Review

Chinese herbal medicine in the treatment of lung cancer

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Abstract

Chinese herbal medicine has been the traditional treatment for numerous human diseases for thousands of years. It has performed well clinically and, for this discussion, it has shown great promise for the treatment of many symptoms which modern medicine has associated for centuries with lung cancer. Many medicinal plants have been tested for anticancer activity such as antofine, acutiaporberine, etc. The compounds which have been isolated from these medicinal herbs include a variety of alkaloids, triterpenoids, flavonoids, terpenoids, and polysaccharides. Some of the formulas used in clinical tests have been combined with chemotherapy. Traditional Chinese Medicine (TCM) formulae such as shenyi capsule and aidi injection contain numerous ingredients so that they may be considered to have anit-lung cancer activity as well as serving as immunomodulators. They have been demonstrated to ameliorate or prevent adverse effects as a result of the use of single drugs. Research on Chinese herbal medicine for the treatment of lung cancer has not only been shown to aeffect lung cancer, but to also provide important methods for the study of lung cancer therapy. This report reviews some of the findings resulting from the use of Chinese herbal medicine in the treatment of lung cancer.

Key words: lung cancer; Chinese herbal medicine; medicinal plants; traditional Chinese formulae

Lung cancer is the leading cause of cancer death among both men and women. There will be an estimated 162, 460 deaths caused by lung cancer (90, 330 among men and 72, 130 among women) in 2006, accounting for around 28 % of all cancer deaths. More people die of lung cancer than from colon, breast, and prostate cancers [1]. As classified by the World Health Organization, there are four major types of lung cancer: (1) squamous cell (epidermoid) carcinoma, (2) small-cell (oat cell) carcinoma, (3) adenocarcinoma, and (4) large cell carcinoma. Based on its biology, therapy, and prognosis, lung cancer is divided into two major classes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [2]. Non-small cell lung cancer accounts for 75 % to 80 % of all lung cancer cases. Small cell lung cancer (SCLC) accounts for 15 % to 25 % of all lung cancer. About 98 % of SCLC is attributed to cigarette smoking [3 -5].

Conventional treatment of either form of lung cancer is fairly ineffective.

Therefore, attention has been paid to natural, active substances. To date, many of the chemotherapeutic agents are medicinal plants or are derived from medicinal plants. Interestingly, herbs have been used in the treatment of various cancers for a long period of time and their therapeutic effects involving anticancer

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properties have been scientifically evaluated both *in vitro* and *in vivo*. Herbal medicine, recorded in many countries (e.g., Chinese Pharmacopoeia), has been prescribed for lung cancer over centuries and has begun to draw increasing scientific attention. Based on recent scientific research on herbs, herbal therapies have been considered alternative treatment for some malignancies [6-7]. Various components in herbs may have synergistic activities or buffer toxic effects of other components. In addition, extracts from a mixture of herbs may have more therapeutic or cancer-preventive activities than a herb alone. Several studies have demonstrated that extracts from some herbal medicines or their mixtures have anticancer potential and can inhibit cancer cell proliferation *in vitro* and/or *in vivo* [8].

Since CHM has performed well clinically and has shown promise for the treatment of several lung cancer symptoms, it has attracted the interest of many investigators. A number of TCM formulae have synergistic effects due to multiple ingredients which inhibit lung cancer at different stages, strengthen impaired immune system function, and improve the overall symptomatology. In addition, they have been demonstrated to ameliorate or prevent adverse side effects associated with the use of single drugs. Many studies reported that many TCM treatments increase the body's resistance to invading pathogens infectious agents that cause disease which can lead to an increase in a patient's lifespan. These treatments can also help some patients who can not accept surgery or radiotherapy.

The purpose of this review is to present those medicinal herbal extracts and compounds which have been tested for activity against lung cancer *in vitro*. Specifically, the Traditional Chinese formulae that have been tested in laboratory and clinical studies for the treatment of lung cancer will be discussed.

