

Research Progress on the Antitumor Mechanism of Compound Kushen Injection

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Abstract: Compound Kushen Injection (CKI), as a clinical traditional Chinese medicine preparation, has prominent antitumor effect but with several side effects. A large number of studies have shown that CKI plays an antitumor role by regulating tumor cell proliferation, inducing tumor cell differentiation and apoptosis, inhibiting tumor cell invasion and metastasis, reducing tumor angiogenesis, regulating the immunity, and so on. Clinically, CKI is widely used to treat various tumors, where it is often combined with surgery, chemotherapy, radiotherapy, targeted therapy, and other antitumor treatments. This article reviews the antitumor mechanism of CKI and the progress of its clinical application in order to provide a theoretical basis for further clinical application.

Keywords: Compound Kushen Injection; Gastrointestinal neoplasms; Immunity; Drug resistance

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1. Introduction

With the changes of people's living habits and the increasing aging population, the number of patients with malignant tumors in China is increasing, which seriously endangers the health of the nation. Therefore, it is urgent to find an effective treatment. At present, surgical treatment, chemotherapy, and radiotherapy are often used for malignant tumors but the adverse reactions from these treatments are large in addition to their low compliance. CKI is made up of *Heterosmilax japonica* Kunth and *Radix Sophorae Flavescentis*, which are processed by modern technology. It has many functions, such as hemostasis, relieving pain, enhancing immunity, improving hematopoietic function, inhibiting the proliferation and metastasis of malignant tumor cells, as well as improving patients' quality of life. In recent years, research have shown that CKI has good curative effect for various gastrointestinal tract tumors, such as esophageal cancer, gastric cancer, and colorectal cancer, and has become a commonly used antitumor therapeutic drug in clinical practice.

2. Antitumor mechanism of CKI

CKI is mainly composed of matrine, oxymatrine, and other matrine alkaloids, which have various pharmacological activities, of which the most significant is its antitumor activity^[1]. The alkaloids from *Sophora flavescens* have antitumor properties, where they regulate tumor cell proliferation, induce tumor cell differentiation and apoptosis, inhibit tumor cell invasion and metastasis, reduce tumor angiogenesis, regulate immunity, and so on. As aforementioned, in recent years, research have shown that CKI has good curative effect for gastrointestinal tract tumors, such as esophageal cancer, gastric cancer, and colorectal cancer, without serious adverse reactions. Several studies have shown that matrine can significantly inhibit

the proliferation and promote the apoptosis of a specific esophageal cancer cell line (Eca-109). Its effect may be achieved by the blocking of the cell cycle at the G2 phase ^[2] or due to the downregulation of immunoglobulin heavy-chain-binding protein (BiP) gene expression of endoplasmic reticulum stress-related gene and the transcriptional activation of C/EBP cyclic adenosine monophosphate response element binding transcription factor homologous protein (CHOP) gene ^[3]. Wenlu Zhang and other researchers ^[4] found that CKI can induce the apoptosis of a human gastric cancer cell line (SGC-790) by enhancing the expression of Bak, caspase-3, and other apoptotic proteins. Matrine, the active component of CKI, can induce apoptosis and inhibit proliferation of a specific human colon cancer cell line, SW480. Its mechanism may be related to inhibiting the activation of Akt signaling pathway ^[5]. In addition, matrine can also regulate the drug resistance of human colon cancer drug-resistant cell lines, whereby its mechanism may be related to its inhibition of c-Jun N-terminal kinase or stress-activated protein kinase (JNK/SAPK) signaling pathway ^[6]. Oxymatrine, which is another active component of CKI, can significantly inhibit the proliferation of LoVo cells and induce their apoptosis. The suggested mechanism is that oxymatrine promotes the stagnation of the cell cycle of LoVo cells at G2 and S, as well as reduces the expression of p53 gene that is related to LoVo cell apoptosis ^[7].

