Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Anticancer effects of Chinese herbal medicine, science or myth?*

RUAN Wen-jing[1], LAI Mao-de[†‡1], ZHOU Jian-guang[2]

([1]*Department of Pathology, School of Medicine, Zhejiang University, Hangzhou 310006, China*)

([2]*Department of Dermatology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China*)

[†]E-mail: lmp@zju.edu.cn

Received July 17, 2006; revision accepted Sept. 26, 2006

Abstract: Currently there is considerable interest among oncologists to find anticancer drugs in Chinese herbal medicine (CHM). In the past, clinical data showed that some herbs possessed anticancer properties, but western scientists have doubted the scientific validity of CHM due to the lack of scientific evidence from their perspective. Recently there have been encouraging results, from a western perspective, in the cancer research field regarding the anticancer effects of CHM. Experiments showed that CHM played its anticancer role by inducing apoptosis and differentiation, enhancing the immune system, inhibiting angiogenesis, reversing multidrug resistance (MDR), etc. Clinical trials demonstrated that CHM could improve survival, increase tumor response, improve quality of life, or reduce chemotherapy toxicity, although much remained to be determined regarding the objective effects of CHM in human in the context of clinical trials. Interestingly, both laboratory experiments and clinical trials have demonstrated that when combined with chemotherapy, CHM could raise the efficacy level and lower toxic reactions. These facts raised the feasibility of the combination of herbal medicines and chemotherapy, although much remained to be investigated in this area.

Key words: Chinese herbal medicine, Anticancer
doi:10.1631/jzus.2006.B1006 **Document code:** A **CLC number:** R28; R979.1

BACKGROUND OF CHINESE HERBAL MEDICINE (CHM)

CHM is one branch of traditional Chinese medicine (TCM). TCM and western medicine have different ethnic and social backgrounds. The main difference between TCM and western medicine rests how to deal with illness. TCM, focusing on holism and naturalism, combines Chinese medical experience with Chinese culture. In general, Chinese practitioners focus on the "yin" and "yang" balance in the body, which is in accordance with the law of nature. The body will be healthy if it keeps balance between "yin" and "yang". Diseases will occur if the balance is disrupted.

CHM is empirically based and has a history of over 4000 years. The biological ingredients of herbal remedies are extracted from natural substances: plants, animal parts, shells, insects and even stones and minerals. The drugs used in CHM often result from a combination of multiple ingredients, called formula, to ensure effective actions on different targets simultaneously (Attele *et al*., 1999). The composite formulas usually have greater efficacy than single ingredients. This may be due to the synergistic interactions of the ingredients (Xue and Roy, 2003). In Chinese herbalism, every herb has its own properties. Chinese herbalists believe that illness can be effectively treated by combining herbs based on their various characteristics and the patient's overall status. The composition of the formula and the dosage of the individual ingredients depend on the signs and symptoms of the patient, which is the basic principle of CHM. These formulas can be modified to fit specific individuals more closely. This theory is in accordance with the idea of "individual therapy" in western medicine. CHM is very popular in China, and has been historically used in treating chronic diseases, such as constipation, dermatitis, insomnia, among other conditions.

‡ Corresponding author

* Project (No. 011107607) supported by the Science and Technology Foundation Grant of Zhejiang Province, China

ANTICANCER ROLE OF CHM

Recently, modern biomolecular science has contributed to the interpretation of the anticancer effects of CHM. As more information becomes available, CHM is becoming recognized worldwide. The gap between East and West is narrowing. Although the anticancer role of CHM needs further investigation, the achievements in this field do give us some important information.

Literature searches were conducted through PubMed until Feb. 2005. Additional manual searches were carried out on relevant medical journals. Search items were "herb", "anticancer mechanism", "traditional Chinese medicine", and "cancer therapy". No restrictions were placed on the language of publication. Only primary data or data that superseded earlier work were included. Case reports were not included. Anticancer clinical trials using CHM in patients and studies investigating anticancer mechanisms of CHM from a western perspective were included. The anticancer effects of CHM have been reported in many Chinese journals. Studies lacking controls were excluded. Two authors independently assessed the quality of the studies, and extracted data.

Laboratory evidence emerging recently

Experiments in test tubes and animals explored the mechanisms for the anticancer role of CHM (Table 1). It was demonstrated that CHM plays its anticancer role by inducing apoptosis and differentiation, enhancing the immune system, inhibiting angiogenesis, reversing multidrug resistance (MDR), etc. Many herbal remedies played their anticancer roles through multiple mechanisms (Ikezoe *et al*., 2003a; 2003b; Cheng *et al*., 2003a; Hong-Fen *et al*., 2001; Hsieh *et al*., 2002; Wartenberg *et al*., 2003).

1. Characters of anticancer effect of herbal remedies

The synergistic effects of various components in *Scutellaria baicalensis* extract [*baicalin* (80%), *wogonoside* (16%), *baicalein* (2%), *wogonin* (1%) and other compounds in trace amounts] were demonstrated (Zhang *et al*., 2003). Both the extract and its pure compound-*baicalein* inhibited cancer cell growth (in vitro). The extract could inhibit prostaglandin E2 (PGE2) production, whereas its pure compound, *baicalein*, could not. Another pure compound *wogonin* significantly inhibited cyclooxygenase 2 (COX-2) activity in lipopolysaccharide (LPS)-stimulated macrophages. The various components in the herb act on different anticancer pathways such as COX-dependent and COX-independent pathways.

