Lung Cancer Prevention and Therapy Using the JinFuKang Herbal Mixture

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Abstract Traditional Chinese Medicine (TCM) plays an indispensable role in China for both cancer prevention and adjuvant treatment in platinum-based chemotherapy. A number of naturally occurring products from Chinese herbal extracts have shown inhibitory effects against carcinogenesis. One example is JinFuKang which is a mixture of 12 Chinese herbs and has been used widely in China for the prevention and treatment of lung cancer. JinFuKang has been shown to inhibit tumor growth in human lung and liver cancer xenograft mouse models. Among all the herbal agents that contain the *Astragalus membranaceus* (Fisch), JinFuKang was found to be effective in improving the 24-month survival of lung cancer patients in combination with platinum-based chemotherapy. This review article will discuss the application of JinFuKang to cancer prevention and treatment.

Keywords Traditional Chinese Medicine · Chinese herbs · JinFuKang · Cancer · Prevention · Therapy

Abbreviations

ACF	Aberrant crypt foci
β-Ep	β-Endorphin
BUN	Blood urea nitrogen
CR	Complete remission
CRE	Serum creatinine
CTL	Cytotoxic T lymphocyte
CTX	Cytoxan
DDP	Di-N-Decyl phthalate
DMH	1, 2-Dimethyl hydrazine
E2	Estradiol
EGFR	Epidermal growth factor receptor
EGFR-TKIs	Epidermal growth factor receptor-tyrosine kinase inhibitors
GI	Gastrointestinal
GP	Gemcitabine/cisplatin
GPT	Glutamate pyruvate transaminase
IL-2	Interleukin-2
JFK	JinFuKang
KPS	Karnofsky Performance Status
LAK	Lymphokine-activated killer cells
LRP	Lung resistance protein
MAP	Mitomycin, doxorubicin, and cisplatin
MRP	Multidrug resistance associated protein
NC	No change
NK	Natural killer
NS	Normal saline
NSCLC	Non-small cell lung cancer
OKT4+	Helper/inducer T cells
PD	Progression of disease
P-EGFR	Phosphorylated-EGFR
PLT	Platelet
PR	Partial remission
RCT	Randomized controlled trial
TCM	Traditional Chinese Medicine
Th cells	T helper cells
Th1	T helper 1
Th2	T helper 2
VEGF	Vascular endothelial growth factor
WBC	White blood cell

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Introduction

JinFuKang was originally developed in Shanghai Longhua Hospital, one of the largest traditional Chinese medicine hospitals in China [1, 2, 3••]. In addition to the extensive clinical use of JinFuKang as an adjuvant therapy in cancer patients in China [1, 2, 3••, 4•], JinFuKang has been shown to inhibit tumor growth in animal models by reducing tumor volume in nude mice receiving xenografts of human lung and liver cancer cells [5, 6•]. Among all the herbal agents that contain the herb *Astragalus membranaceus* (Fisch), JinFuKang was found to be one of the most effective agents in improving survival of lung cancer patients as an adjunctive therapy given with platinum-based chemotherapy [4•]. Based on these studies, JinFuKang became one of the major herbal formulations dispensed to lung cancer patients in China. JinFuKang was approved by the Chinese State Food and Drug Administration in 1999 for the treatment of lung cancer (State Approval Number Z19991043). Although the specific constituents of JinFuKang are a trade secret, the individual components and their proportions in the mixture have been previously disclosed (see Table 1 for details) [7••]. JinFuKang is formulated as syrup sealed in glass bottle. Even though the active ingredients in JinFuKang are not known at this moment, their pharmacological, pharmacokinetic, and biopharmaceutical properties have been reported [6•, 8, 9•, 10]. These results also suggest that JinFuKang could be a potent cancer chemopreventive agent, and future preclinical and clinical studies should explore this important area.

