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CLINICAL RESEARCH PROGRESS OF COMPOUND KUSHEN INJECTION ON ANTI-TUMOR EFFECT

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Abstract: *Kushen*, a traditional Chinese medicine, has the functions of clearing away heat and dampness, reducing inflammation and detoxifying, and its alkaloids are its main anti-tumor substances. In recent years, as the extract of *Kushen*, compound *Kushen* injection has the characteristics of significant anti-tumor efficacy and few side effects, it is often combined with various anti-tumor treatments such as surgery, chemotherapy, radiotherapy, and targeted therapy in clinical practice in China. This paper summarizes the animal and clinical experiments of cervical, breast, gastric, and colon cancer through the drug effect of the compound *Kushen* injection. Many studies have shown that compound *Kushen* injection mainly exerts its anti-tumor effect by regulating tumor cell proliferation, inducing tumor cell apoptosis, reducing tumor angiogenesis, and improving body immunity. Based on traditional anti-tumor therapy, adding the compound *Kushen* injection can have a more apparent therapeutic effect on patients, reduce the side effects of anti-

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tumor therapy, improve patients' quality of life, and prolong patients' survival time. This paper significantly summarizes the research on the anti-tumor treatment of compound *Kushen* injection, further clarifies the anti-tumor effect of the effective extracts of traditional Chinese medicine, which provides a basis for future anti-tumor research of compound *Kushen* injection and a basis for the clinical promotion of the drug.

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

Compound *Kushen* injection (CKI) is a sterile solution. *Kushen* and *Baituling* are the primary raw materials in CKI and through a series of modern processing technologies to extract. Recently, it has been widely used as a traditional Chinese medicine injection for anti-malignant tumor treatment in the clinic (Wang et al., 2020). The CKI has properties such as heat-clearing and disinfection, cooling the blood and removing toxins, activating blood and removing blood stasis, dispersing masses, and relieving pain (Meng, 2020). The current research examined the CKI anti-tumor mechanism in inhibiting cell proliferation, invasion, and metastasis, inducing cell differentiation, apoptosis, angiogenesis, and regulating the body's immunity in cancer cells (Dong et al., 2019). Recent studies have shown that CKI has outstanding efficacy in anti-lung, gastric, and breast cancer and has a synergistic effect with chemotherapeutics (Zhang & Zhang, 2019). Compound *Kushen* injection is safer and can inhibit other adverse reactions of chemotherapy. It can increase efficacy and reduce toxicity in anti-tumor treatment, have few adverse reactions, and alleviate patients' pain. It is a clinically mature anti-tumor treatment drug (Li & Liu, 2020). This article systematically reviewed the relevant literature in recent years and reviewed the chemical components, pharmacological effects, and clinical applications of CKI. Figure 1 shows the CKI used in the clinic.

Figure 1 Compound *Kushen* Injection

1. CHEMICAL COMPOSITION

Compound *Kushen* injection is the Chinese patented medicine injection made from extracting and processing various Chinese medicines such as *Kushen*, *Baituling,* and others. It contains matrine, oxymatrine, sophorine, sophocarpine, saponins, and other chemical ingredients, in which matrine and oxymatrine are the two main anti-tumor active ingredients (Dai, Liu, Tian, & Chen, 2020). Matrine is a tetracyclic quinolizidine alkaloid (Xiao et al., 2018). Existing studies have shown that the pharmacological effects of matrine have anti-cancer, anti-oxidation, and anti-inflammatory (Li & Liu, 2020). Matrine can scavenge oxidative free radicals and promote tumor cell differentiation, apoptosis, and autophagy (Liu & Mu, 2017). It regulates tumor cell reproduction and invasion (Shi et al., 2018) and shrinks or stabilizes the tumor. It also strengthens the body's immunity, inhibits the drug resistance mechanism of tumor cells, and works as an anti-tumor agent that strongly inhibits tumor neovascularization (Zhang et al., 2018).