Some herbs were most effective on cancer of a certain type. It was demonstrated that artesunate (ART) was most active against leukemia and colon cancer cell lines [mean GI50 values: (1.11±0.56) μmol/L and (2.13±0.74) μmol/L, respectively]. Non-small cell lung cancer (NSCLC) cell lines showed the highest mean GI50 value [(25.62±14.95) μmol/L] indicating the lowest sensitivity towards ART (Efferth *et al*., 2002). This may be due to the herb's affinity for specific organs.

There exists an interesting phenomenon that some herbs might be selective for cancer cells instead of normal cells. It was reported that *Scutellaria baicalensis* demonstrated a strong inhibition in two tested human head and neck squamous cell carcinoma (HNSCC) cell lines, while no growth inhibition of HaCaT cells (a non-tumorigenic cell line) was observed (Zhang *et al*., 2003). The butanol fraction of *Mylabris phalerlata* was specifically cytotoxic on human monocytic leukemic U937 cells rather than on peripheral blood mononuclear lymphocytes (Huh *et al*., 2003). The herb formula PC-SPES inhibited proliferation of HL-60, NB4, U937 and THP-1 human leukemia cells with ED_{50} of 0.17, 0.09, 0.18, 0.32 μl/ml respectively. On the contrary, PC-SPES (0.1 μl/ml) stimulated growth of normal myeloid committed stem cells by 1.4 fold of control (P=0.03) (Ikezoe *et al*., 2003a). It was demonstrated that magnolol at concentrations of 3~10 μmol/L inhibited DNA synthesis and decreased cell number in cultured human cancer cells (COLO-205 and Hep-G2) in a dose-dependent manner but not in non-transformed human cells such as keratinocytes, fibroblasts, and human umbilical vein endothelial cells (HUVEC). When magnolol concentration was increased to 100 μmol/L, apoptosis was observed in COLO-205 and Hep-G2 cells, but not in cultured human fibroblasts and HUVEC (Lin *et al*., 2002). Triptolide was also demonstrated to sensitize lung cancer but not normal human bronchial epithelial cells to Apo2L/TRAIL-induced apoptosis (Frese *et al*., 2003), However, it is still unclear how this tumor-specific killing occurs. Further investigation is needed to

Table 1 Anticancer effects of CHM (laboratory experiments)

Type of cancer	Model	Herb	Mechanism	Ref.
HNSCC	SCC-25 and KB cell lines, four nude mice with s.c. inoculation of KB cells	*Scutellaria baicalensis*	Inhibition of cell growth in vitro and in vivo, inhibition of PGE2 synthesis via suppression of COX-2 expression	Zhang *et al*., 2003
	KB, KBv200 cell lines	*Asiaticoside*	Induction of apoptosis and enhancement of the anti-tumor activity of vincristine	Huang *et al*., 2004
Leukemia	U937 cell line	*Mylabris phalerlata*, *Scutellaria barbata*	Induction of apoptosis	Huh *et al*., 2003; Cha *et al*., 2004
	NB4, HL60 cell lines	*Red orpiment*	Induction of apoptosis	Zhong *et al*., 2003
	AKR/J mice	*Echinacea purpurea*	Enhancement of nonspecific immune or cellular immune systems (or of both)	Hayashi *et al*., 2001
	CCRF-CEM, CEM/E1000, CEM/VLB (100) cell lines	*Artesunate* (ART), *Bufalin*	ART significantly increased daunorubicin accumulation in CEM/E1000 cells, but not in CEM/VLB (100) or CCRF-CEM parental cells. Bufalin caused a small, but significant increase in daunorubicin accumulation in CEM/VLB (100) and CEM/E1000 cells	Efferth *et al*., 2002
	NB4 cell line	Arsenic trioxide	Induction of apoptosis	Chen *et al*., 1996
	HL-60 cell line	Hydrolysable tannis from *Eugenia jambos* L.	Induction of apoptosis	Yang *et al*., 2000
	HL-60, NB4, U937 and THP-1 cell lines	PC-SPES	Inhibition of growth, induction of differentiation and apoptosis	Ikezoe *et al*., 2003a
Colorectal carcinoma	CoLo205 cell line	*Magnolol*	Induction of apoptosis	Lin *et al*., 2002
	Mice bearing colon26/ clone 20 carcinoma cells	*Coptidis rhizome* and *Berberine*	Reduction of IL-6 mRNA levels and protein levels in tumors and sera	Iizuka *et al*., 2002
Gastric cancer	MGC-803 cell line	*Isoliquiritigenin*	Induction of apoptosis	Ma *et al*., 2001
	AGS cell line	*Astragali* (AR)	Cytostatic	Lin *et al*., 2003
	MNK45 and KATO-III cell lines	*Anemarrhena asphodeloides*	Induction of apoptosis	Takeda *et al*., 2001
Hepatic cancer	Hep-G2 cell line	*Magnolol*	Induction of apoptosis	Lin *et al*., 2002
	SMMC-7221 cell line	*Isoverbascoside*	Induction of differentiation	Chen *et al*., 2002a
Lung cancer	A549 cell line	*Bupleuri radix*	Inhibition of telomerase activity and activation of apoptosis	Cheng *et al*., 2003a
	Lung cancer cells	*Triptolide*	Induction of apoptosis in combination with Apo2L/TRAIL	Frese *et al*., 2003
Breast cancer	95-D cell line	*Acutiaporberine*	Induction of apoptosis	Chen *et al*., 2002b
	F344 rats	Anticancer-number-one	Increasement of NK cell activity and inhibition of tumor metastasis	Hong-Fen *et al*., 2001
	MCF-7 cell line	*Rosemary*	Reversing MDR	Plouzek *et al*., 1999
	MCF-7 cell line	Tea and tea polyphenlos	Suppression of fatty acid synthase (a key enzyme in lipogenesis)	Yeh *et al*., 2003
	MCF-7 and MCF-7/ADM cell lines	*Asiaticoside*	Enhancement of the anti-tumor activity of vincristine	Huang *et al*., 2004
Ovarian cancer	SKOV3, CAOV3 and OVCAR-3 cell lines	*Scutellaria barbatae*	Induction of apoptosis	Powell *et al*., 2003
Prostate cancer	LNCaP cell lines	PC-SPES	Activation of the JNK/c-Jun/AP-1 signal pathway resulting in growth arrest and apoptosis of prostate cancer cells	Ikezoe *et al*., 2003b
	Prostate carcinoma cells	*Equiguard*	Down-regulation of expression of androgen receptor and prostate-specific antigen, induction of apoptosis	Hsieh *et al*., 2002
	Embryoid bodies and multicellular DU-145 prostate tumor spheroids	*Baicalein*, *Epicatechin*, *Berberine*, *Acteoside*	Down-regulation of MMP expression, inhibition of angiogenesis	Wartenberg *et al*., 2003
Glioma	Rat C6 glioma cells	*Saikosaponin a*, *b*	Induction of differention	Tsai *et al*., 2002
	Mice that injected with LZEJ-C3 cells subcutaneously	Dang-gui-bu-xai-tang	Increasement of the population of CTLs and NK cells, and down-regulation of activated T helper cells (CD4+/CD25+) in spleen and TDLN	Hsieh *et al*., 2003

