

Progress in pharmacodynamics and clinical studies of active components of Coix Seed (Semen Coicis) and its preparation - Kanglaite Injection (KLT)

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[ABSTRACT] Objective: A brief summary of recent progress in pharmacodynamics and clinical studies of active components of a TCM herbal medicine-Coix Seed and its preparation-Kanglaite Injection. **Method:** Based upon the references published at home and abroad, a review has been written on the pharmacological actions of Coix Seed and its preparation-Kanglaite Injection as well as its clinical studies. **Results:** Coix Seed and its preparation-Kanglaite Injection have antitumor and immunomodulating actions.

[KEY WORDS] Coix Seed; Coix Lacryma-jobi; Active component; Preparation; Kanglaite (KLT); Pharmacodynamics; Antitumor action; Immunomodulation; Mechanism of action; Clinical studies

Introduction

Coix Seed is the dried seed obtained by removing the hard husk of the fruit of *Coix Lacryma-jobi* L. Var. *ma-yuen* (Roman) Stapf (a cultivated plant of grass family). It is mainly cultivated in provinces such as Zhejiang, Fujian, Hebei, and Liaoning of China and used as Traditional Chinese Medicine. The drug has been recorded in many ancient medical and herbal books such as 《Compendium of Materia Medica》 as well as in Chinese Pharmacopoeia 2005 edition Part I, in which it is described to have functions of invigorating the spleen for eliminating dampness, removing stagnation and arresting diarrhea, clearing away heat and drainage of pus, and thus can be used for treating edema, beriberi, oliguria, damp arthralgia and spasm, diarrhea due to hypofunction of the spleen, pulmonary abscess, acute appendicitis, and flat wart.

It is well known that Coix Seed has been widely used in prescriptions by Chinese doctors in treatment of tumors. Starting from 1975 the author began to study the method to extract the anticancer component from Coix Seed and found that glyceride in Coix Seed possessed antitumor action. Afterwards, the author successfully developed the intravenous Kanglaite Injection (hereinafter referred to as KLT) (US patent No.: US5444089), which has also been industrialized. The drug was approved to use clinically as a prescription antitumor drug in China and Russia. The new compounds-triglycerides of Coix Seed discovered by the author had obtained invention patents in countries like China, Japan, USA, etc. According to incomplete statistics, KLT has been used in treating over 600,000 cancer patients and become one of the ideal comprehensive antitumor drugs in domestic clinical oncology.

Modern pharmacological studies have demonstrated that Coix Seed and its preparation-KLT possessed extensive pharmacological activities. This paper will make a complete review on the progress in pharmacological activities studies on antitumor and immunomodulation.

1. Pharmacodynamic studies

Early modern pharmacological studies had demonstrated that Coix Seed possessed antipyretic, analgesic, and sedative effects and had stimulant effect to isolated heart, intestinal tract and uterus. Starting from 1960's, scholars at home and abroad had successively reported Coix Seed's pharmacological activities such as antitumor and immunomodulation.

1.1 Studies on antitumor activity

In 1961, Ukita Chunoshin, a scholar in Tokyo University, Japan, discovered for the first time the inhibition of multiplication of Ehrlich Ascitic carcinoma cells and prolongation of animal's survival time by the ethanolic extraction of Coix Seed given to tumor-bearing mice through intraperitoneal injection. Afterward, he confirmed that the acetone extract of Coix Seed could significantly inhibit cervical carcinoma 14(U14) and Ascitic hepatic carcinoma cells thus manifested marked antitumor activity. And he considered coixenolide to be the active antitumor component^[1]. In 1987, Japanese scholar Hikino H studied the anticancer activity of linolic acid to nude mice, mice and human cancer cell strains. His experiments revealed that the unsaturated fatty acid-linolic acid was the major anticancer component. In 1994, Numata and Mitsuhiro et al. from Bio-molecular lab, Japan National Health Institute, reported that the acetone extract of Coix Seed could significantly inhibit the activity of mice's ascitic carcinoma S180 cells and prolong the survival time of cancer-carrying mice. This antitumor component was related to certain acidic fragment which was composed of four different free fatty acids, i.e. palmitic, stearic, oleic and linolenic^[3] after infrared spectrometric analysis, GC and LC analysis. Kubota and Terumasa et al. from Tamanoi Vinegar Co., Japan, also found that the vinegar made from Coix Seed through fermentation could kill Ehrlich Ascitic carcinoma cells resulted from S180 sarcoma^[4].