Classification of CHM for lung cancer

According to TCM theory, lung cancer is included under the categories describing "lung-masses", "expanding-masses", "cough", "cough blood" and "chest pain". Several ancient medical books make reference to it. For example, in "*Summary from the Golden Chest"* (Han Dynasty 206-220AD) under the five organs section, it states "the [lung] mass cannot be easily removed." In the *Huang Di Nei Jing Su Wen*, another famous book written during the Han dynasty, it refers to "difficult breathing [with lung cancer] without having difficult eating." TCM believes that lung cancer results from having a lack of healthy energy and from the accumulation of exogenous evils (outside influences that invade the body and cause illness). Lung cancer can be divided into 5 different syndromes including: 1. Yin Deficiency and Interior Heat Syndrome **(**The symptoms here include a cough without sputum or a cough with thick sputum). 2. Spleen Deficiency and Phlegm Dampness Syndrome (These symptoms include a cough that produces a great deal of sputum and chest tightness accompanied by shortness of breath.). 3. Deficiency of Qi and Yin Syndrome (These symptoms include a low and weak sounding cough, which produces a small amount of sputum which can be bloodstained). 4. Deficiency of Yin and Yang Syndrome**.** 5. Stagnation of Qi and Blood Stasis Syndrome [9].

Approximately 133 Chinese herbal medicines have been reported to possess anti-lung cancer effects. They are categorized into the five subgroups listed below [10].

Clearing heat and toxins

Herba Hedyotis Diffusae, Herba Scutellariae Barbatae, Herba Houttuyniae, Herba Solani Nigri, Fructus Bruceae, Rhizoma Paridis, Pseudobulbus Cremas-trae Seu Pleiones, Herba Selaginella Doederleinii, Herba Salviae Chinensis, Spica Prunellae, Radix Trichosanthis, Radix Rehmanniae, folium Rabdosiae Rubescentis, Radix Codonopsis, and Vene-num Bufonis.

Resolving dampness and phlegm semen

Coicis，Polyporus, Radix Stephaniae Tetran-drae, Fructus Trichosanthis, Radix Stemonae, Rhizoma Pinelliae, Bulbus Fritillariae Thunbergii, Sargassum, Thallus Laminariae or Thallus Eck-loniae, Rhizoma Arisaematis, and Semen Lepidii or Semen De scurainiae.

Regulating Blood and Qi

Rhizoma Curcumae, Radix Notoginseng, Semen Vacearíae, Radix Paeoniae Rubra, Semen Persicae, Herba Agn-moniae, Fructus Akebiae, and Pericarpium Citri Reticulatae.

Reinforcing Qi

Radix Astragali, Radix Ginseng, Radix Codonopsis, Herba Gynostemma-tis, and Cordyceps.

Nourishing Yin

Bulbus Lilii., Radix Glehniae，Radix Adenophorae，Radix Ophiopogo-nis，Radix Asparagi，and Plastrum Testudinis.

Laboratory studies

In vitro studies

The majority of laboratory studies of anticancer activities in lung cancer investigated individual CHMs. and a few have also studied immunomodulation effects. These studies have been undertaken in established animal models, such as Lewis lung carcinoma, and in human lung cancer cell lines. Based on the large body of chemical and pharmacological research, some bioactive compounds isolated from medicinal plants have been used to treat lung cancer. Each herbal medicine has specific chemical constituents which have different pharmacological and toxicological profiles. A variety of chemical constituents isolated from medicinal herbs have been studied extensively and tested for anticancer activity. The date compiled in Table 1 revealed that extracts of plant species from a wide range of families have significant anticancer activities *in vitro* and that a number of active plant-derived compounds are from various chemical classes such as akaloids, triterpenoids, flavonoids, terpenoids and polysaccharides.

Alkaloids

Solamargine (SM) [11] is an alkaloid isolated from an herb, Solanum incanum. It was found to be a powerful cytotoxic agent in four human lung cancer cell lines. Half-inhibitory concentration (IC_{50}) is the concentration of a compound needed to reduce growth of a population of cells by 50 percent *in vitro*. SM had IC_{50} value for the lung cancer cell lines, IC_{50} = 500 ng/ml. H441, H520, H661 and H69, of 3, 6.7, 7.2 and 5.8 μM, respectively. SM-induced apoptosis of these cells determines by PS (PS: phosphatidylserine, turmor necrosis factor receptor) externalization in a dose-dependent maner and increased the percentage of cells in the sub-G1 fraction of the cell cycle. SM treatment was found to increase the binding activities of TNF-alpha and TNF-beta to lung cancer cells. Then the cell lines that were intrinsically TNF-resistant became susceptible to both TNF-alpha and -beta. In addition, SM induced several apoptotic processes: release of cytochrome C from mitochondria, downregulation of anti-apoptotic Bcl-2 and Bcl-xL, increase of caspase-3 activity, and DNA fragmentation. Thus, SM can induce apoptosis and modulate expression of TNFRs and Bcl-2. Therefore, SM is a potential anticancer agent for human lung cancers that display TNF- and Bcl-2-related resistance.

