

Advances in the study of anti-tumor effects of Rhodiola rosea

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Abstract: Rhodiola rosea is a genus of Rhodiola in the family Rhodiola Rosea, and is a top-quality medicine for strengthening and tonic deficiency. Modern research has found that Rhodiola rosea has various pharmacological effects such as anti-fatigue, anti-oxidant, anti-aging, anti-inflammatory and anti-tumor. As the main active ingredient of Rhodiola rosea, Salidroside can exert anti-tumor effects by inhibiting tumor cell proliferation, inhibiting cell migration, promoting apoptosis, inducing autophagy, inhibiting neovascularization and infiltration and metastasis, and enhancing immunity, with concentration-dependent mechanism. This paper summarizes the relevant antitumor studies of Rhodiola rosea and Rhodioloside on different types of common tumors, in order to provide some theoretical basis for the clinical application of Rhodiola rosea.

1. Introduction

Rhodiola rosea is a perennial herb or subshrub of the genus Rhodiola in the family Rhodiola, and is often used clinically as a root, rhizome, or whole herb to strengthen the root, nourish the blood, clear heat and moisten the lung, etc. It was first published in the Four Medical Classics ^[1], and has been widely used throughout China as an important medicine for strengthening and tonifying the deficiency. It is also distributed in the north of China, from Xinjiang, Tibet, Shanxi, Hebei, Jilin, etc., and Europe to Russia, Mongolia, Korea, Japan, etc. Modern pharmacological research has found that rhodiola not only has antioxidant, anti-fatigue, anti-aging and anti-inflammatory effects, but also has anti-tumor effects.

Relevant phytochemical studies have shown that there are six main classes of important components in Rhodiola rosea rhizome, including phenylethanol and its glycosides, phenylpropanoids, flavonoids, monoterpenes, triterpenes, and phenols, and many other components, such as organic acids, proteins, and fats ^[2-4]. Phenylethyl alcohol and its glycosides, phenylpropanoids are representative compounds in Rhodiola rosea, and phenylethyl alcohols are represented by rhodiol glycosides. Salidroside (Sal), the main active component of Rhodiola rosea, is used in the Chinese Pharmacopoeia as the main quality indicator of the medicinal value of Rhodiola rosea ^[5]. Chai Yaqing et al ^[6] isolated and purified the chemical constituents in large plants of Rhodiola rosea and identified their compound structures, and found that among them, rhodioloside had a significant inhibitory effect on tumor cells. A review of the studies related to the

antitumor effects of *Rhodiola rosea*, especially rhodiol glycosides on various common tumors, is presented in order to provide more basis for clinical applications.

1.1 Lung cancer

Lung cancer is one of the most common malignant tumors, with a high incidence rate and the highest mortality rate in China and even worldwide ^[7], and its treatment options are changing rapidly. Surgery, radiotherapy, targeted and immunotherapy all play a pivotal role in the treatment of lung cancer, but the treatment process can be interrupted due to tumor metastasis, drug resistance, adverse reactions and physical condition, so people have started to focus on traditional medicine. Zhang Min et al ^[8] studied the effects of different concentrations of *Rhodiola rosea* extract on Lewis lung cancer cells, and the results showed that regardless of the concentration of *Rhodiola rosea* extract could inhibit the value-added of LLC tumor cells, inhibit the growth of transplanted tumors in nude mice, and promote apoptosis of tumor cells, but its anti-tumor effect was altered in a dose-related manner. It was found that both salidroside and cisplatin groups could destroy tumor cell structure and induce apoptosis of tumor cells, thus inhibiting the growth of human lung cancer A549 cells transplanted tumor in nude mice, and the efficacy of high-dose salidroside group was even better than that of cisplatin group, which may be related to the inhibition of MAPK/ERK1 /2 signaling pathway and reduction of p - ERK1 /2 level ^[9]. It was found that salidroside inhibited NSCLC proliferation and metastasis by regulating miR103-3p/Mzb1. Salidroside upregulated miR-103-3p expression in cell lines and clinical tissue samples of NSCLC, while miR-103-3p was able to inhibit metastasis of A549 and H460 lung cancer cells by inhibiting the function of Mzb1 ^[10]. Previous clinical and laboratory studies by our group found that Da Zhu Hong Jing Tian injection combined with cisplatin thoracic perfusion could effectively reduce pleural effusion, lower serum VEGF , CEA, CYFRA21-1, CA125, and NSE levels, and the adverse effects were significantly lower than those in the cisplatin control group ^[11]. Zhou Xiaolong et al ^[12] used *Rhodiola rosea* injection for the treatment of advanced non-small cell lung cancer, which reduced tumor markers, improved TCM symptom scores, and improved immune function compared with the control group of compound bitter ginseng injection.