Preclinical Studies

JinFuKang has undergone a series of preclinical studies that revealed inhibition of cancer cell growth as well as enhancing immune function (see Tables 2 and 3). The mechanisms include improvement of the T cell immunity [12, 13], reversion of drug resistance [16], inhibition of cancer cell proliferation [15], and induction of apoptosis [19].

JinFuKang prevented colon carcinogenesis in animal models and, thus, could be further developed in colon cancer prevention. In the mouse model of 1,2-dimethylhydrazine (DMH)-induced aberrant crypt foci (ACF), JinFuKang reduced the number of proliferating cells significantly [1, 2]. In KunMing mice implanted with liver cancer cells, JinFuKang at a dose of 75 g/kg/day inhibited liver cancer cell growth by 54.1 % compared with the control group ($P<0.05$) [5]. In BALB/c nude mice implanted with a human hepatocellular carcinoma cell line, JinFuKang, at 75 g/kg/day, inhibited liver cancer cell growth by 32.9 % when compared with the control group ($P<0.05$) [5]. This study also found that low dose (10 g/kg/day) of JinFuKang is ideal for increasing the production of interleukin-2 (IL-2) [5]. Modulating immune response has been linked to tumorigenesis and cancer progression. The T helper cells (Th cells) play an important role in the immune system, particularly in the adaptive immune system. JinFuKang significantly increased the Th cells in C57BL/6 male mice implanted with B16 melanoma cells [14]. Another animal study showed that JinFuKang dramatically enhanced the antitumor immune response by increasing the production of T helper 1 (Th1) cytokines while inhibiting production of classical Th2 cytokines in tumor-bearing mice [13]. In C57BL/6 male mice implanted with Lewis lung adenocarcinoma cells, JinFuKang (30 g/kg/day) enhanced the cytotoxic T lymphocyte (CTL) in the tumors and tumor growth was significantly inhibited in the JinFuKang group when compared with the control group ($P<0.01$) [12]. In vivo studies relying on Lewis lung carcinoma grafts also revealed that JinFuKang inhibits tumor growth, increases weight in mice, elevates natural killer (NK) cell number,

Table 1 Composition of JinFuKang (adapted from reference [7••])

Latin name	Chinese name	Plant part	Weight[a] (g)
Astragalus membranaceus	Huang Qi (黄芪)	Root	146
Glehnia littoralis	Bei Sha Shen (北沙参)	Root	146
Asparagus cochinchinensis	Tian Men Dong (天门冬)	Root	49
Ligustrum lucidum	Nv Zhen Zi (女贞子)	Fruit	49
Selaginella doederleinii	Shi Shang Bai (石上柏)	Leaf	146
Paris polyphylla	Chong Lou (重楼)	Root	73
Epimedium sagittatum	Yin Yang Huo (淫羊藿)	Leaf	49
Gynostemma pentaphyllum	Jiao Gu Lan (绞股蓝)	Leaf	49
Cornus officinalis	Shan Zhu Yu (山茱萸)	Leaf	49
Salvia chinensis	Shi Jian Chuan (石见穿)	Fruit	146
Ophiopogon japonicus	MaiDong (麦冬)	Root	49
Trigonella foenum graecum	HuLuBa (葫芦巴)	Seed	49

[a] Amounts of materials needed to produce 1 L of finished product, which is syrup. Each dosage contained 10 mL

