to the conventional chemotherapy agent, adriamycin and increased the intracellular adriamycin concentration of the cells by down-regulating the expression of PGP, thereby reducing the efflux of intracellular adriamycin.[58]

CONCLUSION

This is a review of studies conducted, primarily in China, that illustrate the positive effects of selected Chinese herbal formulas and individual Chinese herbs on cancer models in laboratory animals and tumor cell lines. The effects of traditional Chinese medicine include: cancer prevention, anti-mutagenesis, reduction of cancer gene expression, altered cell nucleic acid metabolism, inhibition of tumor cell development, altered tumor cell membranes and information conduction, inhibition of tumor cell proliferation, induction of tumor cell apoptosis, enhancement of immune function and anti-cancer capabilities, inhibition of neovascularization to prevent tumor growth and metastasis, alteration of the physical and chemical properties of blood cells to prevent cancer cell metastasis, blocking cancer cell cycle, inhibition of telomerase activity and reversal of drug resistance to enhance the effectiveness of chemotherapy. For the results of the clinical trials, Chinese herbs improved patient survival time, quality of life, alleviation of symptoms, and decreased side-effects of marrow toxicity. Selected herbs together with conventional protocols (chemotherapy or surgery) demonstrated a promising outcome in lymphoma and breast cancer in both humans and dogs. Although traditional Chinese medicine should not be viewed as a panacea for the treatment of cancer, this review is presented to stimulate new ideas about cancer therapy and provide a foundation for further research and development of new anti-cancer drugs utilizing traditional Chinese medicine alone or in combination with conventional medical cancer treatments.

FOOTNOTES

a. Wei Qi Booster, Stasis Breaker, Max's Formula, Dr. Xie's Jing Tang Herbal Inc, USA

b. Mammosol, Natural Solutions, Inc at 176 Montauk Highway Speonk, NY

REFERENCES

1. Bronson RT. Variation in age at death of dogs of different sexes and breeds. Am J Vet Res. 1982; 43(11):2057-9.
2. Withrow and MacEwen. Small Animal Clinical Oncology, 5th edition. 2013.
3. Boerkamp KM, Teske E, Boon LR, et al. Estimated incidence rate and distribution of tumours in 4,653 cases of archival submissions derived from the Dutch golden retriever population. BMC Vet Res. 2014; 10:34. doi: 10.1186/1746-6148-10-34.
4. Merlo DF, Rossi L, Pellegrino C, et al. Cancer incidence in pet dogs: findings of the animal tumor registry of Genoa, Italy. J Vet Intern Med. 2008; 22(4):976-84.
5. http://www.vetmed.ucdavis.edu/CCAH/local-assets/pdfs/UnderstandingCancerinGoldenRetrievers2.pdf (April 3, 2014).
6. Ling Shu Jing (Miraculous Pivot). Beijing: People's Health Press, 1981 (Originally published during Warring States Period, 475 to 221 BC). (In Chinese)
7. Chen ZJ, Guo YP, Wu ZC. Observation on the therapeutic effect of acupuncture at pain points on cancer pain. Zhongguo Zhen Jiu (Chinese Acupuncture). 2008; 28(4):251-3. (In Chinese)
8. Hervik J, Mjåland O. Quality of life of breast cancer patients medicated with anti-estrogens, 2 years after acupuncture treatment: a qualitative study. Int J Womens Health. 2010; 2:319-25.
9. Lu W, Posner MR, Wayne P, et al. Acupuncture for dysphagia after chemoradiation therapy in head and neck cancer: a case series report. Integr Cancer Ther. 2010; 9(3):284-90.
10. Pu CY, Lan VM, Lan CF, et al. The determinants of traditional Chinese medicine and acupuncture utilization for cancer patients with simultaneous conventional treatment. Eur J Cancer Care (Engl). 2008; 17(4):340-9.
11. Kim MS, Xie H, Bannai Y. Application of Acupuncture and Chinese Herbal Medicine for the Treatment of Acanthomatous Epulis in a Dog. J Vet Clin. 2008;25(1): 27-30.
12. Carolina Ortiz-Umpierre. Treatment of an Amelanotic Melanoma in a Horse with Acupuncture and Chinese Herbal Therapy. American Journal of Traditional Chinese Veterinary Medicine. 2006; 1:36-8.
13. Feng B, Zhang J, Xu X, et al. Mechanisms of Action of Chinese Herbal Medicines in the Prevention and Treatment of Cancer. American Journal of Traditional Chinese Veterinary Medicine. 2010; 5:37-47.
14. Cassileth BR, Van Zee KJ, Yeung KS, et al. Acupuncture in the treatment of upper-limb lymphedema: Results of a pilot study. Cancer. 2013; 119(13):2455-61
15. Johnston MF, Ortix Sanches E, Vujanovic NL, et al. Acupuncture May Stimulate Anticancer Immunity via Activation of Natural Killer Cells. Evid Based Complement Alternat Med. 2011; 2011:481625.
16. Yamaguchi N, Takahashi T, Sakuma M, et al. Acupuncture Regulates Leukocyte Subpopulations in Human Peripheral Blood. Evid Based Complement alternat Med. 2007; 4(4):447-53.
17. Ye F, Liu D, Wang S, et al. Effects of electro-acupuncture on T cell subpopulations, NK activity,

