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Research Progress of *Xiaoaiping* Injection on Anti-tumor

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ABSTRACT

Xiaoaiping injection 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 usual common Traditional Chinese medicine anti-tumor drug in recent years. 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. The clinical efficacy and pharmacological effects of *Xiaoaiping injection* 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, in order to provide a more reasonable and effective reference for clinical medication, and further promote the application to international clinical practice.

INTRODUCTION

Xiaoaiping injection 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 usual common Traditional Chinese medicine anti-tumor drug in recent years (D. J. Wang, 2019). Its main chemistry the ingredients are polysaccharides, saponins, alkaloids and others, which are commonly used in anti-tumor treatments in modern clinical applications(Lu et al., 2020).

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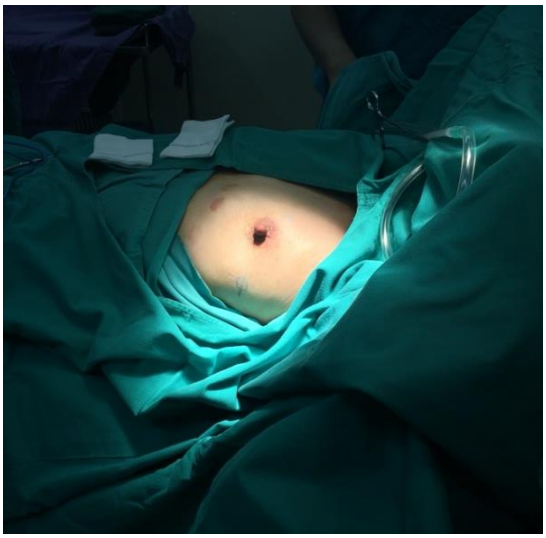
Recently, some studies showed that the anti-tumor mechanism of *Xiaoaiping injection*, it can inhibit angiogenesis and tumor cell proliferation, block tumor cell cycle, and induce tumor cell apoptosis to anti-cancer(Zhang, Zhong, Cheng, Tang, & Ni, 2020). By inducing tumor cell differentiation, reduce the resistance of some anti-tumor drugs, improve 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. Synergistic chemotherapy drugs enhance the killing effect on tumors, and at the same time have important value in extend the survival time and improve their quality-of-life that people who have malignant tumors, and there is no obvious adverse drug reaction(Cheng et al., 2018). In terms of traditional Chinese medicine, *Xiaoaiping injection*'s effect is activating blood and removing blood stasis, clearing heat and detoxification, and dispelling masses and relieving pain(Zhu et al., 2020). For this reason, this article systematically reviewed relevant literature in recent years and compared *Xiaoaiping injection*. This article reviews the chemical composition, pharmacological effects and the drug applied in clinical in recent years.





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, and pigments, etc (T. S. Wang et al., 2019). Many of the active ingredients have anti-tumor effects. The polysaccharides and alkaloids in the active ingredients can enhance the body's specific immune function against tumors; saponins help to inhibit angiogenesis, and phenolic acids can reduce the activity of oxygen free radicals(Zhao, 2018). C21-steroid glycosides have the influence in tumor cell growth and apoptosis (Zhang, Zhong, Cheng, Tang, Ni, et al., 2020). Then, there are scores of C-21 steroidal saponins isolated from the original medicine of *Tongguanteng*, and *Xiaoaiping injection* contains 9 subtypes of C-21 steroidal saponins, it is also the central material basis for its pharmacological effects (Hu et al., 2019) ,and the main component of anti-tumor (Rao & Chen, 2018).

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PHARMACOLOGICAL RESEARCH

Anti-Tumor Effect

Cell Test

After treating the SK-OV-3 human ovarian cancer cell, used 20 and 80 μl/ml *Xiaoaiping injection*, 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(J. Yang et al., 2017). Wen Lina and others in order to detect the SMMC7721 liver cancer cells and HepG2 liver cancer cells's expression of IL-6 mRNA by used Real-time PCR experiments, under the intervention of *Xiaoaiping injection*, and the studies have showed that the *Xiaoaiping injection* was used under the chemical hypoxia environment simulated by CoCl2 6H2O The expression of IL-6 mRNA in HepG2 cells can be inhibited after the action of the liquid(Wen et al., 2018). Yang Jiao and others used MTT method, scratch test, *Transwell* test, *Transwell* coated Matrigel test and western blotting method to prove that *Xiaoaiping injection* has the effect with 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 (J. Yang et al., 2019).