Note: HNSCC, head and neck squamous cell carcinoma; PGE2, prostaglandin E2; COX-2, cyclooxygenase 2; EC: endotheliocytes; NK, natural killer; MDR, multidrug resistance; MMP, matrix metalloproteinase; CTLs, cytotoxic T lymphocytes; TDLN, tumor-draining lymph nodes. Anticancer-number-one, *Panax ginseng*, *Poria cocos*, *Atractylodes macrocephala*, *Anglica sinensis*, *A. membranaceus*, *Curcuma zedoaria*, *Scutellaria baicalensis*, *Phellodenron chinense*, *Coptis chinensis*, *Glycyrrhiza uralensis*, *Crataegus pinnatifida*, *Hordeum õulgare*, *Salõia miltiorrhiza*, *Schisandra chinensis*, *Hedyotis diffusa*, *Ophiopogon japonicus*, *Lobelia chinesis lour*, *Scutellaria barbaba*, *Massa fermentata medicinalis*; PC-SPES, *Reishi mushroom*, *Baikal skullcap*, *Rabdosia*, *Dyer's woad*, *Chrysanthemum*, *Saw palmetto*, *Panax ginseng*, and *Licorice*; Dang-gui-bu-xai-tang, *Radix Angelicae sinensis* and *Radix Astragali membranaceus*

clarify the mechanism behind this interesting phenomenon.

2. Enlarged efficacy of herbal remedies in combination with routine chemical reagents

Some studies have assessed the use of herbs in combination with routine chemical reagents. *Asiaticoside* could enhance the anti-tumor activity of vincristine in several cancer cell lines including KB, KBv200, MCF-7, and MCF-7/ADM. The apoptosis rates and the Bcl-2 phosphorylation levels were much higher in *asiaticoside* plus vincristine groups than in vincristine or *asiaticoside* groups. *Asiaticoside* plus vincristine enhanced S-G (2)/M arrest, up-regulated Cyclin B1 protein expression, and down-regulated P34 (cdc2) protein expression in KB cells (Huang *et al*., 2004). PC-SPES enhanced the antiproliferative and prodifferentiative effects of ATRA (all-trans retinoic acid) on leukemia cells. PC-SPES (0.125 μl/ml) alone, ATRA (10^{-8} mol/L) alone or the combination of the two inhibited growth of HL-60 cells after 4 d of culture, by approximately 40%, 30% and 80%, respectively. Measured by expression of CD11b antigen, the induced differentiation rate was also much higher in the combination group (60%) than in PC-SPES group (27%) or ATRA group (18%) alone (Ikezoe *et al*., 2003a). An extract of the common dietary herb rosemary (*Rosemarinus officinalis Labiatae*) increased the intracellular accumulation of commonly used chemotherapeutic agents, including doxorubicin (DOX) and vinblastine (VIN), in drug-resistant MCF-7 human breast cancer cells (Plouzek *et al*., 1999).