3. Clinical application of CKI in the treatment of various tumors

With concurrent radiotherapy and chemotherapy, CKI can significantly reduce the incidence of adverse reactions which are related to both radiotherapy and chemotherapy as well as improve the quality of life of patients while having obvious curative effect, reducing toxicity, and increasing efficiency ^[8]. Advanced gastric cancer is often complicated with malignant ascites. Studies have shown that CKI combined with intraperitoneal hyperthermic chemoperfusion, performed with cisplatin, can significantly inhibit the occurrence and development of malignant ascites with less adverse reactions ^[9]. In addition, the effect from the combination of CKI and tegafur, an oral chemotherapy drug, in the treatment of advanced gastric cancer is also excellent; it has been widely used in clinics in view of its high safety property ^[10].

4. Conclusion

With the continuous in-depth experimental research on CKI in China, the antitumor mechanism of this drug is much more understood. Studies have shown that CKI can inhibit the proliferation, invasion, and metastases of tumor cells, induce the apoptosis of tumor cells, inhibit gastrointestinal tumors, such as esophageal cancer, gastric cancer, and colon cancer, as well as strengthen the immunity and antitumor immune response of the body. Combined with chemotherapeutic drugs, it can inhibit the proliferation, metastases, and diffusion of tumor cells to a large extent, reduce the tumor recurrence rate postoperatively, and prolong the survival of patients. At the same time, the drug can improve the efficacy of radiotherapy and chemotherapy, reduce the drug resistance toward chemotherapy drugs along with the side effects caused by radiotherapy or chemotherapy, enhance the sensitivity and tolerance of patients to radiotherapy or chemotherapy, as well as improve the quality of life of patients. Although there are many research on the antitumor mechanism of CKI, most of them are based on the purified alkaloids from *Sophora flavescens*. The antitumor mechanism of CKI with these alkaloids as the main component still requires more comprehensive and in-depth research.

Disclosure statement

The authors declare that there is no conflict of interest.

References

- [1] Yang LY, Fan HZ, 2016, Research Progress on the Mechanism and Clinical Application of Matrine and Oxymatrine in the Treatment of Digestive Tumor. *Practical Clinical Medicine*, 17(5): 97-100.
- [2] Du HX, Cao YP, Geng GJ, et al., 2012, Effects of Matrine on Proliferation and Apoptosis of Human Esophageal Cancer Cell Line Eca-109. *Guangming Journal of Chinese Medicine*, 27(6): 1096-1101.
- [3] Cao S, Zhou HR, Zhu YQ, 2014, Effect of Matrine on the Expression of BIP and CHOP mRNA in Esophageal Cancer Eca-109 Cells. *Journal of Zhengzhou University (Medical Science)*, 49(1): 1-4.
- [4] Zhang WL, Cui HX, Wang Y, 2012, Inducing Effect and Mechanism of Compound Kushen Injection on Apoptosis of Gastric Cancer Cell Line SGC-7901. *Guangdong Medical Journal*, 33(14): 2061-2063.
- [5] Yang P, Zhang S, Guo S, et al., 2017, Matrine Inhibits Akt Signaling Pathway and Induces Apoptosis of Colon Cancer SW480 Cells. *Chinese Journal of Experimental Traditional Medical Formulae*, 23(7): 109-113.
- [6] Li JZ, Chen NN, Dai MQ, et al., 2017, Effects of Matrine on the Growth, Migration and Invasion of Colon Cancer Cells. *Journal of Chinese Medicinal Materials*, 40(9): 2161-2165.
- [7] Wang W, Zheng B, Ren R, et al., 2018, Effects of Matrine on Oxaliplatin Resistance in Colon Cancer. *China Journal of Modern Medicine*, 28(30): 20-25.
- [8] Han L, Peng Y, Sun J, et al., 2012, Research on Effects of Oxymatrine on Cell Proliferation and Apoptosis of Colon Cancer LoVo Cells. *Liaoning Journal of Traditional Chinese Medicine*, 39(8): 1455-1459.
- [9] Ma QH, Fang IM, Chen R, 2017, Application of Compound Kushen Injection in Cisplatin Intraperitoneal Infusion Chemotherapy in Patients with Malignant Ascites of Gastric Cancer and Its Effect on Immune Function. *Chinese Journal of Biochemical Pharmaceutics*, 37(2): 109-112.
- [10] Pu Y, Zheng ZD, Tang L, et al., 2016, Analysis on Efficacy and Safety of Tegafur Combined with Compound Kushen Injection in the Treatment of Advanced Gastric Cancer in the Elderly. *Chinese Clinical Oncology*, 21(6): 535-539.