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

Animal Experiment

Recently, the pharmacological studies evidenced that *Xiaoaiping injection* has obvious anti-tumor activity, which can differentiate cancer cells in the normal direction and induce tumor cell apoptosis; in vivo experiments have shown that it can significantly inhibit the growth of transplanted tumors in mice(Liang et al., 2019). Liu Lei and others established liver cancer model mice and used *Xiaoaiping injection* and other corresponding drugs to treat the control experiments. The studies cleared that *Xiaoaiping injection* has obvious impact the growth of tumors in liver cancer model rats with diethylnitrosamine, reduce liver index, spleen index, improve liver function of rats, reduce rat serum IL-17, IL-6, TNF-α levels, increase serum IL-2 levels, and improve immune function(L. Liu et al., 2017). Wang Pengzeng established a Lewis lung cancer mouse model and used *Xiaoaiping injection* and other drugs to treat it and observe the survival status of the mice, analyze the rate of tumor inhibition, and use the method of immunohistochemical determine to the expression level of VEGF. The results showed that *Xiaoaiping injection* can block tumor cells in the G1 stage. At the same time, the inhibition rate of *Xiaoaiping injection* combined with *lacomycin* group is the strongest, and the strong VEGF positive rate of *Xiaoaiping injection* combined with fluorouracil group is the highest. *Xiaoaiping injection* can significantly improve the survival status of mice. As well, it has an obviously inhibitory effect on Lewis's mice transplanted tumors and can reduce the mortality of mice. The anti-tumor effect of combined *Xiaoaiping injection* is stronger than that of G1 alone and the cell cycle specific chemotherapeutic agent, may be the *Xiaoaiping injection*'s anti-tumor effect is concern with the regulation of tumor cell cycle and suppression of tumor angiogenesis(P. Z. Wang, 2016).

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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 *Xiaoaiping injection* and other combined drugs to observe and record the general condition, weight, and tumor of the mice. Volume, rate of tumor inhibition. The studies showed that the nude mice with heterotopic xenograft tumors in experiment, the tumor inhibition rate of the control and paclitaxel groups were clearly lower than it in the high-dose combination group (J. Yang et al., 2017).Wang Yuan and others constructed a mouse model of Lewis lung cancer. By injecting different doses of *Xiaoaiping injection* 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 spleen and thymus. The results show that *Xiaoaiping injection* can significantly inhibit tumor growth in lung cancer model rats, and the VEGF and EGFR proteins in tumor tissues are significantly reduced. At the same time, tumor weight, tumor inhibition rate, and immune organ index of spleen and thymus are significantly higher than model controls. Group(Y. Wang et al., 2019). Wen Lina and others established a liver cancer model by intermittent intraperitoneal injection of diethylnitrosamine, intraperitoneal injection of low-dose and high-dose *Xiaoaiping injection* respectively and observed the *Xiaoaiping injection* through the scratch healing experiment under the hypoxic environment induced by CoCl2 influence with the liquid on the SMMC-7721 liver cancer cells and HepG2s' migration. The results showed that the rats of liver tissue in the low-dose group and high-dose group of *Xiaoaiping injection* 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).