Current status of clinical trials

Simultaneously, clinical trials of different phases have been conducted. The critical data from the seven clinical trials, searched from PubMed, are listed in Table 2. These studies were carried out in the USA (Wheeler *et al*., 2003; Oh *et al*., 2004; Soignet *et al*., 1998), Egypt (Mabed *et al*., 2004), China (Shen *et al*., 2004; Piao *et al*., 2004), Russia, Bulgaria and Ukraine (Semiglasov *et al*., 2004) from 1998 to 2004. Various kinds of herbs were used, including *Semen coicis*, Arsenic trioxide, *Viscum fraxini*-2, standardized *mistletoe* extracts, PC-SPES. Various types of cancer have been investigated, including acute promyelocytic leukemia, thyroid cancer, nasopharyngeal carcinoma, esophagus cancer, mesothelioma, NSCLC, hepatocellular carcinoma, pancreatic cancer, colon cancer, prostate cancer, breast cancer, ovarian cancer, carcinoid, and liposarcoma.

Sample sizes in the clinical trials ranged from 12 to 272. Dropouts and withdrawals were mentioned in (Wheeler *et al*., 2003; Oh *et al*., 2004; Soignet *et al*., 1998; Shen *et al*., 2004; Semiglasov *et al*., 2004; Piao *et al*., 2004). Adverse effects of CHM were reported in all of the clinical trials. In these trials, patients received herbal medicine alone (Wheeler *et al*., 2003; Mabed *et al*., 2004; Oh *et al*., 2004; Soignet *et al*., 1998) or along with standard tumor destructive treatment (Shen *et al*., 2004; Semiglasov *et al*., 2004; Piao *et al*., 2004). The phase I trial (Wheeler *et al*., 2003) focusing on *Semen coicis* demonstrated the safety of the drug. The six phase II trials (Mabed *et al*., 2004; Oh *et al*., 2004; Soignet *et al*., 1998; Shen *et al*., 2004; Semiglasov *et al*., 2004; Piao *et al*., 2004) showed that these herbs were helpful against cancer, alone or in combination with chemotherapy. It is demonstrated that herbs could improve survival (Mabed *et al*., 2004; Shen *et al*., 2004), increase tumor response (Mabed *et al*., 2004; Oh *et al*., 2004; Soignet *et al*., 1998; Shen *et al*., 2004), improve quality of life or reduce chemotherapy toxicity (Semiglasov *et al*., 2004; Piao *et al*., 2004).

DISCUSSION

Benefits and concerns

Science has long acknowledged the value of healing substances found in nature, such as digitalis, aspirin, penicillin, insulin, steroids, etc. There has been a resurgence of interest, both scientifically and popularly, in the utilization of natural approaches.

Experiments in test tubes and in animals demonstrated that CHM played its anticancer role by inducing apoptosis and differentiation, enhancing the immune system, inhibiting angiogenesis, reversing multidrug resistance (MDR), etc. However, the mechanism of the anticancer role of CHM has not yet been fully elucidated. Further research is needed to explore the molecular mechanism of CHM. The pharmacological effects of CHM are still not clear although it is proved to be effective against disease, which is also the major reason preventing CHM from being accepted worldwide. Although the clinical

Table 2 Anticancer effects of CHM (clinical trials)

Patients		Herb	Herb dosage	Treatments	Effect	Reference
Type of cancer	No.					
Lung Esophagus Prostate Mesothelioma Colon Carcinoid Pancreas Thyroid Liposarcoma	3 3 2 2 2 1 1 1 1	Kanglaite injection, an extract of the coix seed	10000 mg/d up to 50000 mg/d, for 21 consecutive days every 4 weeks (increased by 10000 mg/d in each of four subsequent levels)	Herb	No dose limiting toxicities were observed in the first cycle up to the maximum dose of 50000 mg/d. A maximum tolerated dose (MTD) could not be defined.	Wheeler *et al*., 2003
HCC	23	Viscum fraxini-2	2 ampoules (10000 ng/ml), subcutaneously, once weekly	Herb	CR: 13.1%; PR: 8.1%; 39.1%: progressive; 39.1%: no evaluation of response due to early death	Mabed *et al*., 2004
Prostate cancer	90	PC-SPES	960 mg orally, t.i.d., (DES 3 mg orally q.d. as control)	Herb	PSA declines ≥50% were noted in 40% with PC-SPES and 24% with DES	Oh *et al*., 2004
APL	12	Arsenic trioxide	0.06 to 0.2 mg/(kg·d), cumulative doses, 160~515 mg	Herb	Complete remission: 92%	Soignet *et al*., 1998
APL	61	Arsenic trioxide	ATRA: 25 mg/m^2 per day; Arsenic trioxide: 0.16 mg/kg per day	Arsenic trioxide+ ATRA (appropriate chemotherapy)	The time to achieve complete rates was the shortest one in the combination group	Shen *et al*., 2004
Breast cancer	272	sME	0.5 ml (10, 30, 70 ng/ml) twice weekly subcutaneously for 15 consecutive weeks	Herb+CMF chemotherapy	QoL was significantly improved (P<0.01) with the medium dose (30 ng/ml)	Semiglasov *et al*., 2004
Breast cancer Ovarian cancer NSCLC	68 71 94	sME	1 mg up to 200 mg, subcutaneously, 3 times per week	Herb+chemotherapy (Breast cancer: CAP, CAF; Ovarian cancer: CP, IcP; NSCLC: VP, MViP)	QoL was significantly (P<0.05) improved	Piao *et al*., 2004