Table 2 Chemopreventive effects of Chinese herbs in animal models

References	Models in vivo	Antitumor effects	Mechanism
[1, 2]	DMH-induced colon cancer	Anti-proliferation of ACF Middle colon: 24 h: JFK 1.99±0.42; Ctr 5.10±0.26 48 h: JFK 2.86±0.20; Ctr 5.10±0.26 Descending colon: 24 h: JFK 2.42±0.29; Ctr 4.56±0.18 48 h: JFK 2.40±0.27; Ctr 4.24±0.13 Anti-apoptotic of ACF Middle colon: 24 h: JFK 2.98±0.13; Ctr 1.22±0.24 48 h: JFK 2.44±0.27 Ctr 1.46±0.12 Descending colon: 24 h: JFK 2.44±0.15 Ctr 1.40±0.14 48 h: JFK 2.20±0.30; Ctr 1.44±0.15 $P<0.05$ (Ctrl: blank model, dose of JFK=1.33 mL/kg, gavage/day)	Anti-proliferation and induction of apoptosis of ACF
[5]	KunMing mice implanted with HAC liver cancer cells	Tumor load=JFK (18.75 g/kg) 1.71±0.59 g* JFK (37.50 g/kg) 1.50±0.56 g* JFK (75.0 0 g/kg) 1.11±0.44 g* CTX (100 mg/kg, i.p.×days 1, 3, 5) 0.52±0.09 g NS Ctr 2.42±0.88 g	Enhanced the antitumor activity of IL-2
[5]	BALB/C nude mice implanted with human QGY liver cancer tissue	Tumor load=JFK (37.50 g/kg) 1.20±0.31 g* JFK (75.0 0 g/kg) 1.08±0.53 g* CTX (100 mg/kg, i.p.×days 1, 3, 5) 0.28±0.08 g NS Ctr 1.61±0.86 g	Enhanced the antitumor activity of IL-2
[6•]	Human lung adenocarcinoma cells Lax-83 transplanted in nude mice	Tumor load=JFK (37.50 g/kg) 1.22±0.46 g* DDP (1 mg/kg days 1–10) 0.86±0.28 g* NS Ctr 2.43±1.05 g	Induced apoptosis and abrogated tumor growth
[11]	C57BL/6 inbreeding coefficient mice with Lewis lung cancer	Tumor number of pulmonary metastasis=JFK (64.40 g/kg) 14.4±3.37* CTX (0.02 g/kg, i.p.×days 1–10) 17.2±1.98* JFK+CTX 14.8±2.9* NS Ctr 23.36±3.52 Tumor load=JFK (64.40 g/kg) 1.57±0.37 g* CTX (0.02 g/kg, i.p.×days 1–10) 1.73±0.28 g* JFK+CTX 1.48±0.26 g* NS Ctr 2.48±0.33 g	Inhibited the growth in tumor, increased weight in mice, elevated NK, LAK, IL-2 levels, and decreased β-Ep and E2 level
[12]	C57BL/6 male mice implanted with Lewis lung adenocarcinoma cells	Tumor number of pulmonary metastasis=JFK (15 g/kg) 5.2±1.52* JFK (30 g/kg) 3.9±1. 73* JFK (60 g/kg) 4.8±2.28* CTX (30 mg/kg, i.p.×days 1, 3, 5, 7, 9, 11, 13) 4.0±1.90* NS Ctr 8.5±2.68 Tumor load=JFK (15 g/kg) 3.16±1.29 g JFK (30 g/kg) 2.49±0.36 g* JFK (60 g/kg) 2.90±1.05 g* CTX (30 mg/kg, i.p.×days 1, 3, 5, 7, 9, 11, 13) 1.36±0.80 g* NS Ctr 4.39±1.25 g	Enhanced the CTL avidity
[13]	C57BL/6 male mice implanted with Lewis lung adenocarcinoma cells	Tumor load=JFK (25 g/kg) 1.0±0.44 g JFK (12.5 g/kg) 0.63±0.28 g* JFK (50 g/kg) 0.75±0.36 g* DDP (1 mg/kg, i.p.×6) 0.72±0.30 g* NS Ctr 1.20±0.44 g	Inhibited tumor growth by promoting Lewis adenocarcinoma of lung C57BL/6's spleen cell secreting Th1 cellular factor, and improve T cell immunity

Table 2 (continued)