humoral immunity and leukocyte count in patients undergoing chemotherapy. J Tradit Chin Med. 2007; 27(1):19-21.
18. Wu B, Zhou RX, Zhou MS. Effect of acupuncture on immunomodulation in patients with malignant tumors. Zhongguo Zhong Xi Yi Jie He Za Zhi (Chinese Journal of Integrated Traditional and Western Medicine).1996;16(3):139-41. (In Chinese)
19. Meng MB, Cui YL, Guan YS, et al. Traditional Chinese medicine plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. J Altern Complem Med. 2008; 14(8):1027-42.
20. Yu Y, Lang Q, Chen Z, et al. The efficacy for unresectable hepatocellular carcinoma may be improved by transcatheter arterial chemoembolization in combination with a traditional Chinese herbal medicine formula: a retrospective study. Cancer. 2009; 115(22):5132-8.
21. Chen Z, Chen HY, Lang QB, et al. Preventive effects of jiedu granules combined with cinobufacini injection versus transcatheter arterial chemoembolization in post-surgical patients with hepatocellular carcinoma: a case-control trial. Chinese Journal of Integrative Medicine. 2012; 18(5):339-44.
22. Tian HQ, Li HL, Wang B, et al. Treatment of middle/late stage primary hepatic carcinoma by Chinese medicine comprehensive therapy: a prospective randomized controlled study. Chinese Journal of Integrative Medicine. 2010; 16(2):102-8.
23. Wang B, Tian HQ, Liang GW. Effect of ganji recipe combined with Fructus Bruceae oil emulsion intervention on quality of life in patients with advanced primary hepatic cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi (Chinese Journal of Integrated Traditional and Western Medicine). 2009; 29(3):257-60. (In Chinese)
24. Zhu XF. The clinical observation of the effect of kanlaite injection combined with chemoembolization primary on middle and advanced stage liver cancer. Journal of Basic and Clinical Oncology. 2006;19(2):132-4.
25. Chun R. Lymphoma: which chemotherapy protocol and why? Topics in Companion Animal Medicine. 2009; 24:157-62.
26. Garret LD, Thamm DH, Chun R, et al. Evaluation of a 6-month chemotherapy protocol with no maintenance therapy for dogs with lymphoma. J Vet Intern Med. 2002;16:704-709.
27. McMillan FD. Maximizing the quality of life in ill animals. J Am Anim Hosp Assoc. 2003; 39:227-35.
28. Xie H. How to select Chinese herbal medicine for cancer patients. American Journal of Traditional Chinese Veterinary Medicine. 2006; 1(1): 49-52.
29. Li YS, Zhang TD, Li CW, et al. Traditional Chinese and Western medicine in the treatment of 27 patients with malignant lymphoma. Zhonghua Zhong Liu Za Zhi (Chinese Journal of Tumors). 1988;10(1):61-2. (In Chinese)
30. Wang L, Zhang H, Chen B, et al. Effect of magnetic nanoparticles on apoptosis and cell cycle induced by wogonin in Raji cells. Int J Nanomedicine. 2012; 7: 789-98
31. He Y, Zheng X, Sit C, et al. Using association rules mining to explore pattern of Chinese medicinal formulae (prescription) in treating and preventing breast cancer recurrence and metastasis. J Transl Med. 2012; 19(10) Suppl 1:S12.
32. Wang Z, Loo WT, Wang N, et al. Effect of Sanguisorba officinalis L on breast cancer growth and angiogenesis. Expert Opin Ther Targets. 2012;16 Suppl 1:S79-89.
33. Telang NT, Li G, Sepkovic DW, et al. Anti-proliferative effects of Chinese herb Cornus officinalis in a cell culture model for estrogen receptor-positive clinical breast cancer**.** Mol Med Rep. 2012;5(1):22-8.
34. Wen JJ, Johnston K. Long-term Follow-up of Canine Mammary Gland Neoplasia in Eight Dogs Treated with Surgery and a New Chinese Herbal Formula. American Journal of Traditional Chinese Veterinary Medicine. 2011; 6(1):27-31.
35. Carolina Ortiz-Umpierre. Treatment of an Amelanotic Melanoma in a Horse with Acupuncture and Chinese Herbal Therapy. American Journal of Traditional Chinese Veterinary Medicine.2006; 1(1):36-8.
36. Kim MS, Huisheng Xie H, Bannai Y. Application of Acupuncture and Chinese Herbal Medicine for the Treatment of Acanthomatous Epulis in a Dog. J Vet Clin. 2008; 25(1):27-30.
37. Shmalberg J, Hill RC, Scott KC. Nutrient and metal analyses of Chinese herbal products marketed for veterinary use. Journal of Animal Physiology and Animal Nutrition. Epub ahead of print.
38. Zhang JW, Wei YH. Anti-cancer effects of Grailsine-Al-glycoside isolated from Rhizoma Sparganii. BMC Complement Altern Med. 2014; 3(14):82.
39. Chen X, Pei L, Zhong Z, et al. Anti-tumor potential of ethanol extract of Curcuma phaeocaulis Valeton against breast cancer cells. Phytomedicine. 2011; 18(14):1238-43.
40. Li JX, Wang ZB, Zhu LQ, et al. Apoptosis-promoting effect of Panax notoginseng extracts on MNNG-transformed GES-1 cells. Zhong Xi Yi Jie He Xue Bao (Journal of Integrated Traditional and Western Medicine). 2005; 3(2):123-7. (In Chinese)
41. Information Network of Tumor *Bo Sheng*. The Traditional Chinese Medicine Interference Normal Metabolism of Cancer Cell. http://www.bosheng.com/readnews (In Chinese)
42. Li Zhen, Li JS, Li Z, et al. The effect of *Qingre Jiedu* decoction on tumor mouse red blood cell membrane fluidity and blood plasma cyclic nucleotides.