Note: Kanglaite injection, produced by the Chinese company Zhejiang Kanglaite pharmaceutical (ZKP, Hangzhou). APL: Acute promyelocytic leukemia; HCC: Hepatocellular carcinoma; CR: Complete response; PR: Partial response; DES: Diethylstilbestrol; PSA: Prostate-specific antigen; ATRA: All-trans retinoic acid; IA: Idarubicin, Ara-C; sME: Standardized mistletoe extracts; CMF: Cyclophosphamide, methotrexate, fluorouracil; QoL: Quality of life; NSCLC: Non-small cell lung cancer; CAP: Cyclophosphamide, adriamycin, cisplatin; CAF: Cyclophosphamide, adriamycin, 5-fluorouracil; CP: Cyclophosphamide, cisplatin; IcP: Ifosfamide, carboplatin; VP: Vinorelbine, cisplatin; MViP: mitomycine, vindesine, cisplatin

trials showed that herbs were helpful against cancer, these outcomes require further confirmation with rigorously controlled trials. In China, many clinical trials focusing on the anticancer effects of herbal formulas have been conducted. Though many of them demonstrated that herbs are helpful against cancer, especially useful in improving survival and quality of life in patients suffering from advanced cancer, the lack of controls and reporting bias have been severe flaws. Researchers must pay attention to the scientific rigor of studies of CHM in the future to improve the status.

Some Chinese herbs may be harmful to the human body if they are used improperly. Some herbs may cause serious toxicity when taken excessively or under inappropriate circumstances (Chan *et al*., 2005). Herbal remedies should be prescribed carefully by qualified practitioners according to the herb character and the whole body condition of the patient. Also, potential herb-drug interactions should be taken into consideration if multiple drugs are prescribed simultaneously (Cheng *et al*., 2003b).

Herbal therapies have already led to the development of a number of anticancer drugs. The key to

choosing the anticancer CHM is to optimize an effective formula. With the development of modern science and medicine, CHM modernization is on the way. Using state-of-the-art technology in CHM extraction, purification and drug production can efficiently improve the CHM industry. Traditionally, herbs have been made into pills, powders and astopical plasters. Today, herbal companies have developed other forms like capsules, tablets and injections which are more convenient and palatable. Kanglaite injection is an extract produced from coix seed (*Semen coicis*). The anticancer mechanisms of Kanglaite injection have been widely explored in China. It has been proven to play its anticancer role through inhibition of the mitosis of tumor cells during G2/M phases, induction of apoptosis and inhibition of the formation of newly generated blood vessels (Li, 2001). This botanical drug, which is approved in China for treatment of lung cancer, hepatic cancer and gastric cancer, has been extensively used in more than 2000 hospitals around the country. After one year of clinical experiments which proved its beneficial effects in the treatment of lung cancer and gastric cancer, it has been recently permitted by the Russian health authorities for clinical application for cancer treatment. A phase I trial for Kanglaite in Salt Lake City, USA, has been completed, verifying the safety of the drug (Wheeler *et al*., 2003). The phase II trial, approved by the United States Food and Drug Administration (FDA), will pair Kanglaite with another chemotherapy to treat NSCLC. The global market of CHM for anticancer therapy will probably be prosperous from this new start.

However, caution should be used. Due to contamination with undeclared prescription drugs, such as DES, indomethacin and warfarin, PC-SPES was withdrawn from the market in 2002. The withdrawal of PC-SPES can be viewed as due to inadequate quality control in the production of the herb remedies. The product should be fully characterized and standardized, properly labelled for its contents. It is unclear whether these prescription drugs account for the anticancer effect of the herb remedies. Future research is required to determine which ingredients are effective. However, PC-SPES did have anticancer effects against prostate cancer. If PC-SPES free of contaminating drugs is not as effective as the drug-containing PC-SPES, the original mixture (combining herbs and drugs) may provide valuable clues for researching and developing anticancer drugs in the future.

Combination of CHM and chemotherapy

Although much remains to be determined regarding the objective effects of CHM in vitro and in human in the context of clinical trials, Arsenic trioxide has confirmed efficacy against APL. Arsenic trioxide has proven to be very effective in obtaining high clinically complete remission rates in APL patients (Soignet *et al*., 1998). This drug has been widely used on APL patients around the world. Recent study showed that the ATRA/Arsenic trioxide combination for remission/maintenance therapy of APL lead to much better results than either of the two drugs alone in terms of the quality of complete remission and the status of the disease-free survival (Shen *et al*., 2004). The authors also conducted experiments to explore the possible underlying molecular mechanisms. As a result, ATRA and Arsenic trioxide were shown to have synergistic effect on apoptosis and degradation of PML-PARα oncoprotein. This successful research, together with other studies demonstrating the enlarged efficacy and lowered toxicity of the combination therapy in vitro (Huang *et al*., 2004; Ikezoe *et al*., 2003a; Plouzek *et al*., 1999) and in clinical trials (Shen *et al*., 2004; Semiglasov *et al*., 2004; Piao *et al*., 2004) holds the promise of better treatment of cancer. However, the possibility of detrimental effects from the combination cannot be ruled out. Further studies, including basic experiments conducted in different systems and rigorously controlled clinical trials, are required to better define the objective effects of the combination therapy. Western therapies, including surgery, chemotherapy, and radiotherapy are tumor destructive. From the Chinese practitioners' viewpoint, the whole unhealthy condition should be treated successfully to cure the patients suffering from cancer. The two different systems of medicine target "cancer" from different perspective. This is due to difference in the way of thinking. Westerner usually use the direct thinking way. When they want to target "A", they usually try their best to target "A" itself, with that requisite, they will impair the factors related to "A"-B, C, D. Chinese usually use the indirect way of thinking. When they want to target "A", they are apt to first target the