Since 1995, numerous research institutes at home and abroad conducted in-depth studies on the antitumor and immunomodulation of Coix Seed and KLT, and further confirmed its antitumor activity.

Young Ju Cha et al. from Dongxin University in South Korea discovered that the inhibitory effect of methanolic extract of Gamma-irradiated Coix Seed on the growth of human carcinoma cell strains such as MCF-7 (human breast carcinoma), Calu-6 (human lung carcinoma), and SNU-601 (human stomach carcinoma) was significantly superior to that of no Gamma-irradiated one. It also had a chemotherapeutic sensitizing effect in strengthening the cytotoxicity of vincristine to AML-2/D100^[5].

A study conducted by Chang Hui-Chiu et al., Gaoxiong Medical University of Taiwan, demonstrated that methanolic extract of Coix Seed could inhibit the proliferation of A549 lung carcinoma cells through arresting cell cycle and inducing cell apoptosis. It had also been found that a dose-effect relationship existed in the inhibition of the tumor growth by methanolic extract of Coix Seed. They also demonstrated that a diet containing 30% pulverized Coix Seed would reduce the incidence of lung cancer by 50%^[6]. Another study from the university on human lung carcinoma showed that treatment with methanolic extract of Coix Seed could reduce serum PGE2 levels and inhibit the expression of COX-2 in the tumor organ of nude mice^[7].

Liang Zhiyong et al. of the Chinese Academy of Medical Sciences discovered in their studies on effect of KLT combined with gemcitabine on transplantable human pancreatic carcinoma in nude mice that the inhibition rates of KLT alone and gemcitabine alone groups were 12.24% and 13.26% respectively, while it was 40.11% in the combination therapy group which was significantly higher than those of simple therapy groups. This indicated that the combination of KLT and gemcitabine brought about synergistic effect on the inhibition of transplantable human pancreatic carcinoma in nude mice^[8]. Li Ying et al. from Dept. of Oncology, PLA's General Hospital, China, had conducted an in vitro study on KLT's synergistic effect to Taxotere (DOCETAXEL) with a human lung carcinoma 95D cells as the object. They found that KLT had antitumor and synergistic effects on human lung carcinoma cells in vitro study and the addition of KLT 18h before Taxotere had the strongest inhibitory effect on 95D cells^[9].

Prof. Li Bingsheng et al. of Shanghai Institute of Pharmaceutical Industry, China, conducted systemic pharmacological studies on KLT and confirmed that KLT had marked inhibitory effect on four xenograft human tumor models in nude mice, i.e. Lewis lung carcinoma, B16 melanoma lung metastasis, W256 carcinosarcoma, and human liver carcinoma (QGY)^[10].

Studies conducted by Li Chunhai et al. of the Military Academy of Medical Sciences, China, had shown that KLT could reduce MUCJ's expression level from 0.849 before medication to 0.244 after medication and modulate the interaction between tumor cells and stroma cells as well as vascular endothelium cells so as to inhibit the metastasis of tumor cells^[11]. Bao Ying et al. of Shanghai No.2 Medical University, China, discovered that KLT could significantly inhibit the growth of human pancreatic carcinoma 8988 cells and manifested a time and concentration dependency. There present apoptosis in 8988 cells after KLT treatment and the expression of gene P53 was significantly enhanced, while the expression of gene bel-2 declined^[12]. In addition, when they studied the effect of Coix Seed extraction on the apoptosis of human pancreatic carcinoma cells and its ultramicroscopic structure, they found that the cell apoptosis rates were $7.1\% \pm 0.6\%$, $11.3\% \pm 0.3\%$, and $15.1\% \pm 2.9\%$ respectively after the effect of 20 $\mu\text{l/ml}$ extraction of Coix seed for 24, 48, and 72 hours. These figures were significantly higher than $2.4\% \pm 1.1\%$ ($P < 0.01$)^[13] in control group. Studies from Shi Tingzhang et al. of PLA's General Hospital, China, discovered that KLT's actions on A549 cells were mainly in the

