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Research Progress of Xiaoaiping Injection on Anti-tumor

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Abstract: *Xiaoaiping* injection is an injection solution of effective substances extracted from the traditional Chinese medicine *Tongguanteng*, which has the effects of reducing inflammation and phlegm, clearing heat, and detoxifying. *Xiaoaiping* injection has no apparent side effects, and the price of *Xiaoaiping* injection is low. *Xiaoaiping* injection is commonly used in clinical anti-tumor therapy in China and is often combined with tumor therapy such as surgery, chemotherapy, radiotherapy, and targeted therapy, and it has an excellent curative effect. Doctors and patients widely praise it. This paper summarizes the therapeutic effect of *Xiaoaiping* injection in treating breast cancer, liver cancer, lung cancer, and esophageal cancer in clinical and animal experiments. Many studies have supported that *Xiaoaiping* injection can regulate the proliferation and apoptosis of tumor cells, reduce tumor angiogenesis, and improve human immunity to achieve anti-tumor effects. During combined chemotherapy treatment, *Xiaoaiping* injection can also alleviate the adverse reactions caused by chemotherapy and significantly improve patient's quality of life. This paper summarizes the research on the anti-tumor therapy of *Xiaoaiping* injection, which provides a basis for the clinical promotion of the drug and assistance in developing traditional Chinese medicine.

Keywords: *Xiaoaiping Injection, Anti-cancer, Traditional Chinese Medicine, Clinical Application*

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Xiaoaiping injection (XAPI) is a sterile solution prepared by water extraction and alcohol precipitation from the dried cane of *Tongguanteng* through a series of modern processes. It is a common Traditional Chinese medicine anti-tumor drug in recent years (Wang, 2019). Its main chemistry ingredients are polysaccharides, saponins, alkaloids, and others, which are commonly used in anti-tumor treatments in modern clinical applications (Lu et al., 2020). Recently, some studies show that the anti-tumor mechanism of XAPI, can inhibit angiogenesis and tumor cell proliferation, block the tumor cell cycle, and induce tumor cell apoptosis to anti-cancer (Zhang, Zhong, Cheng, Tang, & Ni, 2020). Inducing tumor cell differentiation reduces the resistance of some anti-tumor drugs and improves the immunity of chemotherapy patients and others to exert their anti-tumor activity (Rao & Chen, 2018).

Traditional Chinese medicine has unique advantages in the field of treatment and development of malignant tumors. In clinical practice, some Chinese medicines have good clinical effects in the adjuvant treatment of tumors. For example, they can improve the sensitivity of patients to radiotherapy and chemotherapy drugs, enhance the effect of chemotherapy, and reduce the toxicity of chemotherapy. Synergetic chemotherapy drugs can enhance the killing effect of cancer, and it is of great value to prolong survival time and improve quality-of-life of patients with cancer, and there are no significant side effects (Cheng et al., 2018). In traditional Chinese medicine, XAPI's effect is activating blood and removing blood stasis, clearing heat and detoxification, dispelling masses, and relieving pain (Zhu et al., 2020). For this reason, this article systematically reviewed relevant literature in recent years and compared XAPI. This article reviews the chemical composition, pharmacological effects and the drug apply in clinical in recent years.