At the same time, matrine also significantly improves the side effects of chemotherapy, advanced cancer pain, fever, fatigue, and other symptoms (Sun et al., 2019). Some of the pharmacological effects of oxymatrine are anti-cancer, anti-viral, and anti-inflammatory (Fang et al., 2019). Its anti-cancer mechanism induces the differentiation of cancer cells, apoptosis, and autophagy. It can also inhibit the proliferation of cancer cells, invasion, and metastasis (Chen et al., 2019). Zhang and colleagues reported that it could regulate tumor angiogenesis, reverse the drug resistance of tumor cells, and improve the sensitivity of chemotherapy drugs (Zhang et al., 2017).

2. PHARMACOLOGICAL RESEARCH

2.1 ANTI-TUMOR EFFECT

2.1.1 CELL TEST

Zheng et al. (2019) used the Tetramethylazolium salt colorimetric method (MTT), flow cytometry, and clone formation test to detect the radiosensitivity of CKI to H1299 cells. The results showed that H1299 cells have a specific dose and time dependence on toxicity under the treatment of different concentrations of CKI. The apoptosis rate, cell proliferation inhibition rate, and cell survival rate of the CKI group were better than the control group. Compound *Kushen* injection can increase lung tumor H1299 cells' apoptosis by radiation-induced procedures, thereby increasing the radiosensitivity of lung cancer H1299 cells (Zheng et al., 2019). Jin (2017) adopted the MTT method and TUNEL (Terminal-deoxynucleotidyl Transferase Mediated Nick End Labeling) method to observe CKI's influence on human breast tumor cells with different estrogen receptor expressions to anti-cancer, such as MCF-7 (ER+) and MDA-MB-231 (ER-). The research showed that CKI can significantly inhibit these two-cancer cell proliferation and induce the MCF-7 human breast tumor cells and MDA-MB-231 human breast tumor cells to undergo apoptosis. The results were compared to a blank control group and a docetaxel-positive control group (Jin, 2017). Zheng et al. (2019) used the MTT method, flow cytometry, and clone formation experiment to detect the radiosensitivity effect of CKI on nasopharyngeal carcinoma CNE-2 cells. This research found that the different concentrations of CKI treated with CNE-2 cells had a higher proliferation inhibition rate than cells that were not treated with CKI. It was dose-dependent; the survival rate of CNE-2 cells in the combination group was much shorter than in the radiation group. The experiments suggested that the CKI affects the radiation-induced apoptosis of nasopharyngeal carcinoma CNE-2 cells, promoting a radio sensitization effect on CNE-2 cells (Zheng et al., 2019).

2.1.2 ANIMAL EXPERIMENT

Liu et al. (2019) established a mouse H22 liver cancer model to determine CKI efficacy as an anti-tumor. The study showed differences between the model control group and the CKI group. CKI group had significantly inhibited the tumor weight of the transplanted tumor of liver cancer H22 in mice, and it is concentration-dependent. It significantly prolonged the survival days of mice with liver and ascites cancer, and the life extension rate could reach 57.71~86.28% (Liu et al., 2019). Xie (2020) established the Lewis lung cancer mouse model and compared the tumor weight, tumor inhibition rate, and other indicators of the CKI. They were grouped into the cisplatin, control, and TCM combination groups. TUNEL staining and Western blot were used to detect CKI and cisplatin anti-tumor effects by Lewis lung tumor mice. The studies showed that the CKI group of mice had the best general condition, and the mice in the combination group had the best tumor weight and inhibition rate. The CKI group and the combination group can increase the apoptosis index, and the combined group has a more substantial effect than the CKI group. The combined group can significantly up-regulate the caspase-3 cleavage site, while the other groups have no significant effect. Experiments suggested that the CKI combined with cisplatin can promote substantially tumor cell apoptosis, and combining the two had synergistic effects. The mechanism may influence the cleaved caspase-3 protein highly expressed in tumor tissues (Xie, 2020). Sun et al. (2020) established an *in-situ* lung cancer mouse model using RT-PCR and Western blot skills to discover MDR1 mRNA and P-gp protein's expression and to study the relationship between CKI and MDR1-mediated P-gp expression affects morphine tolerance. The research indicated that CKI had influenced MDR1 and P-gp lower expressed by morphine and, at the same time, can significantly improve morphine tolerance (Sun et al., 2020).