References	Models in vivo	Antitumor effects	Mechanism
[14]	C57BL/6 male mice implanted with B16 melanoma cells	Tumor number of pulmonary metastasis=JFK (60 g/kg) 19.5±6.74* DDP (1 mg/kg, i.p.×days 1–21) 18.50±7.13* NS Ctr 29.10±9.35	Strengthened the immune functions, aroused the antitumor ability
[8]	BALB/C nude mice implanted with LAX 83 human lung adenocarcinoma cells	Tumor load=JFK (60 g/kg) 1.5±0.5 g* DDP (1 mg/kg, i.p.×days 1–21) 1.57±0.57 g* NS Ctr 2.75±0.89 g	Inhibited the proliferation and downregulation of the expression of gene
[15]	C57BL/6 male mice implanted with Lewis lung adenocarcinoma cells	Tumor load=JFK (30 g/kg) 1.71±0.49 g JFK (60 g/kg) 1.76±0.55 g JFK (120 g/kg) 1.49±0.52 g* NS Ctr 2.14±0.69 g	Blocked the cancer cells entering the S phase of the cell cycle

*$P<0.05$, compared with Ctr

lymphokine-activated killer (LAK) cells, and IL-2 levels, while simultaneously decreasing β-endorphin (β-Ep) and estradiol (E2) levels [11]. JinFuKang also inhibited lung cancer development by 49.2 % versus control in Lax-83 human lung adenocarcinoma cells transplanted in nude mice [6•]. JinFuKang had inhibitory effect on the metastasis with 33.0 % inhibition in C57BL/6 male mice implanted with B16 melanoma cells [14].

Many in vitro studies have revealed that JinFuKang may inhibit the proliferation of lung cancer cell lines, induce apoptosis, and alter gene expression. Han et al. [15] found that the inhibitory effects of JinFuKang were due to its inhibition of cell cycle progression in both human lung adenocarcinoma cell line SPC-A-1 and murine Lewis lung cancer cells. JinFuKang significantly reduced the number of S phase cells, increased G2 and M phase cells, and inhibited the proliferation of both human lung adenocarcinoma cell line SPC-A-1 and murine Lewis lung cancer cells [12]. JinFuKang's inhibitory effect on cell cycle progression was associated with downregulation of tumor and proliferative markers such as Ki-67 and c-Myc [8, 15]. JinFuKang also induces apoptosis in lung adenocarcinoma cancer cells LAX-83 by inhibition of Bcl-2 expression and induction of the expression of both Bax and Fas [6•].

JinFuKang reversed the multidrug resistance of tumor cells. One of the mechanism of the effect on reversing the multidrug resistance is reducing the expression of the drug efflux transporters. A previous study by Sun JL et al. [18] has shown that combination of low-dose JinFuKang and Di-N-decyl phthalate (DDP; 320 μmol/L) can enhance the inhibitory effect of DDP on A549 human lung adenocarcinoma cells from 47.8 to 73.3 %. It also reduced the expression of multidrug resistance associated protein (MRP) and lung resistance protein (LRP) at the mRNA level in human lung adenocarcinoma A549 cell line [18]. PC-9 is a cell line derived from a patient with lung adenocarcinoma, harboring an epidermal growth factor receptor (EGFR) exon 19 in-frame deletion [E746-A750] that is highly sensitive to EGFR-TKIs [20]. PC-9/GR is a gefitinib-acquired resistant cell line that was established by chronic exposure of PC-9 cells to the medium with increasing concentrations of gefitinib [21]. JinFuKang also could reverse the resistance to gefitinib in PC-9/GR (resistant cells) cell lines by inducing tumor cell apoptosis, downregulating the expression of phosphorylated-EGFR [16], and enhancing G2/M cell cycle arrest while increasing expression of caspase-3 and capase-8 [17].