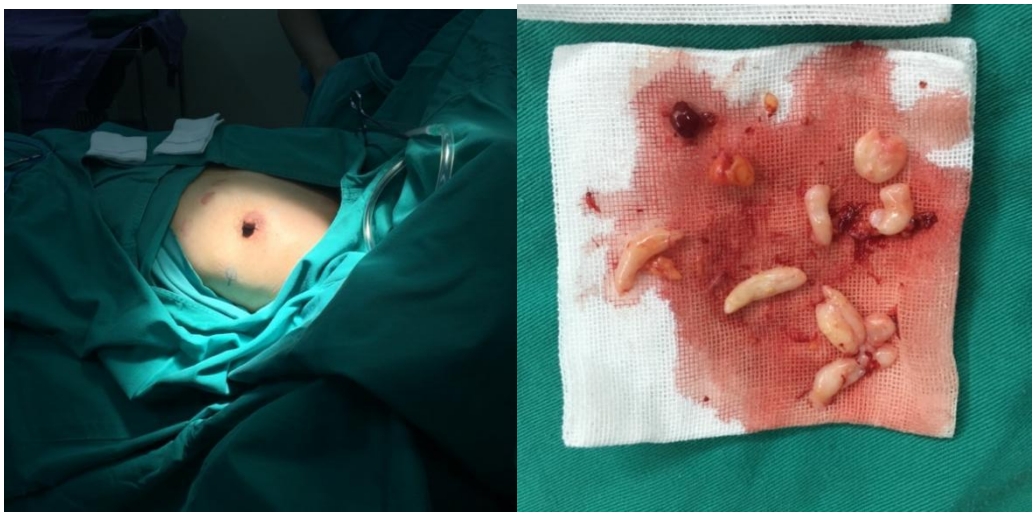

Figure 1. Breast Cancer Surgery

1. CHEMICAL COMPOSIYION

Xiaoaiping injection is a Chinese medicine injection made from dried cane stems of *Tongguanteng* through water extraction and alcohol precipitation with modern technology. The main active ingredients of *Tongguanteng* are saponins, C21-steroidal glycosides, alkaloids, polysaccharides, and chlorogenic plants. Acids, phenolic acids, organic acids, resins, pigments, etc. (Wang et al., 2019). Many of the active ingredients have anti-tumor effects. The polysaccharides and alkaloids in the active components enhance the specific immunity of the human body, while the saponins inhibit angiogenesis, and the phenolic acids decrease the oxygen free radical activity (Zhao, 2018). C21-steroid glycosides influence tumor cell growth and apoptosis (Zhang, Zhong, Cheng, Tang, Ni, et al., 2020). Moreover, there are scores of C-21 steroidal saponins isolated from *Tongguanteng*. XAPI contains 9 subtypes of C-21 (Hu et al., 2019), and a major ingredient of anti-cancer (Rao & Chen, 2018).

2. PHARMACOLOGICAL RESEARCH

2.1 ANTI-TUMOR EFFECT

2.1.1 CELL TEST

After treating the SK-OV-3 human ovarian cancer cell, using 20 and 80 μl/ml XAPI, Yang Jiao and others used the MTT method to detect cell survival. The results showed that their proliferation was inhibited, and with the drug as the concentration increases, cell apoptosis is significantly enhanced (Yang et al., 2017). When Lina and other people tested the IL-6 mRNA expression of SMMC7721 and HepG2 liver cancer cells with Real-time PCR, the results showed that XAPI could be used in a chemical hypoxic environment simulated by CoCl2 6H2O. After the effect of the liquid, IL-6 mRNA expression in HepG2 cells could be suppressed (Wen et al., 2018). Yang Jiao and others used the MTT method, scratch test, Transwell test, Transwell coated Matrigel test, and western blotting method to prove that XAPI has an effect on the invasion and metastasis of HepG2 and MHCC97H liver cancer cells, and its inhibitory effect may be related to the regulation of MYOF to inhibit the matrix metalloproteinases MMP-2 and MMP-9 expression (Yang et al., 2019).

Pu Zhongjian and others used experimental methods such as fluorescent staining, flow cytometry, and immunohistochemistry to prove the XAPI combined with oxaliplatin's apoptosis effect on HepG-2 liver cancer cells its related mechanisms. The fluorescence staining method showed that XAPI can cause HepG-2 cell apoptosis, and the apoptosis rate of the combined drug group was more obvious; the results of flow cytometry showed that XAPI can cause HepG-2 cell apoptosis, and the combination The medication group was more obvious, and it was observed that XAPI could block HepG-2 cells in G0/G1 stage, and the combination of XAPI and oxaliplatin group can block HepG-2 cells in S period. Immunohistochemistry showed that both the XAPI and combination drug groups were weaker than the control group's Survivin coloring ability, and the combination drug coloring ability was weaker (Pu et al., 2020).