3. CLINICAL APPLICATION

3.1 CLINICAL RESEARCH ON THE TREATMENT OF LUNG CANCER

Wei, Hong, & Pan (2021) recruited 102 patients into two groups, the observation and the

control groups, to observe the treatment efficacy for non-small cell lung cancer patients. The treatment group was CKI combined with apatinib (a commonly used chemotherapy drug for lung cancer). These results showed that the effective rate of recent treatment CKI + apatinib drug group was better than in the apatinib single group. At the same time, the apatinib alone had a higher adverse reaction rate than the CKI + apatinib group. After the treatment, the measurements for cancer antigen of CEA, CA125, and CYFRA21-1 were better in CKI + apatinib group compared to apatinib alone. Patients with non-small cell lung cancer treated with CKI combined with apatinib showed excellent signs, in which the tumor shrinks or disappears and reduced adverse drug reactions (Wei, Hong, & Pan, 2021).

In another clinical observation, Wang (2017) recruited 42 patients into two groups. Each group had 21 patients. The groups were categorized as CKI combined with the chemotherapy group and a single chemotherapy control group to study the combined treatment effect on peripheral blood regulatory T and B lymphocytes in patients with advanced lung cancer. The study showed that the group of CKI combined chemotherapy after treatment was better than the chemotherapy alone group's Tregs level. The study suggested lung cancer patients who employed CKI combined chemotherapy can reduce their chemotherapy immunity and improve their quality-of-life (Wang, 2017).

Fu & Ke (2020) recruited 98 primary lung cancer patients and divided them into a chemotherapy-only group and a CKI + chemotherapy group. They observed the medication effect and the effect on thyroid transcription factor 1 (TTF-1) levels and D-dimer (D-D). This research showed that after short-term treatment, CKI + chemotherapy effect was better than the chemotherapy alone. The CD3+, CD4+, and CD4+/CD8+ levels in the chemotherapy group were not significantly higher than in the observation group, but its CD8+ level was higher than in the observation group. The observation group levels with TTF-1 and D-D were shorter than those in the control group, and these differences were statistically significant. CKI combined with chemotherapy can improve the patient's body's immune level, reduce TTF-1 and D-D levels, and improve short-term treatment efficiency (Fu & Ke, 2020).

Chen, Deng, Liao, & Fu (2018) collected 136 patients and treated them using CKI combined with docetaxel (a commonly used chemotherapy drug for lung cancer) + cisplatin regimen (DP regimen) in the observation group and docetaxel-only group. They examined the effects of the treatments on patients with advanced non-small cell lung cancer and examined the serum vascular endothelial growth factor-vascular endothelial growth factor (VEGF) in patients. The studies showed that in this treatment, the total rate of improving *Karnofsky* Performance Scale (KPS) score in the CKI + docetaxel group was higher than in the docetaxel-only group. In the observation group, the incidence of adverse reactions and serum VEGF levels during treatment were less than in the control group (Chen, Deng, Liao, & Fu, 2018).

Zhang et al. (2018) screened 60 elderly advanced non-small cell lung cancer patients to observe the treatment of CKI combined with Tigio capsule (a commonly used chemotherapy drug for lung cancer) chemotherapy therapeutic effect in the control group and observation group. This research showed that patients had improved quality-of-life in the observation group. Meanwhile, on average, progression-free survival and overall survival time were better than in the Tigio capsule group. The CEA level, Cyfra21-1, hematology, and gastrointestinal adverse reactions in CKI + Tigio capsule group were less than in the Tigio capsule group (Zhang et al., 2018).

Wu et al. (2020) divided 82 patients into two groups (observation group and control group). They compare these two groups for the curative effect, *Karnofsky* score, immune function, and adverse reactions. They also observed the short-term effect, efficacy, and impact on advanced non-

small cell lung cancer patients treated by CKI + chemotherapy. The results proved that after treatment, the observation group's total effective rate, KPS score, CD3+, CD4+, and CD4+/CD8+ were better than those in the control group. The adverse reactions such as gastrointestinal reactions, thrombocytopenia, leukopenia, bone marrow suppression, and liver and kidney dysfunction were all less than that in the chemotherapy alone. Compound *Kushen* injection improved patients' quality-of-life and immunity (Wu et al., 2020).