Pharmacokinetics (PK) Studies

In a reported pharmacokinetic study, changes in docetaxel pharmacokinetics in 21 patients with advanced non-small cell lung carcinoma (NSCLC) were determined. The area under

Table 3 Antitumor effects of JinFuKang in vitro models

References	Cell culture in vitro	Antitumor effects	Mechanism
[16]	Human lung adenocarcinoma cell lines PC-9 gefitinib-acquired resistant cell line PC-9R	MTT: JFK+gefitinib: 48 h IC_{50}=0.2 μmol/mL, reverse gefitinib resistance multiples=2.5, Q value=2.32 P-EGFR mRNA expression Blank Ctr 5.57±1.05 JFK 2.84±0.10* Gefitinib 3.12±0.44* JFK+gefitinib 1.51±0.04**	Reversed gefitinib resistance by downregulate p-EGFR expression
[17]	Gefitinib-acquired resistant cell line PC-9R	G2 cycle cell number JFK+gefitinib 25.44±0.65 Gefitinib 15.907±1.22*** JFK 6.90±0.38*** Ctr 3.97±0.86 Apoptosis JFK+gefitinib 13.06±1.71 gefitinib 8.57±3.07*** JFK 5.93±0.63*** Ctr 4.54±0.85 Increased positive expression rates of caspase-3 and capase-8 ($P<0.05$)	Reversed resistance to apoptosis of human lung adenocarcinoma cell line PC-9R with gefitinib resistant by increasing expression rates of caspase-3 and capase-8
[18]	Human lung adenocarcinoma A549/DDP line cell	JFK low-dose drug serum can reverse multidrug resistance of A549/DDP line cell to DDP; reversing resistance multiples is 3.45 JFK low-dose drug serum+DDP (320 μmol/L) raise the rate of inhibition of DDP to A549/DDP from 47.75 to 73.32 % and Q value >1.15	Reduced the expression of MRP mRNA-LRP mRNA of A549/DDP line cell. JinFuKang oral liquid can reverse multidrug resistance of tumor line cell maybe by reducing the expression of the member transport-protein
[6•]	Human lung adenocarcinoma cell line LAX-83	Apoptotic rate JFK 17.5±3.6 (%) DDP 11.2±2.5 (%)**** Ctr 10.1±1.4 (%)****	Lowering the Bcl-2 gene protein expression, protein expression is closely related to the increased Bax and Fas gene
[15]	Human lung adenocarcinoma cell line SPC-A-1 and murine Lewis lung cancer cells	The proportion of cells in S phase of the treated groups with JFK was lower than that of the control group ($P<0.05$) JFK (120 g/kg/day): 72.6 % of the cells were stag noted in G0/G1 phase ($P<0.05$) JFK (2 mg/mL): The inhibiting rates of DNA, RNA, and protein in murine Lewis lung cancer were 7.4, 23.73, and 23.31 %, respectively. In SPC-A-1 cell line, the inhibiting rates were 9.3, 10.1, and 14. 7 %, respectively ($P<0.05$)	Blocked the cancer cells entering the proliferative phase resulted from its inhibition of DNA

*$P<0.05$, compared with Ctr; **$P<0.05$, compared with gefitinib; ***$P<0.05$, compared with JFK+gefitinib; ****$P<0.05$, compared with JFK

the curve at infinity was estimated to be 104, whereas clearance rate was estimated 3.8 L/h. More than 40 % of patients experienced at least a 33 % increased level of docetaxel; a trend is seen although the association is not statistically significant that JinFuKang alters the pharmacokinetics of docetaxel [7••]. In 271 cases of stage II–IV NSCLC patients, there is no change of liver and renal function of 127 cases in the JinFuKang group and 80 cases in the JinFuKang combined with mitomycin, doxorubicin, or cisplatin (MAP) in chemotherapy [9•]. In another larger sample randomized controlled study with 290 cases, this chemotherapy regimen, without the addition of JinFuKang, resulted in a 63.3 % decrease in total white blood cell (WBC) numbers, 26.7 % decrease in platelets (PLT), 14 % increase of glutamate pyruvate transaminase (GPT), and 12.2 and 7.8 % increase of blood urea nitrogen (BUN) and serum creatinine (CRE). Gastrointestinal (GI) reaction and hair loss were 52.2 and 74.4 %, respectively. However, when chemotherapy was combined with JinFuKang; many of these adverse events were attenuated. Specifically, the combination of traditional chemotherapy with JinFuKang resulted in a 43 % decrease in WBC, 18 % decrease of PLT, 3 % increase of GPT, and 4 % increase in BUN and CRE levels. GI reaction and hair loss were 17 and 35 %, respectively. Not only that it causes no side effects, JinFuKang also reduces toxicity of chemotherapy occurrence rates [3••].