2.1.2 ANIMAL EXPERIMENT

Recently, XAPI has been proved to be an effective anti-tumor agent. It can differentiate cancer cells and induce apoptosis, and in *vivo* studies have demonstrated that XAPI can inhibit the growth of transplanted tumors in mice (Liang et al., 2019).Liu Lei and others established liver cancer model mice and used XAPI and other corresponding drugs to treat the control experiments. The results showed that XAPI significantly affected tumor growth in rats with diethylnitrosamine, decreased liver index and spleen index, improved liver function, decreased IL-17, IL-6, and TNF-α in rats, raised serum IL 2, and improved immunity (Liu et al., 2017). Wang Pengzeng established a Lewis lung cancer mouse model and used XAPI and other drugs to treat it, observe the mice's survival status, analyze the tumor inhibition rate, and use immunohistochemical determination to the expression level of VEGF. The results showed that XAPI can block tumor cells in the G1 stage. Moreover, in the experimental group combined with XAPI, the inhibition rate of lincomycin group was the strongest, and the strong positive rate of VEGF in the fluorouracil group was the highest. *Xiaoaiping* injection can significantly improve the survival status of mice. As well, it has an obviously inhibitory effect on Lewis mice transplanted tumors and can reduce the mortality of mice. The anti-tumor effect of combined XAPI is stronger than that of G1 alone and the cell cycle-specific chemotherapeutic agent may be the XAPI's anti-tumor effect is concerned with the regulation of tumor cell cycle and suppression of tumor angiogenesis (Wang, 2016).

Yang Jiao and others established the nude mouse model of heterotopic xenograft tumors of female human ovarian cancer cell SK-OV-3, injected different doses of XAPI and other combined drugs to observe and record the general condition, weight, and tumor of the mice, volume and rate of tumor inhibition. The studies showed that in the nude mice with heterotopic xenograft tumors in the experiment, the tumor inhibition rate of the control and paclitaxel groups was clearly lower than it in the high-dose combination group (Yang et al., 2017). Wang Yuan and others constructed a mouse model of Lewis lung cancer. By injecting different doses of XAPI to observe the growth of transplanted tumors in each group of mice, the expression of VEGF and EGFR proteins in tumor tissues, and the index of immune organs such as the spleen and thymus. The results showed that XAPI could significantly inhibit tumor growth in lung cancer model rats, and the VEGF and EGFR proteins in tumor tissues are reduced considerably. At the same time, tumor weight, tumor inhibition rate, and immune organ index of the spleen and thymus are significantly higher than model control Group (Wang et al., 2019). Lina and others built a liver carcinoma model by injecting diethylnitrosamine and XAPI with different doses respectively into the liver carcinoma model, and observed the effects of XAPI on the migration of SMMC-7721 hepatic carcinoma cells and HepG2s. The results showed that the rats of liver tissue in the low-dose group and high-dose group of XAPI had little pathological damage; *Xiaoaiping* injection can significantly inhibit the migration of

HepG2 cells and SMMC-7721 cells in a hypoxic environment (Wen et al., 2018).