form of necrosis and growth inhibition, while the induction on apoptosis of human progranulocyte line HL60 cells was comparatively apparent. Apoptosis was prominent at small doses and the apoptosis rate reached maximum at a dose of 10 µl/ml, while at a dose of 1000 µl/ml, necrosis became the main appearance^[14]. KLT had evident inhibitory effect on HL60 cells, and also induced apoptosis of tumor cells, with a apoptosis rate of 12.05%^[15].

1.2 Studies on immuno-enhancing effect

Studies from Yonsei University, Seoul, South Korea, demonstrated that addition of Coix Seed and original brown rice into the diet of mice for 5 weeks, there would have significant difference in the number of CD4⁺ T cells and ratio of CD4⁺/CD8⁺ compared with those of the control group (P<0.05). This suggested that KLT could markedly enhance the immunologic function of mesentery^[16]. Studies from School of Medicine in Osaka University, Japan, found that the percentages of CD56⁺, CD16⁺, CD57⁺ were significantly raised after administration of Coix Seed, indicating Coix Seed could raise the number of peripheral blood cells and toxic lymphocytes, thus enhance body immunologic function^[17].

Researchers of Shanghai Institute of Pharmaceutical Industry, China, discovered “Kanglaite soft-gel capsule”, the oral dosage form of KLT could promote the multiplication of mice spleen lymphocytes, NK cell activity and IL-2 production, and could increase the number of WBC against the leucopenia caused by cyclophosphamide in tumor-bearing mice, significantly prolong mice’s hypoxia-tolerant time and swimming time, suggesting that Kanglaite soft-gel capsule had prominent immuno-enhancing effect in tumor-bearing mice, and could strengthen body’s non-specific resistant and anti-fatigue capacity^[19].

Studies by Hou Binzong et al. of School of Medicine, Jinan University, China, found that the peripheral blood NK cell activity in KLT group had been significantly raised after the first treatment course, and it continued to rise and maintained at high level in the 2nd and 3rd treatment courses, while the NK cell activity in control group gradually declined along with the development of tumor⁽²⁰⁾. Zhang Aiqin et al. of Zhejiang Provincial Tumor Hospital, China, discovered through determination of the activities of TNF-α, IL-1, and IL-6 that KLT could kill tumor cells, at the same time, had protective effect on immune organs and immunologic function^[20].

2. Clinical trials

2.1 Phase III clinical trials in China

2.1.1 KLT alone in the treatment of primary lung carcinoma

Prof. Piao Bingkui et al. of China Academy of Traditional Chinese Medicine Affiliated Guang An Men Hospital conducted “Clinical investigation of Kanglaite Injection in the treatment of primary bronchogenic pulmonary carcinoma”. Results showed that the response rate (CR+PR) of KLT treated group was 12.15%, while it was 14.29% in chemotherapy control group. The major symptoms of patients in KLT treated group were significantly improved with an overall improved rate of 78.97%, of which the improvement in chest pain, weakness, cough and short breath was relatively obvious. Patients’ quality of life could also be improved. NK cells activity, IL-2 level, and CD4⁺/CD8⁺ ratio were increased. Body’s immunologic function raised. There was a significant difference when compared with control group. In addition, no obvious impact on peripheral hemogram or no impairment on heart, liver and kidneys was ever observed^[21].