Clinical Trials of JinFuKang in Patients With Lung Cancer

Investigators at Shanghai Longhua Hospital enrolled more than 1000 lung cancer patients in randomized clinical trials (RCT) of JinFuKang, and they have shown that JinFuKang as the first-line therapy could significantly (i) improve the immune function in lung cancer patients [3••, 9•, 14], (ii) improve the quality of life in patients with lung cancer [3••, 9•, 14], and also (iii) JinFuKang improves chemotherapeutic effects and decreases toxicities in adjuvant therapy [3••].

As reported by Liu JX et al. [9•], 271 patients with NSCLCs were enrolled in a clinical trial from 1991 to 1997 in Shanghai Longhua Hospital. The 271 patients were randomly assigned to three groups. In this study, 88 % of the patients treated with JinFuKang combined with chemotherapy showed a positive response compared with 81 % of the patients treated with JinFuKang alone showed a positive response, and 72 % of the patients treated with chemotherapy alone showed a positive response ($P < 0.01$) [9•]. A positive response is defined as patients showing complete remission (CR), partial remission (PR), or stable disease (SD) in response to the treatments. Similarly, distal metastasis was observed in 20 % of the patients treated with JinFuKang combined with chemotherapy, in 23 % of patients treated with chemotherapy alone [9•].

A positive response is defined as patients showing CR, PR, or SD in response to the treatments. The 1-, 2-, 3-, and 4-year survival rates were 73.1, 32.0, 13.2, and 13.2 % in the JinFuKang group, respectively; 71.9, 46.4, 29.2, and 23.4 % in JinFuKang combined with the chemotherapy group, respectively; and 37.6, 13.7, 9.7, and 0 % in the chemotherapy group, respectively. In this study, Karnofsky Performance Status (KPS) was elevated in JinFuKang and chemotherapy combined with the JinFuKang treatment groups versus chemotherapy alone. The results showed that JinFuKang could increase KPS scores by increasing survival rate and the quality of life, and enhancing the immune function of NSCLC patients [9•].

Another study by Liu JX et al. [22] reported that between 1992 and 1994 on 173 lung cancer patients, the response rates were 63.5 % in the JinFuKang group, compared with 60.0 % in the chemotherapy and 71.2 % in the JinFuKang plus chemotherapy group. The 1- and 2-year survival rates were 67.3 and 67.3 % in the JinFuKang group, 40.3 and 0 % in the chemotherapy group, and 66.7 and 66.7 % in the JinFuKang plus chemotherapy, respectively. After treatment, the symptoms, KPS, and immune parameters (NK, LAK, IL-2, $CD3^+$, $CD4^+$) were all improved with the treatment of JinFuKang ($P < 0.05$). The study suggested that JinFuKang could increase survival rate and quality of life and enhance the immune function in NSCLC patients when combined with chemotherapy [22].

In another clinical trial, Wang ZC et al. [23] recruited 115 patients with NSCLCs from 2008 to 2011. They found that the objective response rate (CR+PR+NC) was 68.4 % in the JinFuKang group, compared with 54.3 % in gemcitabine/cisplatin (GP) group and 78.6 % in JinFuKang combined with gemcitabine/cisplatin ($P < 0.05$). JinFuKang plus gemcitabine/cisplatin chemotherapy decreased the incidence rates of new metastases, lymph node metastasis, and distant metastasis versus either JinFuKang or gemcitabine/cisplatin treatment alone ($P < 0.05$). In addition, Wang ZC et al. found that vascular endothelial growth factor (VEGF) blood levels in patients decreased significantly after the treatment of JinFuKang alone or JinFuKang plus gemcitabine/cisplatin ($P < 0.05$) [23]. A clinical study showed that JinFuKang could modulate the ratio of Th1/Th2 cells in patients [24]. The percentage of CTL ($CD8^+CD28^+$) and the ratio of CTL/$CD8^+$ T cells were markedly increased in patients treated with JinFuKang ($P < 0.05$), indicating that JinFuKang could promote activation of CTL and its cytotoxic activity [25].