3. CLINICAL APPLICATION

3.1 CLINICAL RESEARCH ON THE TREATMENT OF LIVER CANCER

He Lilian and others treated the patients with XAPI, 5-fluorouracil, combined treatment of XAPI and 5-fluorouracil, respectively, and analyzed the expression of tumor suppressor gene HepG2 in liver cancer cells. The experimental studies cleared that all genes of P57kip2, P16INK4, and PDCD5 in the combination treatment group and single treatment group had statistically significant differences in liver cancer cells of the proliferation activity. *Xiaoaiping* injection combined with 5-fluorouracil can help to restrain the liver cancer cells proliferation and suppress cancer cell suppressor genes (He et al., 2019). He Qinghong and others made one clinical observation on patients with hepatocellular carcinoma, and observed their short-term efficacy and immune function. One group was a simple control group (hepatic artery chemoembolization), and the other group was an observation group (XAPI was added). The studies cleared that the control group's total effective rate was significantly lower than the rate of the observation group. After treatment, the control group's CD3+, CD4+, CD4+/CD8+ were lower than the observation group; in the treatment time, it was significantly seeing that the observation group had fewer white blood cells, fewer neutrophils, and higher total bilirubin than the control group (He & Shi, 2019).

Liu Yuan et al. studied the influence of XAPI on tumor marker levels (AFP, CA199, CEA, AFU, CA125) by observing the changes of serum values in patients with liver cancer. The experiment was conducted in a controlled design, one group was the control group, which was treated with routine support; the other group was the experimental group, which was treated with XAPI. After 4 weeks, all patients and the changes in serum tumor marker levels, before and after treatment, were observed and evaluated the clinical efficacy. The studies evidenced that the differences in clinical curative effect total effective rate in the control group was clearly lower than it was in the treatment group; and the serum AFP, CA199, CEA, AFU, and CA125 of the treatment group were significantly lower than that in the control group; treatment group's patients had fewer white blood cells, increased total bilirubin, and increased serum alanine aminotransferase than the control group. Same for the control group, by observing the treatment group's clinical efficacy and quality of life improvement rate (Liu et al., 2017). Tong Guangwu and others order to research the XAPI combined with elements injection clinical efficacy in advanced primary liver cancer treatment, to compare the changes in these two groups in the CD3+, CD4+ and CD4+/CD8+ lymphocytes levels, and compared the changes in the serum MMP-2 and MMP-9 levels in these two groups before and after treatment. The studies indicated that CD3+, CD4+, and CD4+/CD8+ were decreased in the control group, which was more significant than in the treatment group; the levels for serum MMP-2 and MMP-9 in the control group increased more clearly than which in the

treatment group. The evidence effect on the treatment of advanced primary liver cancer by using XAPI combined with element injection, and it also has a good clinical efficacy (Tong & Gao, 2016).

3.2 CLINICAL RESEARCH ON THE TREATMENT OF LUNG CANCER

Rao Shijun and others understood the therapeutic efficacy of XAPI by comparing the chest CT, tumor markers, weight, clinical symptoms, and chemotherapy side effects of patients in two groups who used XAPI combined chemotherapy or ordinary chemotherapy. The results indicated that the control group's effective rate was not higher than it of the treatment group, and the treatment group patients gained weight and reduced clinical symptoms (Rao & Chen, 2018). Hu Yanhui and others compared the therapeutic effect in two groups, one in the treatment group (XAPI combined with chemotherapy) and another one in the control group (chemotherapy alone). Observed the effect of XAPI on non-small cell lung cancer patients that the changes in their T lymphocyte subsets. The studies indicated that when the treatment group treatment, its CD3+, CD4+, CD4+/CD8+ were clearly increased, CD8+, CD4+CD25+ were clearly reduced, and their expression level was improved clearly much more than in the control group. Patients in the treatment group after treatment, their mental state, physical performance, and quality-of-life improvement were better than in the control group. Then, *Xiaoaiping* injection can increase the level of CD3+, CD4+, and CD4+/CD8+, reduce CD8+ and CD4+CD25+, and enhance the quality of patient's life and their treatment efficacy (Hu et al., 2019).