factors related to "A"-B, C, D, to change the environment and conditions of "A", which ultimately leads to change in "A". It is difficult to draw a conclusion about which one is superior to the other. They are two ways from different perspective to solve the problem. One might provide a complementary remedy to the other. Chinese practitioners hold the belief that western therapy strongly targets the cancer foci and CHM strongly targets the unhealthy condition of the whole body. Combination therapy, bringing together the advantages of each type of medicine for an overall enhancement of cancer treatment, is regarded as one of the most important principles for the treatment of cancer in China (Fig.1). However, due to the culture difference, the philosophy accepted in China needs further research to verify its scientific basis from the perspective accepted all around the world, which needs the effort from Chinese practitioners and oncologists worldwide.

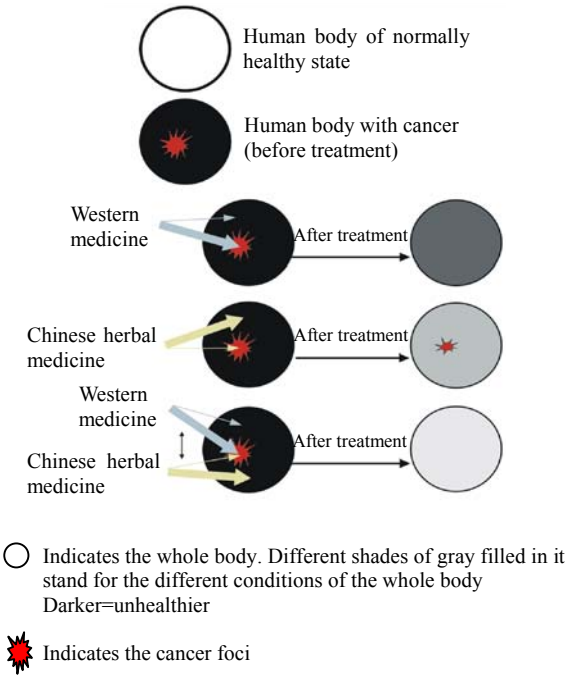

Fig.1 Cancer treatment with western medicine and Chinese herbal medicine

ACKNOWLEDGEMENT

We thank Mari Swift (University of Washington, USA), Janice Lee (Harvard University, USA) for the serious proofreading work, Bingjian Lv, Weiqun Xu, Xiuxu Chen, Jing Deng and Lina Shao for helpful discussion in revising the article, Richard T. Penson (Massachusetts General Hospital, USA), Mohammed Mabed (Mansoura University, Egypt) for critical comments, Peng Fang for help with figure preparation.

References

Attele, A.S., Wu, J.A., Yuan, C.S., 1999. Ginseng pharmacology: multiple constituents and multiple actions. *Biochem. Pharmacol.*, **58**(11):1685-1693. [doi:10.1016/S0006-2952(99)00212-9]

Cha, Y.Y., Lee, E.O., Lee, H.J., Park, Y.D., Ko, S.G., Kim, D.H., Kim, H.M., Kang, I.C., Kim, S.H., 2004. Methylene chloride fraction of Scutellaria barbata induces apoptosis in human U937 leukemia cells via the mitochondrial signaling pathway. *Clin. Chim. Acta*, **348**(1-2):41-48. [doi:10.1016/j.cccn.2004.04.013]

Chan, T.Y., Tam, H.P., Lai, C.K., Chan, A.Y., 2005. A multidisciplinary approach to the toxicologic problems associated with the use of herbal medicines. *Ther. Drug Monit.*, **27**(1):53-57. [doi:10.1097/00007691-200502000-00011]

Chen, G.Q., Zhu, J., Shi, X.G., Ni, J.H., Zhong, H.J., Si, G.Y., Jin, X.L., Tang, W., Li, X.S., Xong, S.M., *et al*., 1996. In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia: As_2O_3 induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. *Blood*, **88**(3):1052-1061.

Chen, R.C., Su, J.H., Ouyang, G.L., Cai, K.X., Li, J.Q., Xie, X.G., 2002a. Induction of differentiation in human hepatocarcinoma cells by isoverbascoside. *Planta Med.*, **68**(4):370-372. [doi:10.1055/s-2002-26759]

Chen, Q., Peng, W., Qi, S., Xu, A., 2002b. Apoptosis of human highly metastatic lung cancer cell line 95-D induced by acutiaporberine, a novel bisalkaloid derived from Thalictrum acutifolium. *Planta Med.*, **68**(6):550-553. [doi:10.1055/s-2002-32546]

Cheng, Y.L., Chang, W.L., Lee, S.C., Liu, Y.G., Lin, H.C., Chen, C.J., Yen, C.Y., Yu, D.S., Lin, S.Z., Harn, H.J., 2003a. Acetone extract of Bupleurum scorzonerifolium inhibits proliferation of A549 human lung cancer cells via inducing apoptosis and suppressing telomerase activity. *Life Sci.*, **73**(18):2383-2394. [doi:10.1016/S0024-3205(03)00648-9]