2.1.2 KLT combined with chemotherapy in the treatment of Non-small cell lung cancers (NSCLC)

Prof. Chu Datong et al. of Chinese Academy of Medical Sciences Affiliated Tumor Hospital conducted “Clinical study of combined Kanglaite Injection and chemotherapy (MVP regimen) in the treatment of Non-small cell lung cancers (NSCLC)”. The study had shown that response rate of KLT+MVP group was 45%(18/40), while that of MVP control group being 22%(7/32). There was significant difference between the two groups. KLT combined with chemotherapy could markedly improve patients’ general conditions, protect and raise blood platelet with no evident adverse reactions observed^[22].

2.1.3 KLT in the treatment of primary hepatic carcinoma

Prof. Li Peiwen et al. of Beijing Sino-Japanese Friendship Hospital, China, conducted “Clinical study of Kanglaite Injection in the treatment of primary hepatic carcinoma”. Results of this study had demonstrated that the response rate (CR+PR) of KLT treated group was 11.43%, while that of control group being 9.80%. The main symptoms of patients in KLT treated group were significantly improved with an overall improved rate of 80.95%. Patients’ quality of life, NK cells activity, CD4⁺/CD8⁺ ratio and body immunologic function were raised after KLT treatment, at the same time, no obvious influence on peripheral hemogram or no impairment on hepatic or renal functions or other adverse reactions were observed^[23].

2.1.4 KLT combined with interventional therapy in the treatment of primary hepatic carcinoma and primary lung carcinoma

Prof. Li Peiwen et al. of Traditional Chinese Medical Hospital of Zhejiang Province, China, conducted “Clinical study on Kanglaite Injection combined with interventional therapy in the treatment of primary hepatic carcinoma and primary lung carcinoma”. Results of this study had shown that (1) Of the primary hepatic carcinoma group, response rate (CR+PR) of KLT+ interventional therapy group was

69.23%, while that of interventional therapy control group being 38.24%. Of the primary lung carcinoma group, response rate (CR+PR) of KLT+ interventional therapy group was 52.11%, while that of interventional therapy control group being 28.95%. The main symptoms of patients in primary hepatic carcinoma and primary lung carcinoma groups could be significantly improved by using KLT with an overall improved rate of 82.31% in primary hepatic carcinoma group and 80.99% in primary lung carcinoma group. Patients' quality of life, NK cells activity, CD4⁺/CD8⁺ ratio and body immunologic function were raised after KLT treatment, at the same time, no obvious influence on peripheral hemogram, or no impairment on hepatic or renal functions or other adverse reactions were observed [24].

2.1.5 KLT combined with radiotherapy in the treatment of malignancy

Prof. Shen Wenjiang et al. of Beijing Medical University, China, conducted a clinical study of KLT combined with radiotherapy in the treatment of malignant tumors such as lung cancer, esophageal cancer, nasopharyngeal cancer, etc. 190 cases of cancer patients were enrolled and randomly divided into KLT + radiotherapy comprehensive group (104 cases) and simple radiotherapy control group (86 cases). The study had shown that response rate (CR+PR) of comprehensive treatment group was 82.2%, while that of control group being 60.5% with significant difference (P<0.001). Therapeutic efficacy gain factor of KLT being $82.2\%/64.4\% = 1.36$ [25].

2.1.6 KLT combined with surgery in the treatment of malignancy

Experts such as Fu Yu, Beijing Thoracic Tumor Hospital and Zhang Nugang, The Tumor Hospital attached to the Chinese Academy of Medical Sciences, and Xu Guangwei, Beijing Municipal Tumor Hospital, and others had united to conducted a therapeutic observation on the application of KLT before surgery. Results revealed that in patients who used KLT before surgery, their post-operative pathologic examination confirmed that large-sized tumor tissue necrosis exceeding >25% accounted for 62.22% (28/450), while in patients who didn't use KLT before surgery the percentage was only 26.67% (8/30). There was a significant difference between the two groups (P<0.05). No impairment on hepatic and renal functions and no influence on peripheral hemogram observed [26].