3.2 CLINICAL RESEARCH ON THE TREATMENT OF GASTRIC CANCER

Liu et al. (2017) observed and compared the total effective rate, adverse reaction rate, and physical strength improvement in the chemotherapy group of OxyContin (a commonly used chemotherapy drug for gastric cancer) combined with CKI and the chemotherapy-only group. This paper studied the effect of CKI combined with OxyContin on advanced gastric cancer pain. The results confirmed that CKI + OxyContin influenced the total effective rate and the physical strength was better than in OxyContin alone. Meanwhile, the adverse reaction rate in the OxyContin-only group was significantly better than in CKI + OxyContin (Liu et al., 2017).

In another study, Chang et al. (2021) divided 106 patients into an observation group (CKI + oxaliplatin + ticgio) and a control group (oxaliplatin + ticgio). Each group had 53 patients. The study observed and compared their differences in clinical efficacy before and after treatments, serum tumor marker levels, T lymphocyte subgroup levels, survival status, and adverse reaction rate. They also examined the effect of combined medication on stage IV gastric cancer. This research has proven that objective remission and disease control rates in the oxaliplatin + ticgio group were lower than in the observation group. Likewise, all CA19-9, CEA, and CA724 in the oxaliplatin + ticgio group were higher than in the observation group. The levels of CD3+, CD4+, CD4+/CD8+ and NK cells were less than in the observation group. The combined CKI with oxaliplatin and tigio treatment in stage IV gastric cancer improved patients' immunity and had sound clinical effects (Chang et al., 2021).

Hu, Zhang, & Chen (2018) randomly divided 120 advanced gastric cancer patients into the observation and control groups. They observed the treatment had clinical efficacy in patients treated with added CKI in the standard chemotherapy treatment of epirubicin (a commonly used chemotherapy drug for breast cancer). The studies showed that in the control group, the disease control rate, the rate of effective treatment, CD3+, CD4+, CD4+/CD8+, and KPS scores were all less than in the observation group (Hu, Zhang, & Chen, 2018).

Yan & Han (2019) established two groups, a control group, and an experimental group. They adopted methods to detect advanced gastric cancer patients' serum T cell subsets, CEA levels, and quality of life. They studied the treatment of CKI combined with a modified FOLFOX6 chemotherapy regimen on patients. The studies showed that after treatment, the experimental group patients' quality-of-life score and their serum CD3+, CD4+, CD4+/CD8+ overtopped the chemotherapy alone group's and its serum level CEA was less than those in the chemotherapy alone group (Yan & Han, 2019).

Similarly, Lin & Zhang (2017) studied the influence of CKI in adjuvant chemotherapy on advanced gastric cancer patients. They divided 83 patients into an observation group (CKI + modified FOLFOX6 chemotherapy) and a control group (only modified FOLFOX6 chemotherapy) to observe and compare the treatment effects, side effects, immune function indexes, and changes in levels of CA19-9 and CEA in these groups. The research found that the CD3+, CD4+, CD4+/CD8+ levels in CKI + modified FOLFOX6 chemotherapy group were higher than in the modified FOLFOX6 chemotherapy-only group, but its CD8+ was higher than observation group. The CA19-9 and CEA levels in FOLFOX6 chemotherapy-only group were lower than in the CKI +

FOLFOX6 chemotherapy group. Besides, the observation group's side effects were slightly less than in the FOLFOX6 chemotherapy-only group. The CKI combined with modified FOLFOX6 chemotherapy was safe and worth promoting in the clinic (Lin & Zhang, 2017).

In the same year, Yang (2017) divided the 118 recruited patients into test and control groups. The researcher observed and compared these two groups' levels of MMP-2, TNF-α, CEA, and adverse reactions to the drug after treatment. The study investigated the influence of CKI combined with FOLFOX4 chemotherapy on advanced gastric cancer patients. The studies reported that the test group's levels of MMP-2, TNF-α, CEA, and adverse reactions to the drug were not more than in the control group (Yang, 2017).