Cheng, K.F., Leung, K.S., Leung, P.C., 2003b. Interactions between modern and Chinese medicinal drugs: a general review. *Am. J. Chin. Med.*, **31**(2):163-169. [doi:10.1142/S0192415X0300093X]

Efferth, T., Davey, M., Olbrich, A., Rucker, G., Gebhart, E., Davey, R., 2002. Activity of drugs from traditional Chinese medicine toward sensitive and MDR1- or MRP1-overexpressing multidrug-resistant human CCRF-CEM leukemia cells. *Blood Cells Mol. Dis.*,

28(2):160-168. [doi:10.1006/bcmd.2002.0492]

Frese, S., Pirnia, F., Miescher, D., Krajewski, S., Borner, M.M., Reed, J.C., Schmid, R.A., 2003. PG490-mediated sensitization of lung cancer cells to Apo2L/TRAIL-induced apoptosis requires activation of ERK2. *Oncogene*, **22**(35): 5427-5435. [doi:10.1038/sj.onc.1206842]

Hayashi, I., Ohotsuki, M., Suzuki, I., Watanabe, T., 2001. Effects of oral administration of Echinacea purpurea (American herb) on incidence of spontaneous leukemia caused by recombinant leukemia viruses in AKR/J mice. *Nihon Rinsho Meneki Gakkai Kaishi*, **24**(1):10-20.

Hong-Fen, L., Waisman, T., Maimon, Y., Shakhar, K., Rosenne, E., Ben-Eliyahu, S., 2001. The effects of a Chinese herb formula, anti-cancer number one (ACNO), on NK cell activity and tumor metastasis in rats. *Int. Immunopharmacol.*, **1**(11):1947-1956. [doi:10.1016/S1567-5769(01)00120-5]

Hsieh, T.C., Lu, X., Guo, J., Xiong, W., Kunicki, J., Darzynkiewicz, Z., Wu, J.M., 2002. Effects of herbal preparation Equiguard on hormone-responsive and hormone-refractory prostate carcinoma cells: mechanistic studies. *Int. J. Oncol.*, **20**(4):681-689.

Hsieh, C.C., Lin, W.C., Lee, M.R., Hsu, S.L., Liu, H.S., Kao, S.T., Hsieh, M.T., 2003. Dang-Gui-Bu-Xai-Tang modulated the immunity of tumor bearing mice. *Immunopharmacol. Immunotoxicol.*, **25**(2):259-271. [doi:10.1081/IPH-120020474]

Huang, Y.H., Zhang, S.H., Zhen, R.X., Xu, X.D., Zhen, Y.S., 2004. Asiaticoside inducing apoptosis of tumor cells and enhancing anti-tumor activity of vincristine. *Ai Zheng*, **23**(12):1599-1604 (in Chinese).

Huh, J.E., Kang, K.S., Ahn, K.S., Kim, D.H., Saiki, I., Kim, S.H., 2003. Mylabris phalerlata induces apoptosis by caspase activation following cytochrome c release and Bid cleavage. *Life Sci.*, **73**(17):2249-2262. [doi:10.1016/S0024-3205(03)00568-X]

Iizuka, N., Hazama, S., Yoshimura, K., Yoshino, S., Tangoku, A., Miyamoto, K., Okita, K., Oka, M., 2002. Anticachectic effects of the natural herb Coptidis rhizoma and berberine on mice bearing colon 26/clone 20 adenocarcinoma. *Int. J. Cancer*, **99**(2):286-291. [doi:10.1002/ijc.10338]

Ikezoe, T., Chen, S., Saito, T., Asou, H., Kyo, T., Tanosaki, S., Heber, D., Taguchi, H., Koeffler, H.P., 2003a. PC-SPES decreases proliferation and induces differentiation and apoptosis of human acute myeloid leukemia cells. *Int. J. Oncol.*, **23**(4):1203-1211.

Ikezoe, T., Chen, S.S., Yang, Y., Heber, D., Taguchi, H., Koeffler, H.P., 2003b. PC-SPES: molecular mechanism to induce apoptosis and down-regulate expression of PSA in LNCaP human prostate cancer cells. *Int. J. Oncol.*, **23**(5):1461-1470.

Li, D.P., 2001. Progresses in basic studies of anticancer mechanisms of Kanglaite injection (KLT). *Zhong Yao Xin Yao Yu Lin Chuang Yao Li*, **12**(2):122-124 (in Chinese).

Lin, S.Y., Liu, J.D., Chang, H.C., Yeh, S.D., Lin, C.H., Lee, W.S., 2002. Magnolol suppresses proliferation of cultured human colon and liver cancer cells by inhibiting DNA synthesis and activating apoptosis. *J. Cell Biochem.*, **84**(3):532-544. [doi:10.1002/jcb.10059]

Lin, J., Dong, H.F., Oppenheim, J.J., Howard, O.M., 2003. Effects of astragali radix on the growth of different cancer cell lines. *World J. Gastroenterol.*, **9**(4):670-673.

Ma, J., Fu, N.Y., Pang, D.B., Wu, W.Y., Xu, A.L., 2001. Apoptosis induced by isoliquiritigenin in human gastric cancer MGC-803 cells. *Planta Med.*, **67**(8):754-757.