Nitidine[12-13], a natural topoisomerase poison, is the well-known benzophenanthridine alkaloid found in the root of *Zanthoxylum nitidum* (Roxb.) DC (Rutaceae). In experimental studies, nitidine exhibited antitumor activity against LLC (lewis lung carcinoma). It is a DNA intercalator that is generally classified as an inhibitor of topoisomerases I and II.

A quaternary phenanthridinium alkaloid，lycobetaine, from *Lycoris radiata* (Amaryllidaceae), was reported to be antineoplastic [14]. At growth-

Table 1. Phytochemical components and mechanism of action of selected medicinal plants used to treat lung cancer

Plants	Plant compound	Cell line affected	Mechanism of apoptosis
Angelica sinensis	Acetone extract	A549 HT29 J5DBTRG-05MG	Activation of caspase 9 3 mediated via the suppression of Bcl-2 and cdk 4 expression. No activation of caspase-8.
Bupleurum falcatum	Saikosaponin D	A549	Increasing the expression of p53 and p21/WAF1proteins and induction of Fas/APO1.
Bupleurum scorzonerifli-um	Acetone extract	A549	Inhibited telomerase activity.
Coxi lachryma	Methanolic extract	A549	Inhibition of cyclin A expression and activation via caspase cascade.
Curcuma longa	Curcumin	A549 HT1299	Decreased expression of p53, bcl-2, bcl-XL.
Lithospermum radix	HIVS	DMS114	Decreased and suppressed the expression of TRAP1.
Thalictrum acutifolium	Acutiaporberine	95-D, PLA-801	Inhibited expression of bcl-2 gene and activated expression of bax gene, p53 independent.
Solanum incanum	Solamargine	A549	Increased the release of cytochrome c. Decreased the bcl-2 and bcl-XL. Increased Bax and caspase-3 activity
Scutellaria barbata	Ethanol extract	A549	Activation through caspase cascade. Increase caspase 3/7. Activation of cell cycle control genes such as STK6, MCM5, etc.
Plant pigments	Acacetin	A549	Via p53 pathway
Liliaceae plants	Isoliquiritigenin	A549	Via p53 pathway
Grapes peanuts pines and other Leguminosae family	Stilbenoids	A549	Via p53 pathway
Xanthium strumarium L	8-epi-xanthatin	A549	Inhibited microtuble interfering
Lycoris radiata (Amaryllida-ceae)	Lycobetaine	LXFL 529	Inhibited topoisomerase I and II
Zanthoxylum nitidum (Roxb.) DC (Rutaceae)	nitidine	LLC	Inhibited topoisomerase I and II
Indigofera tinctoria	Indirubin	LLC	Inhibited DNA polymerse I
Hedera colchica K. Koch	Hederacolchico-side A1	A549	Inhibited DNA synthesis
Hedera helix	beta-hederin	A549	Inhibited DNA synthesis
Nigella sativa L. seeds	alpha-Hederin	P388	Inhibited DNA, RNA, protein synthesis in a dose-and time-dependent manner
Physocarpus intermedius Schn. (Rosaceae)	ursolic acid	A549	Inhibited DNA synthesis
Cynanchum paniculatum Kitagawa	Antofine	A549	Inhibited protein synthesis
Scutellaria baicalensis Georgi	Baicalein	LXFL 529L	Inhibited 12-lipoxygenase

N.B. reference is given in the text.

inhibitory concentrations, lycobetaine inhibited topoisomerases I and II, stabilized the covalent DNA topoisomerase I intermediate (the so-called cleavable complex), and induced apoptosis.

Triterpenoids

Hederacolchicoside A1，an oleanolic acid monodesmoside ，is isolated from *Hedera colchica* K. Koch (Araliaceae) and beta-hederin (another monodesmoside oleanolic acid, isolated from *Hedera helix* and other species) have demonstrated effective cytotoxicity against A549, a human lung cancer cell line, with similar IC_{50} of about 10 mM (cisplatin, the positive control tallied 5 mM). Unfortunately, it was found to affect both cancerous as well as normal cells as similar cytotoxicity was observed for human fibroblasts [15].