CLINICAL APPLICATION

Clinical Research on the Treatment of Liver Cancer

He Lilian and others treated the patients with *Xiaoaiping injection*, 5-fluorouracil, combined treatment of *Xiaoaiping injection* and 5-fluorouracil, respectively, and analyzed the expression of tumor suppressor gene HepG2 in liver cancer cells. The experimental studies cleared that all of P57kip2, P16INK4 and PDCD5 in 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(L. L. He et al., 2019). He Qinghong and others took hepatocellular carcinoma patients as the research object, and the short-term efficacy and immune function of the two groups patients were observed in treatment, one is hepatic artery chemoembolization in the control group, one is *Xiaoaiping injection* in the observation group. The studies cleared that control group's total effective rate was significantly lower than the rate of observation group. After treatment, control group 's CD3+, CD4+, CD4+/CD8+ were lower than observation group; in the treatment time, it was significantly seeing that observation group had fewer white blood cells, fewer neutrophils, and higher total bilirubin than the control group (Q. H. He & Shi, 2019).

Liu Yuan and others are exploring Liver cancer patients' serum to research *Xiaoaiping injection*'s effect of the tumor markers level (AFP, CA199, CEA, AFU, CA125), the conventional supportive treatment was treated in control group and *Xiaoaiping injection* adjuvant therapy was treated in experimental group. 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 control group was clearly lower than its in 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,(Y. Liu et al., 2017). Same to control group, by observing

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the treatment group's clinical efficacy and quality of life improvement rate, Tong Guangwu and others in order to research the *Xiaoaiping injection* combined with *elemene injection* clinical efficacy in advanced primary liver cancer treatment, to compared 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 decrease in the control group which was more significant than treatment group; the levels for serum MMP-2 and MMP-9 in the control group increased more clearly than which on treatment group. The evidence effect on the treatment of advanced primary liver cancer by used *Xiaoaiping injection* combined with *elemene injection*, and it also has a good clinical efficacy(Tong & Gao, 2016).

Clinical Research on the Treatment of Lung Cancer

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

Zhu Lina and others compared the treatment of patients in control group (gefitinib treatment) and another group in observation (*Xiaoaiping injection* combined with gefitinib treatment) with hemodynamic indicators, changes in blood coagulation molecule levels and clinical treatment effects to explore the influence in patients who had the advanced non-small cell lung cancer that used *Xiaoaiping injection* combined with gefitinib to define by coagulation function and clinical efficacy. The studies evidenced that the control group after treatment, was clearly lower than observation group, with treatment total effective rate; the control group's patients developed 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 control group were all higher than observation group. *Xiaoaiping injection* can improve the blood hypercoagulability and hyperviscosity people who has 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 proteins expression levels in two groups of lung cancer tissues and observed *Xiaoaiping injection* combined with gefitinib group curative outcome and gefitinib group curative outcome after 28 days of treatment. The results indicated that the control group was clearly lower than observation group in the treatment efficiency and disease control rate. After treatment, Ki67's positive expression rate in *Xiaoaiping injection* combined with gefitinib group was lower than it in gefitinib group, and p53's positive expression rate was same higher than gefitinib group. Patients with lung cancer used *Xiaoaiping injection* combined with gefitinib can regulate the Ki67 and p53 protein expression, effectively inhibit cancer cell infiltration and metastasis(X. H. Wang & Chen, 2016).

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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 *Xiaoaiping injection* 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 efficacy evaluation of the whole group of patients indicated that the rate of objective effective, disease control were 36.6% and 81.2%, respectively; the location of metastasis, the number of metastases, and the ECOG score are significantly correlated with the efficacy of metastatic triple-negative breast cancer patients; patients in 1-year overall survival rate was 81.2%, and the median OS did not reach(Fu et al., 2016). Wu Nianjiang and others selected patients after breast cancer surgery and divided them into two groups and received cyclophosphamide + methotrexate + fluorouracil chemotherapy at the same time. Both the control group and the observation group received chemotherapy, but the observation group added the *Xiaoaiping injection* treatment. The treatment effect, postoperative immune function, inflammatory factors, and vascular endothelial growth factor levels with patients in these two groups were observed the effect of *Xiaoaiping injection* on the postoperative immune function of breast cancer which to be compared. The research demonstrated that, after treatment, Th17 cells ratio in observation group which was lower than control group, while Th17/Treg, CD4+CD25+ Treg cells ratio was higher than it in control group; IL-1, IL-6, tumor cell necrosis factor-α and VEGF levels in control group which were clearly higher than those in 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 + *Xiaoaiping injection*) before and after treatment to observe *Xiaoaiping injection* combined with epirubicin neoadjuvant chemotherapy clinical treatment efficacy in triple-negative breast cancer patients. The results show that the patients' clinical efficacy in the observation group was more significant than which in control group; after treatment, the observation group's IL-6 and IL-8 levels were clearly lower which in control group; and at the same time, the level of TNF-a and the quality-of-life score were significantly higher which in control group; but the adverse reaction rate of the observation group was clearly lower which in control group(X. Z. Yang et al., 2019). Xiao Jiangmin compared patients in two groups who had clinical efficacy after 4 treatment cycles in conventional group (SOX regimen) and observation group (*Xiaoaiping injection* + SOX regimen). The studies cleared that after treatment, the clinical control rate, 82.35% in observation group, 60.61% in routine group, the difference was significantly. *Xiaoaiping injection* combined with SOX chemotherapy improves the disease control effect of advanced triple-negative breast cancer (Xiao, 2021).

