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The mechanism of traditional Chinese medicine in the treatment of gastric cancer using the method of tonifying qi, removing blood stasis, and detoxifying

Chen Liang[1], Xuequan Yao[1,*]

[1]Nanjing University of Chinese Medicine, Nanjing, China
[*]Corresponding author

Abstract: *Gastric cancer (GC) is one of the most common malignant tumors in the world. It is the fourth most common cancer globally and has the second highest mortality rate. Metastasis is an important characteristic and cause of death of GC. Exploring the mechanism of GC metastasis and finding new drug targets has become a focus. Traditional Chinese medicine may have a great potential promising in treating GC. This article reviews the research progress on the anti-metastatic activity of traditional Chinese medicine to promote the clinical development of GC treatment.*

Keywords: *Traditional Chinese medicine science, Metastatic tumors, gastric cancer, cell cyclen*

1. Introduction

Gastric cancer (GC) is the most common malignant tumor in the digestive system and malignant tumor metastasis is one of the main causes of death. China accounts for 42.6% of global gastric cancer cases. With the continuous research on traditional Chinese medicine, a large number of studies have shown that traditional Chinese medicine can improve efficacy and reduce side effects in cancer treatment. Chen et al. [1] found that the use of HCC (a common primary liver cancer in hepatobiliary surgery) by Huaier after therapeutic liver resection is effective, prolonging the recurrence free survival time of tumor patients and reducing extrahepatic recurrence. In addition, Von Hagens et al. [2] pointed out that in a phase I study, long-term oral artesunate for metastatic breast cancer patients can consolidate the initial therapeutic effect and safety. Deeken et al. [3] pointed out that intravenous injection of artemisinin at a dose of 18 mg/kg has good tolerance for the treatment of solid tumors and reduces side effects. Compared with Western medicine chemotherapy and radiotherapy, traditional Chinese medicine attaches great importance to overall regulation, which is an effective treatment method in tumor model systems to reduce side effects, improve survival rates, and prolong survival. Some anti-radiation traditional Chinese medicines have been proven to be effective in improving the sensitivity of chemotherapy and radiation therapy. Evidence from meta-analysis suggests that the combination of traditional Chinese medicine and chemotherapy has a positive effect on the treatment of GC. Therefore, traditional Chinese medicine is of great significance in reducing side effects, safety, and tolerability in adjuvant therapy. The purpose of this review is to elucidate the mechanism of the Yiqi Huayu Jiedu method in the treatment and prevention of GC metastasis with traditional Chinese medicine.

2. Inhibiting the proliferation of GC cells

2.1 Cell cycle arrest

Sophora flavescens extract, Astragalus polysaccharides, and Cinobufotalin can induce G1 cycle arrest. Sun et al. [4] found that cytochrome factors induce cell cycle arrest in the G0/G1 phase of SGC-7901 cells. Extracts of berberine and Cananga odorata can induce G2/M cell cycle arrest and inhibit the proliferation of GC cells.

2.2 Inhibition of telomerase activity

Caliskan et al. [5] found that telomerase activity regulates the expression of human telomerase reverse transcriptase (hTERT) in GC cells, and proposed that inhibiting telomerase activity may be a potential

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anti-cancer therapeutic mechanism. Another study evaluated the telomerase activity of BGC-823 human GC cells using the PCR-TRAP method and found that gambogic acid (GA) can inhibit telomerase activity by inhibiting Akt phosphorylation and reducing hTERT expression. Duan et al. [6] confirmed that piperonamide (PL) exerts anti-cancer effects by inhibiting telomerase activity and cell proliferation.

2.3 Mitochondrial apoptosis pathway

Wang et al. [7] found that the Astragalus membranaceus extract and celastms orbiculatus extracts (COE) can alter the mitochondrial membrane potential of cells, downregulate apoptosis related proteins Bax and caspase, and increase the expression of bcl-2 and PI3K/Akt. They suggest that COE may inhibit the proliferation and metastasis of GC cells by inducing apoptosis.