Kim *et* al. found that seven triterpenes isolated from the stem bark of *Physocarpus intermedius* Schn. (Rosaceae). Of these, 3-*O*-caffeoyloleanolic acid, betulinic acid, and the methyl ester of euscaphic acid (in order of decreasing potency) were the most active *in vitro* against A549 cells, ED_{50} (median effective dose) values of 1.6, 2.0, and 3.7 mg/ml, respectively, whereas the ED_{50} for cisplatin was 11.4 mg/ml. Since ursolic acid was found in a relatively higher concentration in the extract, the authors hypothesized this compound is responsible for the strong cytotoxicity of the extract. Its ED_{50} was determined to be 4.2 mg/ml against A549 cells [16].

Saikosaponin D, one of the major components of *Bupleurum falcatum*, which can also be extracted from other species of Bupleurum and from related genuses, has been used for the treatment of various liver diseases for a long time in China [17]. It can inhibit the proliferation A549 cell line, with an IC_{50} value of 10.18 +/- 0.09 μM [18].

Flavonoids

Flavonoids，a broadly distributed class of plant pigments, universally exist in vascular plants and are responsible for much of the color in nature [19]. They are potent antioxidants that occur naturally in foods and they can inhibit carcinogenesis in rodents. Acacetin (5, 7-dihydroxy-4'-methoxyflavone), a flavonoid compound, has been reported to possess anti-peroxidative, anti-inflammatory and antiplasmodial effects [20]. It was reported that acacetin can inhibit A549 cell proliferation in a dose-dependent manner. Its IC_{50} value was 9.46 μM. The proliferation inhibitory effect of acacetin was observed to be in a dose dependent manner with A549 human lung cancer cell lines. Its IC_{50} value was 9.46 μM. The effect of acacetin on cell cycle progression of A549 with 5 μM increased the population of the G1 phase from 34.7 % to 42.6 %. DNA fragmentation of A549 was found at 12 hours and maximized at 48 hours after exposure of A549 cells to acacetin with 5 and 10 μM. In addition, it was found that acacetin increased the expression of p53 and p21/WAF1 proteins in A549 cells [21].

Quercetin, another flavonoid, can induce the interaction of nuclear factor-kappaB (NF-KB) and hypoxia inducible factor 1α (HIF-1α) in lung adenocarcinoma LA795 in mice, in combination with DDP (diamminedichloroplatinum). Thirty two T739 mice bearing metastatses of LA795 cells were randomized into four groups: a control group, a DDP group, quercetin group and quercetin +DDP group. After 24 days, tumor weight and the tumor growth inhibition rate were determined. The number of lung metastases, and the metastatic foci inhibitory rate were determined. In addition, the comparative NF-KB and HIF-1a levels in subcutaneous tumors were determined by an immunohistochemical method. The results indicated that quercetin and its combination with DDP resulted in a significant inhibition in the growth of LA795 cells *in vivo* ($P<0.05$). The combination group indicated that there was a potent synergetic effect between the two agents in decreasing metastatic foci on the lung surface. The mechanism may be due to the suppression of the expression of NF-KB and HIF-1α [22].

Baicalein, wogonin, their glucopyranosiduronides baicalin and wogonoside, and skullcapflavone II (neobaicalein) are flavonoids isolated from the root of *Scutellaria baicalensis* Georgi (Lamiaceae). They all inhibited the growth of the human tumor cell lines, LXFL and 529L (large cell lung carcinomas) at micromolar rconcentrations. In many forms of cancer, baicalein acts by inhibiting 12-lipoxygenase activity [23].

Terpenoids

A study reported that 8-epi-xanthatin and its epoxide, two xanthanolide sesquiterpene lactones from the methanolic extract of the leaves of *Xanthium strumarium* L. (Asteraceae), potently inhibited proliferation of cultured human tumor cells, including A549 cells. Their IC_{50} values were 4.5 and 3.0 μM, respectively, while cisplatin, used as a positive control, had an IC_{50} of 4.7 mM [24]. At higher concentrations (64 and 58 mM, respectively) the two xantholides showed a promising farnesyltransferase (FTase) inhibitory effect. Synthetic FTase inhibitors have demonstrated activity against various human cancer cell lines, including NSCLC [28]. An earlier study demonstrated that *X. strumarium* extracts are able to effectively inhibit tubuline polymerization in mammalian tissues [25], which could be a plausible mechanism for these findings.