Shandong Journal of Biomedical Engineering. 2001; 20(3):8-l0. (In Chinese)
43. Qin SY, Liu W, Zhang YY, et al. Preliminary study on the anti-tumor effect of the extracts of four traditional Chinese medicines. Northwest Pharmaceutical Journal, 2007; 22(1):16-8. (In Chinese)
44. Si KW, Chen AN, Li P. Study on apoptosis of human hepatoma Cell Line HepG_2 induced by matrine. Acta Academiae Medicine Militaris Tertiae, 2001; 23(7):816-20. (In Chinese)
45. Xu XF, Lu Y. Research of the mechanism of the anti-tumor effects of Chinese herbal medicine.Chinese. Journal of the Practical Chinese Modern Medicine. 2006; 19(22):2679-80. (In Chinese)
46. Kobayashi H, Matsunaga K, Oguchi Y. Antimetastatic effects of PSK (Krestin), a proteinbound polysaccharide obtained from Basidiomycetes: An overview. Cancer Epidemiol Biomarkers Prev. 1995; 4(3):275-81.
47. Liu FJ, Ru XB. Anti-tumor effects and immune-pharmacology of *Di Huang* and *Liu Wei Di Huang Tang* (Decoction). Chinese Traditional and Herbal Drugs. 1996; 27(2):116-8. (In Chinese)
48. Xu XY. Pharmacology of Traditional Chinese Medicine. Beijing, China: People's Medical Publishing House 2005. (In Chinese)
49. Chen TM, Zhu BD. Study of the status quo of the anti-leukemia effects of Traditional Chinese Medicine and naturally occurring drugs. Chinese Journal of Integrated Traditional and Western Medicine. 1995; 15(5):317-320. (In Chinese)
50. Chen RD. Effective Traditional Chinese Medicine Pharmacy for Cancer. Shanghai, China: Medical Science and Technology Press. 1992:317. (In Chinese)
51. Liu YH, Zhang YW, Liang GG, et al. A clinical empirical study on tumor metastasis and micro syndrome of Blood Stasis. Modern Journal of Traditional Chinese Medicine. 1996; 9(4):224-228. (In Chinese)
52. Chen JM, Zhang P. The Clinical observation of the hypercoagulable state of cancer patients. Journal of Traditional Chinese Medicine. 1983; (2):32. (In Chinese)
53. Ma WJ, Cheng GZ. The relationship between hematogenous metastasis and blood viscosity of tumors. Intermediate Medical Journal. 1992; 27(4):8. (In Chinese)
54. Huang J, Ma LH, Liu JX, et al. The application of Traditional Chinese drugs for Activating Blood circulation to dissipate Blood Stasis and tumor metastasis. Forum on Traditional Chinese Medicine. 2001; 16 (4):11-12. (In Chinese)
55. Cui W, Jing SJ, Teng JR, et al. Experimental study of *Huoxue Huayu* on inhibiting tumor cell—platelet aggregation. China Journal of Basic Medicine In Traditional Chinese Medicine. 1997; 3(1):27-28,31. (In Chinese)
56. Pan L, Chen PF. Research on the anti-tumor mechanism of *Qingre Jiedu* Traditional Chinese Medicine. Chinese Archives of Traditional Chinese Medicine. 2007; 25(3):569-571. (In Chinese)
57. Han Y, Bu LM, Ji X, et al. Modulation of multidrug resistance by and rographolid in HCT-8/5-FU resistant cell line. Chinese New Drugs Journal. 2004; 13(5):404-407. (In Chinese)
58. Xie CS, Zhou WS, Feng ZQ, et al. The study on the reversal effects of *Fufang Sangen* Mixture in multi-drug resistant cell Lines K562/ADR and K562/VC. Chinese Journal of Experimental Traditional Medical Formulae. 2003; 9(4):26-30. (In Chinese)