1.2 Colorectal cancer

Colorectal cancer is the most common malignant tumor of the digestive system, and its incidence and mortality rate are increasing year by year, seriously endangering human health. Yan Shengyu et al ^[13] found that salidroside could inhibit the proliferation, induce autophagy and apoptosis of human CRC HT29 cells through the mechanism of inhibiting PI3K/Akt /mTOR signaling pathway in vitro, thus achieving anti-tumor effects with concentration-related changes. Additional studies found that salidroside inhibited HT29 CRC tumorigenesis by increasing the activation of eIF-2 α and JNK and by upregulating and activating PKR upregulating p53, p38 MAPK and caspase-8. this experiment also found that the tumor suppressive effect of salidroside also required inhibition of STAT3 and NF- κ B by a PKR-independent mechanism ^[14]. Experiments have shown that salidroside regulates protein expression at the level of its phosphorylation in the JAK2/STAT3-dependent pathway, downregulates the expression of STAT3 target proteins matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF), and simultaneously blocks SW1116 colorectal cancer cells in the G0/G1 phase, thereby inhibiting cell proliferation and reducing tumor migration and invasion ^[15].

1.3 Stomach Cancer

Gastric cancer is the fourth most common cancer worldwide and the third most common cause of cancer-related death ^[7]. The prognosis of advanced gastric cancer remains poor despite the use of multiple therapeutic modalities such as surgery, chemotherapy and established endoscopic treatments for the treatment of gastric cancer. Li Rong et al ^[16] found that salidroside inhibited the proliferation of gastric cancer AGS cells in vitro and in vivo through the PI3K/Akt/mTOR pathway in a dose-dependent manner and induced apoptosis and autophagy, significantly reducing the tumor size in nude mice. It was also found that rhodiogenin-mediated autophagic response could protect gastric cancer cells from external attack, while the combination of autophagy inhibitor significantly promoted rhodiogenin-induced apoptotic cell death. Huang Wei et al ^[17] found that gastric cancer cells with different degrees of differentiation could be inhibited by the value-added effect of salidroside, and its concentration was linearly correlated, and salidroside could block the cell cycle of gastric cancer cells in G2/M phase. It can also promote apoptosis by down-regulating the expression of anti-apoptotic gene Bcl-2 and Bcl-xl and promoting the expression of apoptotic gene Bax. It was demonstrated that salidroside inhibits horizontal, vertical and directional migration of tumor vascular endothelial cells and thus regulates neovascularization which may be achieved through inhibition of PI3K/AKT and MAPK/ERK signaling pathways ^[18-19].

1.4 Breast cancer

The incidence of breast cancer is located in the first place of female tumor incidence all over the world ^[7], and the treatment of breast cancer at the present stage contains surgery, radiotherapy treatment, endocrine hormone therapy, targeted therapy, etc. Chinese herbal medicine is also an important part of the treatment. Yaqing Chai et al ^[6] used Transwell chemotaxis assay to determine the anti-tumor metastatic effect of large strains of rhodiola rosea compounds and found that salidroside had a significant inhibitory effect on human breast cancer cells, and its chemotaxis inhibition rate was significantly higher than that of other compounds. Lotfi M. Bassa et al ^[20] found that salidroside extract has estrogenic compounds that activate ER-mediated responses in MCF7 breast cancer cells and that prolonged treatment with Rhodiola rosea extract reduced overall proliferation and estrogenic responses in ER+ MCF7 cancer cells and decreased tumorsphere formation in cells, but ER function and activity were not affected. Related experiments investigating the effect of salidroside on MCF-7 breast cancer cells found that the tumor suppression rate of high-dose salidroside was significantly higher than that of paclitaxel and saline, reaching 75.16%, while it inhibited tumor cell proliferation and promoted tumor cell apoptosis by decreasing the expression of anti-apoptotic proteins Bcl-2 and p53 and increasing the expression of pro-apoptotic proteins Bax and caspase 3 ^[21].

1.5 Gynecological tumors

Common gynecological tumors include cervical cancer, ovarian cancer and endometrial cancer, which are common types of female tumors and are a serious threat to women's health. Wang Na et al ^[22] evaluated the immunomodulatory and antitumor effects of salidroside on normal mice by measuring serum hemolysin, antibody-producing cell levels, phagocytic index and phagocytic activity, and immune factor expression, and found that the IgM and IgG contents, phagocytic capacity of mononuclear macrophages, thymic index and serum albumin content of mice treated with different concentrations of rhodiola glycosides were significantly increased, which could enhance the cellular immune function of normal mice. It also inhibits tumor development by increasing the expression of immune factors such as INF- γ , TNF- α and IL-2 in cervical cancer U14

tumor-bearing mice. The tumor suppression rate of the high-dose group was 33.2%, which was significantly higher than that of the low-dose group (21.1%). In order to investigate the effect of salidroside on the proliferation of ovarian cancer cells SKOV3, Mo Rongfian et al compared the inhibition rate and half inhibition concentration of cisplatin and different concentrations of salidroside on SKOV3 cells, and found that the inhibitory effect of both on SKOV3 cell value-added was concentration and time-of-action dependent, and the overall inhibitory effect of both drugs was similar^[23].