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 cell and quality-of-life improvement after treatment between experimental group used the chemotherapy combined with *Xiaoaiping injection* and control group only used chemotherapy. The studies demonstrated that the nausea symptoms and vomiting, appetite loss and choking symptoms, all of them in experimental group were better than that in control group; decline degree in WBC counts in experimental group was shorter the WBC counts in control group. For advanced esophageal cancer patients by the chemotherapy combined with *Xiaoaiping injection* which can influence their avoid leukopenia and the quality of life (Qian et al., 2017). Huangyangyang and others established an observation group (*Xiaoaiping injection* + cisplatin combined with paclitaxel regimen) and the control group (cisplatin combined with

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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 *Xiaoaiping injection* combined with chemotherapy clinically. The research cleared that 70.0% remission rate in observation group was significantly much more than 40.0% remission in control group; and after treatment, observation group with CA199, CEA, SCC-Ag, and CYFRA21-1 levels was decreased more significantly than control group; the leukopenia and neutropenia incidence, after treatment, control group was significantly higher than which in observation group; in the observation group, after treatment, the fatigue incidence and anorexia were significantly shorter control group(Huang et al., 2020).

Wang Dongjian observed patients in two groups, one is *Xiaoaiping injection* 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 total effective rate that 85.00% in control group was clearly shorter 55.00% in treatment group; In the adverse reaction's observation, the leukopenia incidence and thrombocytopenia were clearly difference between in control group and treatment group; *Xiaoaiping injection* combined with PF can decrease toxicity, enhance efficacy and quality of patient's life (D. J. Wang, 2019b). Nan Haifeng and others divided the patients in conventional radiotherapy + chemotherapy group and *Xiaoaiping injection* combined with thalidomide + conventional radiotherapy and chemotherapy group these two groups for treatment. By observing the efficacy after the short-term treatment and long-term treatment, comparing the serum of the two groups tumor markers, VEGF, and their receptors expression 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, observation group survival rate was 96.25% ,which significantly much more than the rate of 86.25% in control group; in 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 clearly compared with control group; after treatment, the serum of the two groups' VEGF and VEGFR-1 expression were clearly inhibited related with before treatment, more significant effect was observed in the observation group; during treatment and follow-up, the higher incidences of vomiting in control group, decreased white blood cells, radiation esophagitis and bone marrow suppression than observation group. *Xiaoaiping injection* combined with chemotherapy and thalidomide adjuvant radiotherapy can significantly reduce the serum tumor markers level in advanced esophageal cancer patients, inhibit the VEGF expression and its receptors, reduce the patients' clinical symptoms and adverse reactions incidence, enhance chemotherapy clinical efficacy (Nan & Ding, 2019).

CONCLUSION

In summary, we have initially achieved considerable results in the current research on *Xiaoaiping injection*, meantime, it also has a kind clinical treatment affect. However, the clinical efficacy and pharmacological effects of *Xiaoaiping injection* 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, in order to provide a more reasonable and effective reference for clinical medication, and further promote the application to international clinical practice.

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