Advances in Research of Anti-tumor Effect of Aconiti Radix

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Abstract In this paper, the anti-tumor effects of Aconiti Radix were reviewed and summarized, and the clinical feasibility of Aconiti Radix as a potential anti-tumor drug was analyzed, in order to provide a useful reference for the future research and development of new anti-cancer drugs of Aconiti Radix.

Key words Aconiti Radix, Anti-tumor, Research advances, Feasibility analysis

1 Introduction

Aconiti Radix is the dried mother root of *Aconitum carmichaeli* Debx of Ranunculaceae. It is pungent and bitter in taste, hot in nature, and toxic. It enters the heart, liver, kidney, and spleen meridians, and has the effects of expelling wind, removing dampness, warming meridians, and relieving pain. *A. carmichaeli* Debx was first recorded in the oldest medical prescription book *Recipes for Fifty-two Ailments*, and Aconiti Radix was first recorded in *Shennong's Classic of Materia Medica*[1-3] and has a long history of medication.

Aconiti Radix is widely used in the treatment of rheumatic arthralgia syndrome. The *Chinese Pharmacopoeia* (2015 edition) recorded 32 prescriptions containing Aconiti Radix, including Xiaohuoluo Pill, Tianhe Zhuifeng Ointment, Shangshi Zhitong Ointment, Dingchuan Ointment, Fugui Gutong Capsule, Shexiang Zhitong Ointment, *etc.*[4]. Modern pharmacological studies have shown that Aconiti Radix has anti-inflammatory, anti-rheumatic[5-7], analgesic, sedative[8-9], vasodilator, cardiotonic[10-12], tumor growth inhibition[13] and other effects. Traditional Chinese medicine has been widely recognized and applied in clinical anti-tumor because of its advantages of multi-component, multi-target and multi-effect[14]. Aconiti Radix has a significant inhibitory effect on a variety of tumor cells, and is expected to provide a new anti-cancer drug of traditional Chinese medicine for clinic, with a broad market prospect. In this paper, we reviewed the anti-tumor effects of Aconiti Radix.

2 Main active components

The major components of Aconiti Radix can be divided into three groups: diterpenoid alkaloids, non-diterpenoid alkaloids, and non-alkaloids. Diterpenoid alkaloids are main chemical components of Aconiti Radix, mainly C-19 diterpenoid alkaloids, including aconitine, hypaconitine, neoaconitine and other toxic diester alkaloids. It is the main anti-tumor active component of Aconiti Radix[15], which can be processed into monoester alkaloids with low toxicity, but can still maintain the original pharmacological activity[16]. Non-diterpenoid alkaloids, including quaternary ammonium salts, pyrroles, aporphines, *etc.*[17-18], have strong physiological activities in cardiotonic and anti-inflammatory aspects. In addition, Aconiti Radix also contains flavonoids, saponins, ceramides and other non-alkaloids[19]. Studies have shown that the polysaccharide contained in Aconiti Radix also has certain anti-tumor activity[20].

3 Anti-tumor effect

3.1 Anti-S180 sarcoma effect Studies have shown that Aconiti Radix decoction, Aconitum injection and Aconitum extract have inhibitory effects on the growth of S180 sarcoma in mice. As early as in the 1980s, it was found that Aconitum injection had inhibitory effect on sarcoma S180 in mice[21]. Using mouse sarcoma S180 cells, Zeng Jin *et al.*[22] established a model and observed the anti-tumor effect of the water decoction of raw Aconiti Radix. The results showed that the water decoction of raw Aconiti Radix had significant inhibitory effect on the growth of mouse S180 solid tumor without significant effect on the survival number of the host and the weight gain of the animal.

3.2 Anti-lung cancer effect Studies have shown that Aconiti Radix can effectively inhibit the proliferation and metastasis of lung cancer, and its inhibitory effect is related to the dose or concentration, and may help to maintain the vital signs of tumor-bearing organisms. Huang Xiuman *et al.*[23] used MTT colorimetric method *in vitro* to determine the effect of Aconiti Radix on the proliferation of mouse Lewis lung carcinoma (LLC) cells, and set up different concentration gradient administration groups. The results showed that Aconiti Radix had a certain inhibitory effect on lung cancer cells, and the inhibitory rate was positively correlated with the drug concentration. Zhao Bei *et al.*[24] established a Lewis mouse model of subcutaneous transplantation and lung cancer metastasis, and took mouse body temperature, blood oxygen saturation, erythrocyte ATPase activity, hemorheology, intratumoral hypoxia, capillary permeability and intercellular communication as evaluation indicators. The results showed that the serum contai-

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ning Aconitum could inhibit the proliferation of Lewis cells, induce the differentiation of Lewis cells and inhibit the adhesion between Lewis cells, while the Aconitum decoction could help to maintain the normal vital signs such as body temperature and blood oxygen saturation of tumor-bearing mice, and inhibit the growth and metastasis of tumors. Another study[25] found that Aconiti Radix decoction could inhibit the proliferation and migration of Lewis lung cancer cells and was positively correlated with the dose of Aconiti Radix decoction by establishing subcutaneous transplantation model of Lewis lung carcinoma and urethane-induced lung cancer model in a low-temperature microenvironment conducive to the occurrence, metastasis and recurrence of tumors.