Pseudolaric acid B (PAB) has been shown to promote apoptosis in various cells. XX has evaluated the molecular mechanism of the anti-tumor activity of PAB in human leukemia U937 cells: U937 cells are activated by the bcl-2-mediated mitochondrial pathway, while caspase dependent activation is regulated by PAB. In addition, the activity of caspase-3 was increased after PAB treatment. Therefore, PAB at least partially promotes apoptosis of U937 cells by activating the pathway of mitochondrial apoptosis.

Mao et al. [8] found that the crocodile bile (rich in bile acids and flavonoids) accelerates GC cell apoptosis through the mitochondrial apoptosis pathway. During this period, the following events occurred simultaneously: a decrease in mitochondrial membrane potential, production of reactive oxygen species, an increase in Bax/Bcl-2 ratio and activation levels of caspase-3, and release of cytochrome c. These events indicate that alligator choline effectively inhibits GC cells through the mitochondrial apoptosis pathway.

2.4 Other aspects of inhibiting GC cells

The literature indicates that traditional Chinese medicine also exerts its anti-GC effect through cell autophagy. For example, curcumin can inhibit the proliferation of GC cells by inducing autophagy and apoptosis. Lei [9] has observed that mulberry anthocyanins can induce autophagy in SGC-7901 cells.

Some studies have shown that traditional Chinese medicine can inhibit tumor cells through reactive oxygen species (ROS). Kim DH et al. [10] reported for the first time that isoliquiritigenin (ISL) liposomes induce apoptosis of Caki cells (human renal clear cell carcinoma skin metastatic cells) by producing ROS, thereby inducing p53 and inhibiting the Stat3 signaling pathway. Silymarin can induce caspase dependent cell death in vitro and inhibit glioma growth in vivo through the Ca2+/ROS/MAPK mediated pathway. There are other natural products that also have anti-cancer effects. Batacharia et al. [11] found that bitter gourd extract (BME) enhances natural killer (NK) cell-mediated HNSCC (head and neck squamous cell carcinoma) killing activity and reveals the potential immunomodulatory effect of BME. In addition, they have shown that BME inhibits cell proliferation in mouse tumors by reducing the expression of proliferating cell nuclear antigen (PCNA) and c-Myc. Mummerd et al. [12] demonstrated that BME achieves anti-tumor activity by inducing autophagy and the AMPK/mTOR pathway. The oral BME feeding effectively inhibited cancer cell growth in both isogenic and xenograft mouse models. Both of their studies indicate that BME has high clinical application potential.

3. Inhibiting the movement of gastric cancer cells

3.1 Transfer and intrusion

Lu et al. [13] reported that fibrinolysin exerts its effect by inhibiting the invasion and metastasis of human GC SGC-7901 cells and downregulating MMP-9 and MMP-2. Yan et al. [14] found that baicalin can inhibit the proliferation, adhesion, invasiveness, and migration ability of SGC-7901 cells. Its potential mechanism is to inhibit the expression of MMP-9 and MMP-2 by inhibiting the activity of the p38 signaling pathway. Zhang et al. [15] demonstrated that Alisol B can regulate the phosphorylation of vasodilator stimulated phosphoprotein (VASP) and inhibit the adhesion and migration of gastric cancer cells.

3.2 Adhesion

Increasing the expression of cell adhesion molecules and degradation of extracellular matrix can

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control cancer metastasis and reduce cancer cell migration.

3.3 Regulating the expression of adhesion molecules

Sun et al. [16] found that serum mice cultured with HepG2 cells were fed Biejia Jianwan, which showed β Low expression of sericin in cytoplasm and nucleus, as well as inhibition of GSK-3 β Phosphorylation and reduction of CD44v6 and VEGF expression.Biejia Jianwan has an inhibitory effect on the proliferation and invasion of cancer.