One of the largest phase II trial was conducted to evaluate the chemotherapeutic efficacy of JinFuKang in 290 mostly (>72 %) stage II/III NSCLC patients [3••]. Patients that received chemotherapy plus JinFuKang exhibited a 42 % of either complete or partial response, while the patients that received chemotherapy alone showed a 23 % response (either complete or partial response) ($P < 0.01$) indicating that

JinFuKang has a strong efficacy in treating relatively early stages of lung cancer patients [3••]. In addition, the symptoms, KPS, and immune parameters (NK, IL-2, CD3^{+}, CD4^{+}, CD4^{+}/CD8^{+}) were all improved in the JinFuKang group and the JinFuKang plus chemotherapy as compared to the chemotherapy group. The side effects due to toxicity of the chemotherapy were significantly lower in the JinFuKang plus chemotherapy group than the chemotherapy alone group ($P<0.01$). JinFuKang plus chemotherapy has markedly increased efficacy, and JinFuKang appears to have an ability to decrease the side effects of the chemotherapy [3••]. JinFuKang appears to have a strong efficacy in treating early stages of lung cancer patients [3••].

A more recent clinical trial was conducted to evaluate the chemotherapeutic efficacy of JinFuKang in stage IV NSCLC patients (>90 %) [7••]. In this trial, 21 patients received docetaxel (day 1) plus JinFuKang (~40 ml t.i.d., or 75 ml/m^2/day, days 4–28). Only 16 patients completed 1 cycle. After 1 cycle, 9 withdrew because of disease progression (7) or toxicity (2) and only 7 completed 2 or more cycles, and none showed improvement suggesting that JinFuKang has limited effects on very late stage (stage IV) NSCLC patients. The trial was considered to be *unsuccessful* because only 7 patients completed treatments. Since it only enrolled patients with very advanced stages of lung cancer (>90 stage IV patients), the outcome is quite different from the previous large phase II trial [3••]. These studies suggest that JinFuKang is more effective in patients with early stages of lung cancer.

Future Perspectives and Conclusions

To certain degrees, the cancer-preventive effects of Chinese herbs have been supported by results from laboratory animals, cell cultures, and epidemiological and clinical studies. A typical chemopreventive agent should have an outstanding safety profile, efficacious, and be amenable to oral administration, which makes JinFuKang an ideal chemopreventive agent. In additional to the long-term and safe clinical experiences in humans, JinFuKang is orally active. JinFuKang is one of the most promising traditional Chinese herbs for lung cancer chemoprevention because it has been used for a long period of time in China by a large population with a good safety profile. Several clinical studies have been conducted in China with the largest phase II trial to evaluate the chemotherapeutic efficacy of JinFuKang in 290 mostly (>72 %) stage II/III NSCLC patients [3••]. Patients receiving chemotherapy plus JinFuKang exhibited a response rate of 42 % (either complete or partial response), while the patients receiving chemotherapy alone showed a 23 % response (either complete or partial response) ($P<0.01$), which indicates that JinFuKang is efficacious addition to therapy in earlier stage disease in lung cancer patients [3••].

Similarly, JinFuKang is expected to be effective in a chemoprevention setting. Secondly, it is prepared in a GMP facility (GMP refers to the Good Manufacturing Practice Regulations by the US Food and Drug Administration), allowing the standardization for the preparation of the herbal materials. Although JinFuKang has shown profound effects on lung cancer, further mechanistic studies are urgently needed to understand the basis of its efficacy against some types of cancer. In general, future research efforts to develop herbal mixtures should focus on those with lower toxicity and higher efficacy for specific types of cancer through the inhibition of specific molecular targets or pathways.

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