2.17 KLT in the control of cancerous pain and improving quality of life in advanced cancer patients

"Phase III multi-center clinical study on effect of Kanglaite Injection in relieving cancer pain and improving quality of life in patients with advanced cancer" presided by Prof. Li Dongdu from the Tumor Hospital affiliated to Anhui Medical University had demonstrated that the overall remission rate in 328 cases of patients with cancer pain reached 80.49% after KLT treatment. To control cancer pain, KLT could partially or completely replace morphinic analgesics, and the analgesic effect could sustain for

over 1-7 days with no addiction. The quality of life in more than 90% of advanced patients could be raised. Their immunologic function and peripheral hemogram were raised, too. No evident impairment on heart, hepatic and renal functions could be observed^[27].

2.2 Phase I clinical study in U.S

Approved by FDA of the U.S., phase I clinical study of Kanglaite Injection was performed at a designated clinical research centre - Huntsman Cancer Institute, Utah on Mar. 2001. The trial showed that KLT had been quite safe. The stable of disease, increase in weight, improvement in quality of life and general conditions and prolonged survival time after KLT treatment were similar to the results from clinical trial of KLT alone in China^[28].

2.3 Phase II clinical study in Russia

Approved by Russian Ministry of Health, phase II clinical study of Kanglaite Injection was performed at N. N. Blokhin Cancer Research Center of the Russian Academy of Medical Sciences and at Medical Radiological Research Center of Russian Federation Ministry of Health.

The trial verified the efficacy of KLT mono-therapy, sequential chemotherapy, and combined therapy. KLT combined with chemotherapy especially got better efficacy. KLT could improve patient's immunologic function and extend survival time. As to toxicity, KLT had mild side effects which were only manifested as transient hepatic enzyme rise and hypersensitive rash, etc. The safety of its medication was satisfactory^[29].

2.4 Preliminary clinical study for phase III US clinical study regimen

From Nov. 2003 to Oct. 2006, under the guidance and supervision of oncologist David S. Ettinger, US, and Michael Hensley, US expert in oncological drug research and management, and headed by Prof. Chu Datong of CAMS China and Academician A.M. Garlin of RAS Russia, a preliminary clinical study of 60 cases was conducted in a total of seven hospitals in China and Russia against clinical trial regimen "A randomized comparative clinical study of KLT+ Gemzar + Cisplatin regimen (KCG) and Gemzar + Cisplatin regimen (CG) in the treatment of stage IIIb or IV NSCLC" examined and approved by FDA. The preliminary trial had demonstrated that the response rate in KCG group reached 41.38%, and median TTP being 5.31 months, while it was 14.28% and 3.65 months respectively in CG group, with significant difference.

To sum up, a consensus has been reached at home and abroad on the antitumor and immunomodulation effects of Coix Seed's active components and its preparation - KLT. Moreover,

according to the 359 research papers collected in the data bank of Chinese Bio-Medical References: KLT has significant therapeutic effect on various malignant tumors such as lung cancer, liver cancer, and breast cancer, etc; It markedly raises body's immunological function, improves patient's quality of life and extends survival time; It can also improve clinical efficacy and reduce toxic and side effects when combined with radiotherapy and interventional therapy; Pre-operative application of KLT can significantly raise tumor's responsiveness and promote tumor's liquefaction and necrosis thus increase the success rate of the surgery; As for advanced cancer patients, KLT can effectively control cancer pain, increase body weight, and improve patient's quality of life. So far, no impairment on heart, hepato-renal functions and hematopoietic system, and other severe adverse reactions have been observed.

Discussion

Nowadays it is imperative to adopt a comprehensive treatment form with combination of TCM and Western medicine to treat malignant tumors which is significant to raise efficacy, improve patient's quality of life, extend survival time, reduce toxic and side effects of chemotherapy, adjust body's overall status, and strengthen body's immunologic function. In May 2007, FDA promulgated *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*. It explicitly indicated that the approval of an anticancer drug should be based upon the evidence of its clinical benefits such as improvement in survival, life quality and physical functioning, or improvement in tumor-related symptoms^[30]. Studies of KLT have verified that it has no evident toxic or side effects and has notable improvement to overall comprehensive clinical indicators of cancer patients. It has characteristic advantages over other anticancer drugs and has a bright prospect.

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