3.3 CLINICAL RESEARCH ON THE TREATMENT OF BREAST CANCER

In clinical research done by Mao & Yao in 2018, they divided 78 patients into an observation group (CKI + ACT chemotherapy) and a control group (only ACT chemotherapy) to observe the effect of postoperative treatment using CKI combined with ACT chemotherapy. The study also observed the safety of these treatments in patients with breast cancer. The studies displayed that after CKI + ACT chemotherapy treatment, the CEA, CA152, and CA125 levels and adverse reactions were less than the ACT chemotherapy-only treatment. Likewise, the observation group's quality-of-life score was better than the control group, and these differences were statistically significant (Mao & Yao, 2018).

In another study, Wang (2018) observed 87 patients with triple-negative breast cancer that were divided into two groups and received ACT chemotherapy simultaneously. The control and observation groups were given chemotherapy treatment, but the observation group was supplemented with CKI. During the short-term treatment of two groups of patients, their treatment efficacy and adverse reactions were analyzed, and the outcomes of breast cancer patients who used CKI on chemotherapy were observed. The research indicated that after treatment, patients in the observation group had higher short-term efficacy and KPS scores than those in the control group. The observation group's Q-C30 score and adverse reactions were lower than the control group's. It can have excellent clinical use in clinics (Wang, 2018).

Yao et al. (2019) reported in their clinical study that 188 patients with advanced breast cancer were divided into two groups to observe the patient's treatment efficacy and prognosis. The control group had 73 patients treated with TAC (Paclitaxel + Anthracyclines + Cyclophosphamide) regimen neoadjuvant chemotherapy, and the study group had 75 patients treated with CKI combined with TAC regimen neoadjuvant chemotherapy. The studies pointed the adverse reaction rate of the study group was lower than the TAC regimen neoadjuvant chemotherapy alone group. Its survival rate of 2-year and 3-year was significantly more than that in the control group. The patients with levels of CD3+, CD4+, CD4+/CD8+ in TAC regimen neoadjuvant chemotherapy alone were less than those treated with CKI combined with TAC regimen neoadjuvant chemotherapy. However, the CD8+ level exceeded that of the observation group. Compound *Kushen* injection can give a good impression of treatment and prognosis (Yao et al., 2019).

Qin et al. (2018) established an observation group (CKI + lapatinib) and a control group (lapatinib, a commonly used chemotherapy drug for breast cancer) to observe patients with Her-2 positive advanced breast cancer. They investigated the efficacy and influence of CKI on tumor markers. The results indicated that after treatment, the control group's adverse reaction rate, total effective rate, and KPS score were lower than in the observation group. Meanwhile, the ECOG (Eastern Cooperative Oncology Group) score standard was more than the observation group. Significantly higher CEA, CA153, and CA125 levels than the observation group were also reported. In the control group’s peripheral blood, the expressions of CD3+, CD4+, CD4+/CD8+, and CD69

were less than the observation group, but the CD8+ was more than the observation group. Compound *Kushen* injection combined with lapatinib was reported to have an excellent clinical effect on patients with Her-2 positive advanced breast cancer, and it can be promoted in clinical use (Qin et al., 2018).

Zhang, A Da Lai Ti, Ai, Tong, & Zhao (2018) randomly divided 90 patients who had metastatic triple-negative breast cancer into a test group (CKI combined with gemcitabine and carboplatin) and a control group (gemcitabine and carboplatin, which are commonly used chemotherapy drugs for breast cancer) to observe its clinical efficacy. The studies indicated that patients' objective remission rate and KPS score in the experimental group were better than in the gemcitabine and carboplatin-only group. The CEA, CA15-3, CA125 concentration and QLQ-C30 scores were less than those treated by gemcitabine and carboplatin alone. The test group showed a good curative effect for patients with metastatic triple-negative breast cancer treatment, and its treatment plan has clinical promotional value (Zhang, A Da Lai Ti, Ai, Tong, & Zhao, 2018).