To observe the effect of XAPI on advanced non-small cell lung cancer, Zhu Lina and others compared the treatment of patients in the control group (gefitinib alone) and another group (XAPI combined with gefitinin) by observing the coagulation function and clinical efficacy of patients, including the changes of hemodynamic indicators, the level of blood coagulation molecules, and the clinical treatment effect. The studies evidenced that the control group after treatment, was clearly lower than the observation group, with treatment total effective rate; the control group's patients developed a hypercoagulable state, the serum fibrinogen and D-dimer content, and the value of whole-blood viscosity high cut, all of them were clearly much more than observation group; but the low-cut value of whole-blood viscosity, capillary blood viscosity, hematocrit and red blood cell aggregation index in the control group were all higher than observation group. *Xiaoaiping* injection can improve blood hypercoagulability and hyperviscosity in people who have advanced non-small cell lung cancer, and its clinical treatment effect is better (Zhu et al., 2020). Wang Xuehua and others used immunohistochemistry to explore Ki67 and p53 protein expression levels in two groups of lung cancer tissues. They observed XAPI combined with gefitinib group curative outcome and gefitinib group curative outcome after 28 days of treatment. The results indicated that the control group was lower than the observation group in the treatment efficiency and disease control rate. After treatment, Ki67's positive expression rate in XAPI combined with the gefitinib group was

lower than it in the gefitinib group, and p53's positive expression rate was the same higher than the gefitinib group. Patients with lung cancer use XAPI combined with gefitinib can regulate the Ki67 and p53 protein expression and effectively inhibit cancer cell infiltration and metastasis (Wang & Chen, 2016).

3.3 CLINICAL RESEARCH ON THE TREATMENT OF BREAST CANCER

Fu Baihan and others selected metastatic triple-negative patients for inclusion in the study. After all, patients received XAPI combined with chemotherapy for 4-6 cycles, the RECIST 1.1 solid tumor evaluation standard was used to determine the efficacy of the patient and detect the correlation between efficacy and clinicopathological factors. The treatment results showed that the target efficacy and disease control rates were 36.6% and 81.2%, respectively. The site of metastasis, the number of metastases, and the ECOG score (Eastern Cooperative Oncology Group) were significantly related to the effective treatment. After combination therapy, patients in 1-year overall survival rate can reach 81.2% (Fu et al. 2016). Wu Nianjiang and others selected patients after breast cancer surgery and divided them into two groups. Both of the groups simultaneously received cyclophosphamide + methotrexate + fluorouracil chemotherapy, but the observation group added another XAPI to treat. The treatment effect, postoperative immune function, inflammatory factors, and vascular endothelial growth factor levels in patients in these two groups were observed as the effect of XAPI on the postoperative immune function of breast cancer to be compared. The research demonstrated that, after treatment, the ratio of the Th17 cell in the observation group was lower than in the control group, while Th17/Treg, CD4+CD25+ Treg cells ratio was higher than it in the control group; IL-1, IL-6, tumor cell necrosis factor-α and VEGF levels in the control group which was clearly higher than those in the observation group. *Xiaoaiping* injection can usefully enhance patients' immune function with breast cancer chemotherapy, reduce chemotherapy side effects on patients, and improve the treatment effect (Wu & Gao, 2016).

Yang Xiaozhong and others compared the IL-6, IL-8, TNF-a, quality of life, and adverse reactions levels in the control group (Epirubicin neoadjuvant chemotherapy) and the observation group (Epirubicin neoadjuvant chemotherapy + XAPI) before and after treatment to observe XAPI combined with epirubicin neoadjuvant chemotherapy clinical treatment efficacy in triple-negative breast cancer patients. The results showed that the patients' clinical efficacy in the observation group was more significant than which in the control group; after treatment, the observation group's IL-6 and IL-8 levels were clearly lower than in the control group; and at the same time, the level of TNF-a and the quality-of-life score were significantly higher which in the control group; but the adverse reaction rate of the observation group was lower which in the control group (Yang et al., 2019). Xiao Jiangmin compared patients in two groups who had clinical efficacy after 4 treatment cycles in the conventional group (SOX regimen) and observation group (XAPI + SOX regimen). The

studies cleared that after treatment, the clinical control rate, was 82.35% in the observation group, and 60.61% in the routine group. The difference was significant. *Xiaoaiping* injection combined with SOX chemotherapy improves the disease control effect of advanced triple-negative breast cancer (Xiao, 2021).