Polysaccharides

Coriolus vesicolor is also known as Yun Zhi or "cloud mushroom" in Chinese. TCM practitioners of centuries ago understood that this mushroom has special health properties which seem to be useful for maintaining general health and delaying normal aging processes if taken appropriately [9]. Polysaccharopeptide (PSP) is the active ingredient of Yun Zhi responsible for its health benefits. PSP has been shown to manifest immunomodulatory and anticancer properties in both pre-clinical experiments and in clinical trials. Several studies reported that PSP possesses selective anti-cancer activity against certain cancer cells *in vitro*. PSP in dose-dependent and time-dependent manners suppresses proliferation of human cancer cell lines [9]. PSP markedly inhibited the growth of several human cancer cell lines including lung cancer cell lines *in vitro* [26]. Significant reductions in tumor size occurred after prolonged administration of PSP in mice inoculated with Lewis lung carcinoma. Since there is a lack of clinical trials on the efficacy of PSP in lung cancer treatment, a clinical study was conducted by Dr. Kenneth Tsang at the University of Hong Kong's School of Medicine in 1999 on the effect of PSP treatment in patients with advanced non-small cell lung cancer. This study suggested that PSP treatment may be of some benefit in these patients [27-28].

Other extracts from CHM with anticancer potential

Coxi lachryma (or Adlay seed) has long been used not only in TCM, but also as a nourishing food. The methanolic extract of the Adlay seed was tested and found that it inhibited the proliferation of A549 cells in a dose-dependent manner with an IC_{55}-IC_{65} of 100 μg/ml. It (300 μg/ml) also induces time-dependent degradation of PARP from 116 kDa to 85 kDa during treatment of A549 cells [29].

The root of *Angelica sinensis*, also known as “Dang Gui”, is a popular herbal medicine and has been widely used in China for gynecological diseases for some time. Bio-based assay for extracts of *Angelica sinensis* showed that the acetone extract (AE-AS) induced dose-dependent antiproliferative effects in A549, HT29, DBTRG-05MG and J5 human cancer cells. The IC_{50} values of AE-AS in these cell lines ranged from 35-50 μg/ml after 24 h of treatment [30].

Indirubin (isoindigotin, indigo red), named Qing Dai in TCM, has been effectively used as an antileukemic agent. It is a bisindole derivative and the red-color isomer of indigo. It is isolated from *Indigofera tinctoria* (Fabaceae). Indirubin can also be extracted from the leaves of *Baphicacanthus cusia* (Acanthaceae), *Polygonum tinctorium* (Polygonaceae),

Isatis indigotica (Brassicaceae), and *Indigofera suffrutticosa* (Fabaceae) [26]. Indirubin inhibits LLC in mice. It exerts its anticancer effects by inhibiting DNA polymerase I activity and therefore, DNA synthesis. It inhibited DNA synthesis in several cell lines, in a cell-free assay, and *in vivo* in rats with Walker-256 sarcoma [19, 31].

In another study it was found that two types of Chinese traditional herbs, *Rhizoma curcumate zedoariae* and *Herbra trifolii repentis* acted synergistically and in a dose-dependent manner to induce more A549 cell apoptosis than treatment with either agent alone (P<0.01) [32].

Traditional formulas with anticancer effects studied *in vitro*

Traditional formulas containing combinations of herbal medicines have the potential to become therapeutics of choice due to synergistic effects that inhibit lung cancer at different stages, strengthen impaired immune function and improve overall symptomatolgy. The formulas were based on traditional understanding, clinical experience and knowledge of the pharmacological actions of individual herbs.

Chinese medicinal decoction of FU ZHENG HE JI Decoction that had been reported to have anticancer activity against LA795 cells in mice. It had shown the effect of reducing side effects due to chemotherapy. Compared with the control group, the group treated with the herbal formula decreased the effect of IL-6, and increased the quality of TUF- a, IL-2 (cytokines) in mice [33]. This formula contains primarily Codonopsis (*Codonopsis radix*), ligustrum (*Ligustri lucidi* Fructus), astragalus (*Astragali adix*), Chinese angelica (*Angelicae radix*) and yellow essence (*Plugonati rhizoma*). It significantly promotes apoptosis of cancer cells. The formula was shown to spleen Qi, nourish the blood, enrich Yin and supplement the kidney at the same time quicken the blood and transform stasis in the body [9].