Finally, in a recent clinical study by Ma et al. (2021), they divided 76 postoperative patients with invasive breast cancer into two groups to observe the clinical efficacy of the regiment. The observation group was treated with CKI combined with ECT (Taxol+Doxorubicin+Cyclophosphamide) chemotherapy, and the control group was treated with ECT chemotherapy only. The studies pointed out that the observation group's CD3+, CD4+ T lymphocytes, and CD4+/CD8+ ratio after treatment were all more than those before chemotherapy. However, the CD8+ T lymphocytes were less than those before chemotherapy. In the control group, CD3+, CD4+ T lymphocytes, and CD4+/CD8+ ratio had differences before and after chemotherapy treatment, and its CD8+ T lymphocytes were more than before chemotherapy. In the observation group, KPS score and quality-of-life improvement rate overtopped those in the ECT chemotherapy alone group. The CKI can enhance a patient's immune function and quality-of-life (Ma et al., 2021).

3.4 CLINICAL RESEARCH ON THE TREATMENT OF CERVICAL CANCER

In the treatment of cervical cancer, CKI proves to have an effect in improving patients' quality-of-life too. A study by Qu, Cheng, Liu, & Yin (2018) divided 61 patients with advanced cervical cancer into a control group with 31 patients and an observation group with 30 patients. They observed the therapeutic effect and patient's immune function after the treatment of CKI combined with docetaxel and nedaplatin. The studies claimed that in the observation group, its clinical benefit rate, total effective rate, and quality-of-life improvement rate after treatment exceeded those of the docetaxel and nedaplatin therapeutic group. The levels of CD3+, CD4+, CD4+/CD8+ and NK cells were more than that in the observation group. The adverse reaction incidence in the observation group was less than in the control group. The observation group showed an excellent curative effect on advanced cervical cancer patients and can enhance their immune function (Qu, Cheng, Liu, & Yin, 2018).

In another clinical study by Yan, Hou, & Song (2021), a random controlled trial of 67 patients was divided into two groups. The observation group (CKI + chemotherapy) had 34 patients, and the control group (chemotherapy only) had 33 patients. These two groups of patients' immune function and serum tumor markers were observed. These results pointed out that in the observation group, CD3+, CD4+, and CD4+/CD8+ ratios after treatment had increased. However, in the control group, the CD4+/CD8+ ratio decreased significantly. According to their report, immune function cell levels in the observation group were more than in the control group. In the observation group, serum CEA and CA125 levels were less than in the control group. The chemotherapy complemented with CKI positively affected advanced cervical cancer patients' serum tumor markers and immunity (Yan, Hou, & Song, 2021).

Yin, Zheng, Dong, Ji, & Xu (2021) clinically observed 102 patients in two groups during their study. The first group was the observation group with 50 patients (CKI + neoadjuvant chemotherapy), while the second group was the control group with 52 patients (neoadjuvant chemotherapy only). The effects of these two groups on CA125, CA199, and CEA were observed. The experimental results showed that the observation group's total remission rate overtopped the control group after the treatment. On the other hand, its side reactions ratio was lower than the neoadjuvant chemotherapy alone group. In the observation group, CA125, CA199, and CEA levels were not more than neoadjuvant chemotherapy alone. Likewise, its levels of CD4+, CD3+, CD4+/CD8+ exceeded the control group, except its CD8+ level was evidently less than the control group. The neoadjuvant chemotherapy complemented with CKI can reduce patients' tumor markers levels and reduce their neoadjuvant chemotherapy adverse reactions (Yin, Zheng, Dong, Ji, & Xu, 2021).

In a similar clinical study by Zhang, Zhang, Wan, & Lv (2018), they randomly divided 120 patients into two groups to observe the efficacy of the two groups on cervical cancer. The first group of patients was treated with CKI + radiotherapy, and the second group was treated with cisplatin combined with radiotherapy. The studies indicated that after the treatment, the experimental group's CD3, CD4, CD8, and CD56 exceeded the control group, except the IL-6 was less than the cisplatin combined with the radiotherapy group. Patients treated with CKI + radiotherapy had toxic side effects, which had apparent differences from the control group. The radiotherapy treatment added with CKI was worthy of clinical application (Zhang, Zhang, Wan, & Lv, 2018).