3.4 CLINICAL RESEARCH ON THE TREATMENT OF ESOPHAGEAL CANCER

Qian Xiaolan and others observed the curative effect of advanced esophageal cancer by comparing the count of white blood cells and quality-of-life improvement after treatment between the experimental group that used the chemotherapy combined with XAPI and the control group that only used chemotherapy. The studies demonstrated that the experimental group's nausea and vomiting, appetite loss, and choking symptoms were better than those in the control group; the decline degree in WBC counts in the experimental group was shorter than in the WBC counts in the control group. For advanced esophageal cancer patients, chemotherapy combined with XAPI can influence their avoid leukopenia and their quality-of-life (Qian et al., 2017). Huangyangyang and others established an observation group (XAPI + cisplatin combined with paclitaxel regimen) and the control group (cisplatin combined with paclitaxel regimen) to observe the differences in the clinical efficacy of chemotherapy, tumor markers, and improvement of quality-of-life in each group in order to observe the advanced esophageal cancer treatment used in XAPI combined with chemotherapy clinically. The study found that the rate of remission of 70.0% in the observation group was significantly higher than that of the control group of 40.0% ; and after treatment, the CA199, CEA, SCC-Ag and CYFRA21-1 were significantly lower than those in the control group, and the incidence of leucopenia and neutropenia was significantly higher in the control group (Huang et al., 2020).

Wang Dongjian observed patients in two groups, one is XAPI combined with PF regimen group and another is PF regimen alone group for treatment and observation and evaluation of curative effect after 2 cycles. The studies evidenced a total effective rate that 85.00% in the control group was clearly shorter than 55.00% in the treatment group; in the adverse reaction observation, the leukopenia incidence and thrombocytopenia were different between the control group and the treatment group; *Xiaoaiping* injection combined with PF can decrease toxicity, enhance efficacy and quality of patient's life (Wang, 2019). Nan Haifeng and others divided the patients into conventional radiotherapy + chemotherapy group and XAPI combined with thalidomide + conventional radiotherapy and chemotherapy group these two groups for treatment. By observing the efficacy after the short-term and long-term treatment, comparing the serum of the two groups of tumor markers, VEGF, and the expression of their receptors before treatment and after treatment. Then, the incidence of adverse reactions during treatment and follow-up in the two groups was counted. The research cleared that after 1 year of treatment, the observation group survival rate was

96.25%, which was significantly much more than the rate of 86.25% in the control group; before treatment, the serum of MIP-3α, CA125, CE A, NSE, and CYFRA21-1 levels in these two groups increased different with those after treatment, and the observation group decreased compared with the control group; after treatment, the serum of the two groups VEGF and VEGFR-1 expression were clearly inhibited related with before treatment, a more significant effect was observed in the observation group; during treatment and follow-up, the higher incidences of vomiting in the control group, decreased white blood cells, radiation esophagitis, and bone marrow suppression than observation group. The combination of XAPI and Thalidomide Adjuvant Radiation can decrease serum tumor markers, inhibit the expression of VEGF and its receptors, decrease the incidence of clinical symptoms and side effects, and improve the clinical effect of chemotherapy (Nan & Ding, 2019).

4. CONCLUSION

In summary, we have initially achieved considerable results in the current research on XAPI; it also has a kind of clinical treatment effect. However, the clinical efficacy and pharmacological impact of XAPI are still in the preliminary exploration stage. The research on its chemical components is not in-depth, and the anti-tumor pharmacological mechanism has not yet been elucidated. It also requires systematic pharmacodynamics and pharmacokinetics. Further in-depth research on compatibility, contraindications, and adverse reactions, to provide a more valuable and practical reference for clinical medication and further promote the application to international clinical practice.

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