The effects of Yi Qi Huo Xue (YQHX) on human cancer cell lines, A549 and small cell lung cancer (NC-H446), were studied *in vitro*. Several methods were used to exam cell proliferation and migration, including cytometry, imunohistochemistry, imaging techniques, a Boyden chamber method and expression of E-CD for cell migration. The quantity of two strains of cells crossed Matrigel and polyvinylpyrrolidone-free polycarbonate filter were significantly more than the controlled group (P<0.01). YQHX inhibited the proliferation of A549 or NC-H446 cells while enhancing the expression of E-CD. In addition, it decreased migration of these cells *in vitro* [34].

Sangenquliu decoction and Sansi mixture demonstrated inhibitory effects on Lewis lung carcinoma growth and metastasis in mice [35, 36]. Some other formulae had anti-tumor activity due to modulation of the host's immune system. It is reported that the QiJia Mixture had antitumor effects in Lewis lung carcinoma-bearing mice and that this was probably due to augmentation of T and B lymphocyte activity [37].

Metastasis in advanced stages of cancer has significant implications for prognosis and clinical management. Studies of administering the herb mixture Xiao Chai Hu Tang in mice suggested that it effectively inhibited Lewis lung carcinoma growth and metastasis and that these effects might be associated with macrophage activation and augmentation of NK cell activity, as well as increases in interferon activity and interleukin-6 levels in serum [38].

Clinical studies

Human studies and potential health and therapeutic applications

TCM may elevate the efficacy of chemotherapy. Often the combined treatment of western medicine and TCM produces better outcomes than using either method alone. TCM may reduce symptoms and improve

physical performance and clinical efficacy [9]. It should be mentioned that the combinations of chemotherapy and Chinese medicine and herbal products are commonly used by patients [39].

To evaluate the effect of Chinese herb medicine Wei Mai Ning on the quality of life (QOL) and immune function of patients with advanced lung cancer, 63 patients with advanced lung cancer and prognoses of more than 3 months survival underwent 3 cycles of treatment. The QOL in the chemotherapy plus Wei Mai Ning group improved significantly compared with the group treated with chemotherapy alone (P<0.01). The clinical benefis were evaluated using Karnofsky Performance Status (KPS) scores. The KPS score is a system that evaluates changes of physical fitness of patients and changes in body mass. The stability rate of KPS scores and of body mass in the chemotherapy plus Wei Mai Ning group were significantly higher (65 % and 38 %, P<0.05) than those of the group treated with chemotherapy alone (68 % and 34 %, P<0.01). The toxicity response was evaluated according to the classification of the World Health Organization (WHO) criteria (0-IV rating). The white cell number was reduced and nausea and vomiting were more serious in the group treated with chemotherapy alone compared with the group treated with chemotherapy plus Wei Mai Ning (P<0.05 and P<0.01. Treatment with the combination did not induce any serious toxicity. Clinical symptoms such as cough and shortness of breath in both groups were released. In addition, the number of T cells in the group treated with three cycles of chemotherapy plus Wei Mai Ning was increased compared with the number present prior to treatment (after, (2.23± 0.7)，before, (1.90±0.6), P<0.051). So Wei Mai Ning combined with chemotherapy yields low toxicity and significantly improves the QOL and immune function of patients with advanced lung cancer [40].

Treatment with Jin Fu Kang Oral Liquid compounded with *Radix Astragali, Radix Glehnine, Radix Ssparagi, Fructus Liqustri Lucidi, Rhizoma Paridis et al*. were studied in a group of 290 NSCLC inpatients that were in a prospective prognostic sdtudy by a cooperative group. They were divided randomly into 4 groups: group A treated with JFK, group B treated with chemotherapy, group C treated with JFK plus chemotherapy. After treatment, the symptoms, KPS score (measuring QOL) and immune parameters (serum levels of NK, IL-2, CD^{3+}, CD^{4+}, CD^{8+}) were all improved in groups A and C, compared with those in group B. No deleterious side effects occurred in group A. In group B there were toxicities mainly in bone marrow depression, decreases of blood white blood cells, and hair loss. However, the toxicities were lower in group C than in group B (P<0.01) [41].