Dong, Zhang, Xu, & Qu (2020) divided 74 patients with cervical cancer as research subjects into two groups to observe and compare their treatment effects; one was the control group (simple radiotherapy and chemotherapy), and another one was the observation group (CKI + radiotherapy and chemotherapy). The studies indicated that the observation group's disease control rate was better after the treatment than the simple radiotherapy and chemotherapy group. The observation group's CD3+, CD4+/CD8+, and NK levels were higher than in the simple radiotherapy and chemotherapy group. Its toxic and side effects were less than in the control group too. The treatment of radiotherapy and chemotherapy with CKI had a better curative effect and can simultaneously improve the patient's immunity (Dong, Zhang, Xu, & Qu, 2020).

Ma & Ma (2018) observed the clinical treatment effect of cervical cancer patients treated with combined CKI treatment and chemotherapy. They divided the 80 patients into two groups to compare their treatment effects. The research showed that the chemotherapy + CKI group's T lymphocyte subsets and NK cell levels were higher than the chemotherapy alone group. The chemotherapy + CKI group's IFN-γ and IL-2 levels were increased, but its IL-4, IL-6, and IL-10 levels were remarkably reduced. Thus, CKI was helpful for patients with cervical cancer and can improve their cellular immune function during radiotherapy and chemotherapy. Therefore, it had clinical promotional value (Ma & Ma, 2018).

Liu, Yang, Peng, Xie, & Zhang (2020) selected 90 patients with advanced cervical cancer and divided them into an observation group (CKI combined with chemotherapy and intensity-modulated conformal radiotherapy) and a control group (chemotherapy and intensity-modulated conformal radiotherapy), to compare and to observe the clinical effects between them. The research indicated that in the control group after treatment, its total effective rate and quality-of-life were lower than in the observation group. The observation group's serum MMP-9 and OPN levels were remarkably less than in the control group. Its serum IL-6 and IL-4 levels were also lower in the control group. The levels of its serum IL-2 and IFN-γ were significantly exceeded those in the control group. Its adverse reaction incidence was lower than in the control group. Whereas its 2-year survival rate was

higher than in the chemotherapy and intensity-modulated conformal radiotherapy group. Treating chemotherapy and intensity-modulated conformal radiotherapy with the addition of CKI can enhance the therapeutic effects, strengthen the patient's immunity, and alleviate adverse reactions (Liu, Yang, Peng, Xie, & Zhang, 2020).

3.5 CLINICAL RESEARCH ON THE TREATMENT OF COLON CANCER

Many clinical reports have supported using CKI to treat colon cancer. Among the published research articles is the clinical trial by Wang (2021), who divided 98 postoperative patients with advanced colon cancer into two groups to observe their treatment effect; a control group (FOLFOX4 regimen chemotherapy) and an observation group (CKI + FOLFOX4 regimen chemotherapy). The research examined that CKI + FOLFOX4 regimen chemotherapy group's total effective rate was better than that in the chemotherapy group. Its CD4+, CD4+/CD8+, and NK cell levels exceeded the chemotherapy alone group, except its CD8+ level was less than in the chemotherapy group. The FOLFOX4 chemotherapy added with CKI has an excellent therapeutic effect on patients and enhances their immune function (Wang, 2021).

In another clinical study, Zhu, Xiong, Gu, He, & Li (2017) divided 70 elderly patients with colorectal cancer into two groups. The control group was treated with chemotherapy alone, and the observation group was treated with CKI + chemotherapy. They studied the different treatment influences in elderly advanced colorectal cancer patients. The research examined that the effectiveness rate in the observation group was better than in the chemotherapy alone. Similarly, its CD3+, CD4+, and CD4+/CD8+ levels exceeded the control group, but its CD 8+ level was less than in the control group. The chemotherapy added with CKI can influence elderly patients with colorectal cancer treatment. It is also helpful to improve their immunity and has clinical application value (Zhu, Xiong, Gu, He, & Li, 2017). Zhang & Wu (2017) selected 82 patients who had colorectal cancer and divided them into two groups, one was the control group (CKI + FOLFOX4 chemotherapy), and another one was the treatment group (FOLFOX4 chemotherapy only), and observed their clinical efficacy. The experimental results showed that after the treatment, the remission and disease control rates of the control group were less apparent than in the treatment group. With regard to the incidence of untoward effects such as myelosuppression and gastrointestinal effects, the control group had more incidences than the treatment group. In the control group, its CD3+, CD4+, CD16+/CD56+, and CD4+/CD8+ peripheral blood were significantly lower than in the treatment group, but its CD8+ was considerably higher than in the treatment group. Likewise, the control group's survival rate was lower than that of the treatment group. FOLFOX4 chemotherapy with CKI had good effects on colorectal cancer patients' survival time and can be clinically promoted (Zhang & Wu, 2017).