Mabed, M., El-Helw, L., Shamaa, S., 2004. Phase II study of viscum fraxini-2 in patients with advanced hepatocellular carcinoma. *Br. J. Cancer*, **90**(1):65-69. [doi:10.1038/sj.bjc.6601463]

Oh, W.K., Kantoff, P.W., Weinberg, V., Jones, G., Rini, B.I., Derynck, M.K., Bok, R., Smith, M.R., Bubley, G.J., Rosen, R.T., *et al*., 2004. Prospective, multicenter, randomized phase II trial of the herbal supplement, PC-SPES, and diethylstilbestrol in patients with androgen-independent prostate cancer. *J. Clin. Oncol.*, **22**(18): 3705-3712. [doi:10.1200/JCO.2004.10.195]

Piao, B.K., Wang, Y.X., Xie, G.R., Mansmann, U., Matthes, H., Beuth, J., Lin, H.S., 2004. Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small cell lung cancer patients. A prospective randomized controlled clinical trial. *Anticancer Res.*, **24**(1):303-309.

Plouzek, C.A., Ciolino, H.P., Clarke, R., Yeh, G.C., 1999. Inhibition of P-glycoprotein activity and reversal of multidrug resistance in vitro by rosemary extract. *Eur. J. Cancer*, **35**(10):1541-1545. [doi:10.1016/S0959-8049(99)00180-X]

Powell, C.B., Fung, P., Jackson, J., Dall'Era, J., Lewkowicz, D., Cohen, I., Smith-McCune, K., 2003. Aqueous extract of herba Scutellaria barbatae, a chinese herb used for ovarian cancer, induces apoptosis of ovarian cancer cell lines. *Gynecol. Oncol.*, **91**(2):332-340. [doi:10.1016/j.ygyno.2003.07.004]

Semiglasov, V.F., Stepula, V.V., Dudov, A., Lehmacher, W., Mengs, U., 2004. The standardised mistletoe extract PS76A2 improves QoL in patients with breast cancer receiving adjuvant CMF chemotherapy: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Res.*, **24**(2C):1293-1302.

Shen, Z.X., Shi, Z.Z., Fang, J., Gu, B.W., Li, J.M., Zhu, Y.M., Shi, J.Y., Zheng, P.Z., Yan, H., Liu, Y.F., *et al*., 2004. All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc. Natl. Acad. Sci. USA*, **101**(15):5328-5335. [doi:10.1073/pnas.0400053101]

Soignet, S.L., Maslak, P., Wang, Z.G., Jhanwar, S., Calleja, E., Dardashti, L.J., Corso, D., DeBlasio, A., Gabrilove, J., Scheinberg, D.A., *et al*., 1998. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *N. Engl. J. Med.*, **339**(19):1341-1348. [doi:10.1056/NEJM199811053391901]

Takeda, Y., Togashi, H., Matsuo, T., Shinzawa, H., Takeda, Y., Takahashi, T., 2001. Growth inhibition and apoptosis of

gastric cancer cell lines by Anemarrhena asphodeloides Bunge. *J. Gastroenterol.*, **36**(2):79-90. [doi:10.1007/s005350170135]

Tsai, Y.J., Chen, I.L., Horng, L.Y., Wu, R.T., 2002. Induction of differentiation in rat C6 glioma cells with Saikosaponins. *Phytother. Res.*, **16**(2):117-121. [doi:10.1002/ptr.752]

Wartenberg, M., Budde, P., de Marees, M., Grunheck, F., Tsang, S.Y., Huang, Y., Chen, Z.Y., Hescheler, J., Sauer, H., 2003. Inhibition of tumor-induced angiogenesis and matrix-metalloproteinase expression in confrontation cultures of embryoid bodies and tumor spheroids by plant ingredients used in traditional chinese medicine. *Lab. Invest.*, **83**(1):87-98. [doi: 10.1097/01.LAB.0000049348.51663.2F]

Wheeler, R.H., Busby, L., Samlowski, W., Gerard, R., 2003. Phase I Study of Kanglaite (KLT) a Botanical Product Based on Traditional Chinese Medicine. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL.

Xue, T., Roy, R., 2003. Studying traditional Chinese medicine. *Science*, **300**(5620):740-741. [doi:10.1126/science.300.5620.740]

Yang, L.L., Lee, C.Y., Yen, K.Y., 2000. Induction of apoptosis by hydrolyzable tannins from *Eugenia jambos* L. on human leukemia cells. *Cancer Lett.*, **157**(1):65-75. [doi:10.1016/S0304-3835(00)00477-8]

Yeh, C.W., Chen, W.J., Chiang, C.T., Lin-Shiau, S.Y., Lin, J.K., 2003. Suppression of fatty acid synthase in MCF-7 breast cancer cells by tea and tea polyphenols: a possible mechanism for their hypolipidemic effects. *Pharmacogenomics J.*, **3**(5):267-276.

Zhang, D.Y., Wu, J., Ye, F., Xue, L., Jiang, S., Yi, J., Zhang, W., Wei, H., Sung, M., Wang, W., *et al*., 2003. Inhibition of cancer cell proliferation and prostaglandin E2 synthesis by Scutellaria baicalensis. *Cancer Res.*, **63**(14):4037-4043.

Zhong, L., Chen, F., Han, J., Shao, N., Ouyang, R., 2003. Effects of red orpiment on cell morphology and expression of PML mRNA and protein in NB4 and HL-60 cells. *Chin. Med. J.*, **116**(1):148-150.