Xu [17] found that Sophora japonica extract can partially reverse epithelial mesenchymal transition (EMT) by reducing the expression of mesenchymal markers N-cadherin and vimentin, and increasing the expression of epithelial cell cadherin. Huaier extract can significantly inhibit the migration and invasion ability of gastric cancer cells. Through the comprehensive clinical analysis, Ma et al. pointed out that Huaier extract may enhance clinical treatment efficacy and reduce the side effects of gastrointestinal cancer.

3.3.1 Inhibition of extracellular matrix degradation

Wu et al. [18] found that the combination of apatinib and AsPs can inhibit the expression of phosphorylated AKT (p-AKT) and MMP-9. Compared with apatinib monotherapy, the combination of apatinib and AsPs has an enhanced inhibitory effect on cell proliferation, migration, and invasion. Jiao et al. [19] found that after incubation with different concentrations of tanshinone IIA (TSN), the migration and proliferation of SGC-7901 cells decreased in a dose-dependent manner. In SGC-7901 cells treated with TSN, the expression levels of Ki-67, PCAN, MMP-2, MMP-9, and FOXM1 decreased, while the expression levels of P21 increased.

3.4 Regulating metastasis related genes to inhibit cancer cell metastasis

The metastasis of gastric cancer cells can be inhibited by regulating the expression of metastasis related genes in gastric cancer. In 2003, Ishikawa et al. [20] reported that VEGF-C and - D genes may be associated with lymph node metastasis in early gastric cancer, suggesting that VEGF-C and - D genes inhibit tumor metastasis. Dai et al. reported that ginsenosides can target vegf-c, vegf-d, and vegfr-3 genes in a mouse model of human gastric cancer cells, inhibiting the progression and metastasis of malignant tumors. Bao et al. [21] reported that naringenin may inhibit the migration and invasion of human gastric cancer SGC-7901 cells by reducing the expression of metastasis related genes MMP-2 and MMP-9. Liu et al. [22] reported that dehydroferphenol can significantly inhibit the migration and invasion of gastric cancer cells in vitro and in vivo. Dehydrofluconazole can inhibit gene promoter activity, affect the expression of vascular mimicry main gene VE cadherin, significantly reduce the expression of metastasis related gene (MMP2) in gastric cancer cells, and effectively inhibit gastric cancer metastasis. The proliferation of gastric cancer cells not only increases the pressure between gastric cancer cells, but also enhances metastasis. Most traditional Chinese medicine exhibits anti metastatic effects by regulating relevant oncogenes and anti-cancer genes, further inhibiting cell proliferation and inducing cell apoptosis. Recent studies have shown that transfer related genes include Bcl-2, Bax, maspin, and p53. Mu et al. [23] found that baicalin has anti apoptotic activity in SGC-7901 cells by downregulating Bcl-2 and upregulating Bax. Qian et al. [24] found that COE can induce apoptosis in human gastric cancer MGC-803 cells overexpressing the maspin gene.

4. Conclusion

This article summarizes how traditional Chinese medicine intervenes at multiple levels and affects multiple targets, thereby affecting the metastasis of GC. However, due to the various ways and complex components of the anti-tumor effect of traditional Chinese medicine, its active ingredients are difficult to determine, which is greatly limiting its potential. In addition, clinical research in traditional Chinese medicine still lacks in-depth research and evaluation standards, its authenticity has not been largely recognized. These findings suggest that the multiple effects of traditional Chinese medicine should be combined with Western medicine, allowing for the use of comprehensive drugs for tumor control. Further rigorous research is expected to demonstrate the clinical significance of traditional Chinese medicine in the treatment of gastric cancer metastasis and improve preventive measures. With the continuous discovery and deeper exploration of the pathogenesis of gastric cancer, as well as the recognition of new molecular targets, people have discovered targets for the treatment of gastric cancer with traditional Chinese medicine. The role of traditional Chinese medicine has been determined at the molecular level,

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providing a foundation for its clinical application.

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