In 2021, Xue compared the observation group with the control group's clinical efficacy, adverse reactions, and levels of CD3+, CD4+, CD4+/CD8+ to study the effect on patients with colon cancer. The patients were treated in the short term by CKI combined with raltitrexed + oxaliplatin chemotherapy, and their immune functions were. The experiment showed that after treatment, the observation group's objective remission and disease control rates were better than in the raltitrexed + oxaliplatin chemotherapy group. Its levels of CD4+, CD8+, CD4+/CD8+ overtopped those in the control group. Its incidence rate of side effects was less than those treated by raltitrexed + oxaliplatin chemotherapy alone. The therapy of raltitrexed + oxaliplatin chemotherapy with CKI can provide a good effect in short-term treatment, improve the patient's immune system, and alleviate chemotherapy side effects in colon cancer patients (Xue, 2021).

Similarly, in 2018, Tong et al.(2018) selected 60 patients with colon cancer after surgery. They divided them into two groups: the observation group (CKI combined with paclitaxel) and the control

group (paclitaxel, a commonly used chemotherapy drug for colon cancer) to study CKI combined with paclitaxel therapeutic effect. These results showed that after treatment, the observation group's total effective rate overtopped those in the control group, but its adverse reaction incidences were less than the control group. In the observation group, its CD3+, CD4+, CD4+/CD8+ levels, and NK cells were more than in the chemotherapy group, except its CD8+ level was less than in the chemotherapy group. The CKI + chemotherapy group's tumor necrosis factor γ and interleukin-2 levels and its T lymphocyte transfer rate exceeded the control group. Likewise, the lymphocyte apoptosis rate was shorter than the control group. Compound *Kushen* injection combined with paclitaxel can effectively inhibit tumor cell proliferation, improve immune function, and have apparent therapeutic effects on colon cancer patients (Tong et al., 2018).

Lastly, Zhang & Bai (2017) randomly divided 46 patients who had advanced colon cancer into two groups to compare and observe their treatment effects: one was the control group (simple radiotherapy and chemotherapy), and another was the treatment group (CKI + radiotherapy and chemotherapy). After the treatment, results indicated that the treatment group's total effective rate was more than that of the control group. Its levels of CD3+, CD4+, CD4+/CD8+, and NK cells also exceeded those in the control group. Its incidence rate of side effects was less than that of radiotherapy and chemotherapy. Compound *Kushen* injection enhanced the curative effect of radiotherapy and chemotherapy, built patients' body's immunity, and reduced radiotherapy and chemotherapy side effects (Zhang & Bai, 2017).

4 CONCLUSIONS

In summary, compound *Kushen* injection is widely evaluated in clinical practice. When combined with radiotherapy and chemotherapy drugs, its anti-tumor effect can enhance the patient's body's immune function, decrease radiotherapy and chemotherapy side effects, enhance patients' life quality, and extend their lifetime. It's often used for lung cancer, gastric cancer, breast cancer, bowel cancer, cervical cancer, and others. However, the CKI contains more ingredients and has more functions. Therefore, the anti-tumor mechanism is still unclear, and the related anti-tumor targets were less reported. These difficulties in CKI research have seriously affected the international promotion of CKI. The anti-tumor mechanism of matrine and oxymatrine, the primary alkaloid components of CKI, still needs comprehensive and in-depth research, as it will be popularized globally very soon.

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