1.6 Other Tumors

Salidroside have anti-tumor effects on many other tumors, such as liver cancer, head and neck tumors, kidney cancer, etc. Jiang Bing et al^[24] observed autophagy in human highly metastatic hepatocellular carcinoma cell line 97H after treatment with salidroside and found that salidroside may induce autophagy in 97H cells by upregulating Beclin-1 mRNA, downregulating p62 mRNA, increasing the ratio of LC3-II to LC3-I, upregulating Beclin-1 protein level, and downregulating p62 protein level. Related experimental studies found that salidroside acting on U87-MG cells significantly decreased cell invasion ability and also induced apoptosis in U87-MG cells, and different concentrations of salidroside were able to participate in and affect the apoptosis-inducing pathway in response to the Caspase-3 cascade apoptotic pathway, decreasing the expression of Bcl-2 anti-apoptotic proteins and increasing the expression of Bax pro-apoptotic proteins^[25]. It was shown that salidroside could elevate the protein expression levels of Bax and Cleaved caspase3 and decrease the reduced protein expression level of Bcl2, thus inhibiting the proliferation of human tongue cancer Tca-8113 cells and inducing their apoptosis, and the mechanism of action was probably related to the inhibition of ERK and P13K/AKT signaling pathways^[26]. The proliferation ability, apoptosis rate, invasion ability, and migration ability of HNE2 cells in nasopharyngeal carcinoma were determined by various experimental methods with different concentrations of salidroside, and it was found that salidroside could target and inhibit IGF-1R expression, inhibit HNE2 cell proliferation, invasion, and migration, and promote HNE2 cell apoptosis, which may be regulated through the miR-99a-5p/IGF-1R signaling pathway^[27]. Zhao Dan et al^[28] found that salidroside could regulate the immune inflammatory response of tumor cells by inhibiting ERK1/2 and STAT3 phosphorylation, which in turn inhibited the proliferation and invasion of kidney cancer A498 cells.

2. Discussion

Rhodiola rosea has been a powerful tonic for deficiency since ancient times, and is a top-quality medicine. The Chinese Pharmacopoeia 2020 edition records that it has the effect of benefiting qi and invigorating blood, opening the veins and calming asthma, and is mostly used in cases of qi deficiency and blood stasis, chest paralysis and heart pain, stroke and hemiplegia, and tiredness and asthma. Modern research has found that salidroside have anti-fatigue, anti-oxidant, anti-aging, anti-inflammatory and anti-tumor effects, and can be used for the treatment of a variety of cardiovascular and cerebrovascular diseases, lung injury, diabetes and other diseases with good results. With the progress of society, the development of modern medicine and the deterioration of living environment, the incidence of tumor continues to rise and the mortality rate takes the first place. At present, there are various tumor treatment methods, which greatly improve the treatment efficiency and five-year survival rate, but due to various reasons such as tumor metastasis, recurrence, drug resistance and adverse reactions, the current treatment methods cannot meet the needs of society, and people start to look for safer and more effective treatment methods. Traditional Chinese medicine has played a huge role in the health of our people from ancient times

to the present, and it is safe and convenient, so more people are looking to traditional Chinese medicine.

Several modern studies have found that salidroside can inhibit tumor cell proliferation, inhibit cell migration, promote apoptosis, induce autophagy, inhibit neovascularization and infiltration and metastasis, and enhance immunity through various signaling pathways to achieve anti-tumor effects, and there is a linear correlation with the concentration of salidroside. The effect of salidroside on cell proliferation and migration was investigated by treating human alveolar basal carcinoma epithelial (A549) cells with LPS, and Sal was found to inhibit the proliferation and migration of human lung cancer cells through AMPK-dependent NLRP3 inflammatory vesicle regulation^[29]. Experiments by Bing Jiang et al demonstrated that salidroside inhibited the proliferation, migration, invasion and apoptosis of HepG2 hepatocellular carcinoma cells and induced apoptosis through the mitochondrial pathway with concentration-dependent changes^[30]. By studying the effects of different doses of salidroside on cervical squamous carcinoma C33A cells, it was found that salidroside could inhibit cell value-added proliferation and invasion, and could promote apoptosis of C33A cells by regulating the expression of apoptotic proteins Bax, caspase-3 and anti-apoptotic protein Bcl-2, and its mechanism of action might be related to the inhibition of JAK2/STAT3 signaling pathway^[31]. Experiments have shown that salidroside induces autophagy in human gastric cancer AGS cells, and inhibition of autophagy promotes its induction of apoptosis^[16]. Many experiments have shown that salidroside have significant inhibitory effects on a variety of tumor cells such as lung cancer, breast cancer, gastrointestinal malignancies, female malignancies, head and neck malignancies, and liver cancer.

Rhodiola rosea has high safety and low adverse effects, and can be used as an antitumor, relieve symptoms, improve the quality of survival and prolong survival time in patients with advanced disease, or can be widely used in clinical practice, but there are few rhodiola preparations for clinical application, including rhodiola injection, rhodiola capsules, rhodiola slices, etc., and there is a lack of more clinical studies based on TCM evidence-based treatment. Further studies to analyze its TCM mechanism of action and increase the content of salidroside in rhodiola preparations may substantially enhance the anti-tumor effects of salidroside.

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