Qing Re Jie Du decoction is another traditional Chinese formula. The efficacy, side effects and QOL of patients treated with vinorelbine (NVB) plus cisplatin (DDP) (NP regimen) alone or combined with the Qing Re Jie Du decoction were compared during studies of NSCLC. A total of 72 patients (stage III-IV) were randomly divided into an observation group (40 patients) and a control group (32 patients). The efficacy rates in the observation group (52.5 %) were significantly higher than those in the control group (45.0 %) with a P value <0.05. In the observation group，the scores calculated by KPS were higher than those in the contro1 group (P<0.001)，and the degrees of hypo1eukocytosis or platelet reduction were lower with a P value < 0. 001) [42].

Ai Di injection, when combined with chemotherapy, was found to be helpful in improving clinical symptoms and the QOL in patients with medium to advanced lung cancer. Seventy two patients were enrolled in a study and divided randomly into two groups. Thirty-seven patients received Ai Di injection in combination with chemotherapy (the study group), and 35 patients received chemotherapy alone (the control group). The response rates in the study group and control group were 51.4 % and 54.3 %, respectively. However, the clinical symptoms and QOL were significantly different between the two groups, P =

0. 035 in the study group and 0.019 in the control. Ai Di is prepared primarily from ginseng (*Ginseng radix*), astragalus (*Astragali radix*), mylabris (*Mylabris*), and *Acanthopanax senticosus*. This preparation has been used to reduce heat fever, resolve toxicity and treat abscesses [43].

A study of 235 patients with lung cancer was performed in Shandong Tumor Hospital, Jinan, China from 1994 to 1997. Treatment was with a formulation containing *Codonopsis Tangshen Radix*, *Astragali Radix*, *Atractylodis Macrocephalae Rhizoma, Ophiopogonis Radix Recens*, *Angelicae Sinensis Radix*, *Spatholobi Caulis*, *Houttuyniae Herba*, *Fritillariae Thunbergii Bulbus*, *Glycyrrhizae Radix*, *Rehmanniae Radix Praeparata*, *and Armeniacae Semen* [44]. Observations were made of the effects of traditional Chinese herbs on chemotherapy sensitivity and toxicity. Patients (139) of the study group were treated with Chinese herbal medicine and combination chemotherapy and 96 patients of the control group were treated with combination chemotherapy alone. The difference in efficacy rates between the study group and the control group was significant with a *P* value < 0. 05. The toxicities of chemotherapy on the digestive tract, bone marrow and liver in study group were less than those in the control group ($P < 0.01$). Chinese herb medicine appears to not only prevent side effects due to chemotherapy in lung cancer, but also enhances the effects of chemotherapy.

Shen Yi capsule combined with chemotherapy can enhance the therapeutic effect and reduce side effects of chemotherapy in patients with NSCLC. Forty-one patients with NSCLC were treated double-blindly with chemotherapy plus Shen Yi capsule (Shen Yi group) and chemotherapy plus placebo (placebo group). The placebo group was compared to the Shen Yi group with respect to response rate, time to progress (TTP), median survival time (MST) and 12 year survival. Shen Yi group : response rate 45.45 %, TTP 6 months, 13 months and MST12 year survival is 68.18 %. There was a statistically significant difference between these two groups ($P < 0.05$) with no adverse reactions found in the two groups [45].

Fu Fang Ban Ao capsule is capable of increasing the activity of NK cells which aid in killing cancer cells [46]. It appears to be useful in the patients who can not accept the chemotherapy. Patients (200) who could not receive surgery in their stage of NSCLC (stage III, IV) were treated with the Fu Fang Ban Ao capsule [46].

Conclusions

Laboratory and clinical studies such as those reported above provide an understanding of some facts of CHM with regard to their effects and potential mechanisms of action in the lung cancer. However, it is important to point out that CHMs are most commonly used as a formula, that is, a with several herbal substances combined. TCM commonly uses herbs not only to relieve symptoms, to stop disease progression, and to restore healthy functioning of the individual, but also to ameliorate or prevent adverse side-effects linked to toxicity of individual drugs. Detailed information concerning formulations, such as the precise ingredients, amounts, and the methods of preparation are critical for interpreting possible benefits of these formulae in the management of lung cancer.

Treatment of lung cancer is complex and appears to be able to benefit from TCM. Therefore, the pharmacological study of TCM medicines should be encouraged. It is hoped that the search for new medicinal compounds is likely to provide more potent anticancer agents. The discovery of anticancer drugs in Chinese botanicals should make important additions to cancer therapy in the future.

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