3.3 Anti-liver cancer effect A number of modern studies have shown that Aconiti Radix can reduce the activity of liver cancer cells and inhibit the occurrence and progression of liver cancer. Huang Xiuman *et al*.[23] established the animal model cells of liver cancer H22 subcutaneous transplantation through *in vivo* experiments, and measured the tumor volume, mass and immune organ index in situ after intragastric administration. The axillary tumor, liver, spleen and thymus of mice in Aconiti Radix group and model group were weighed, and it was found that the tumor mass of mice in Aconiti Radix powder suspension group was decreased, and the thymus and spleen indexes were increased, indicating that Aconiti Radix had a certain inhibitory effect on liver cancer in mice. A study shows that aconite extract can reduce the activity of liver cancer cells, effectively inhibit the proliferation of liver cancer Bel-7402 cells, induce apoptosis and differentiation, block the S phase of DNA replication, and has strong cytotoxicity[26]. Another study has clarified the effect of aconitine on inhibiting the growth, invasion, and migration of hepatocellular carcinoma cells, and also explored its mechanism of action[27]. They used MTT, Transwell and scratch assays to detect the effects of different concentrations of aconitine on the proliferation, invasion and migration of human hepatocellular carcinoma cells, and used Western blot to study the mechanism of action of aconitine and the regulation of cell proliferation, migration and apoptosis by inhibiting the activation of P38/MAPK signaling pathway.

3.4 Anti-colon cancer effect According to a study[22], human colon cancer cell line LoVo was cultured *in vitro* to explore the inhibitory effect of Aconiti Radix decoction on the proliferation of LoVo cells *in vitro*. The results showed that Aconiti Radix decoction had a good inhibitory effect on colon cancer LoVo cells, and the inhibitory rate was positively correlated with the time and concentration of the drug.

3.5 Anti-cervical cancer effect A study[28] observed the inhibitory effect of different extracts of Aconitum powder on the growth of different tumor cells through *in vitro* cell proliferation experiments. The results showed that Aconiti Radix 70% alcohol extract had a significant growth inhibitory effect on lung cancer cell line A549 and cervical cancer cell line Hela cells. The combination of raw Aconiti Radix and Phellodendri Chinensis Cortex showed a good synergistic effect, and the inhibition rate was significantly improved. Zhang Wenwen[29] studied the natural plant extract containing aconitine and established the Hela cervical cancer cell model, and the results showed that the natural plant extract containing aconitine could down-regulate VEGF in serum and inhibit tumor growth.

3.6 Anti-breast cancer effects Compared with the processed Aconiti Radix, the alcohol and aqueous extracts of raw Aconiti Radix exhibited better growth inhibition in breast cancer cell lines (MCF7)[28]. The viability of tumor cells gradually decreased with the increase of drug concentration, and the proliferation of cells was significantly inhibited, which had obvious dose-dependent characteristics. In addition, the human breast cancer bone high metastasis cell line MDA-MB-231BO was used for *in vitro* invasion experiments. The results showed that the combination of the active components of osthole, psoralen, and aconitine in Cnidii Fructus, Psoraleae Fructus, and Aconiti Lateralis Radix Praeparata could significantly inhibit the invasive activity of MDA-MB-231BO cells[30]. Through analysis, we considered that some toxic components in Aconiti Radix, such as diester-type alkaloids, may be more effective for MCF7. After processing, the toxicity of Aconiti Radix was reduced, and its anti-MCF7 effect was also reduced.

3.7 Anti-leukemic effect A study[31] took leukemia cells K562 and K562/DNR (K562 daunorubicin-resistant cell strain) as objects to investigate the effects of neoaconitine on the proliferation and apoptosis of K562 and K562/DNR. It was found that neoaconitine could inhibit the proliferation of these cells and induce their apoptosis. The inhibition rate of proliferation was dependent on concentration and time, and the apoptosis rate was also increased with the increase of concentration. Further studies showed that neoaconitine could induce apoptosis in K562 and K562/DNR cells, and the mechanism of apoptosis was related to down-regulation of *C/EBPa* gene and up-regulation of *Caspase-3* and *p53* genes.

3.8 Anti-pancreatic cancer effect The results of Ji BL *et al*.[32] showed that aconitine inhibited pancreatic cancer cell growth in a dose- and time-dependent manner. The effect of aconitine on miapaca-2 and panc-1 cells induces apoptosis by upregulating the expression of pro-apoptotic factors bax, cl-caspase-3, cl-caspase-9 and cleaved poly (ADP-ribose) polymerase 1 (PARP1) and decreasing the expression of anti-apoptotic bcl-2.

3.9 Anti-skin cancer effect Mice with skin papilloma induced by DMBA/croton oil method were fed with Aconiti Radix decoction, showing that Aconiti Radix had inhibitory effect on the formation of papilloma, and its strong cancer chemoprevention effect was evaluated[33]. Another study evaluated[34] the anticancer activity of aconitine on melanoma cell line B16 *in vitro* and *in vivo*, and found that aconitine can significantly reduce the growth rate and promote apoptosis of B16 cell lines, and the mechanism is to regulate the levels of PCNA protein and mRNA and apoptosis-related signaling molecules by inhibiting PI3K/AKT and MAPK/ERK 1/2 signaling pathways.

3.10 Other effects Pyaskovskaya *et al*.[35] studied the antitumor effect of the aconitine-containing anti-angiogenic agent BC1

combined with dichloroacetic acid on Ehrlich's ascites carcinoma and found that BC1 could enhance the antitumor activity of dichloroacetic acid. In a clinical study[36], it was found that the patient's symptoms improved and the mass shrunk by intramuscular injection of aconitine injection in gastric cancer patients, and no obvious adverse reactions occurred. However, recent experimental studies[28] have shown that the inhibitory effect of aconitine powder on human gastric cancer cells is weak.

4 Reversal of drug resistance

Aconitine can increase the sensitivity of anti-tumor drugs, and has potential application value for tumor resistance reversal. The effect of aconitine on human oral squamous epithelial carcinoma cells is mainly related to reversing their drug resistance. Li *et al.*[37] found that aconitine itself had a weak inhibitory effect on the growth of human oral squamous cell carcinoma (KBv200) cells, but it was sensitizing to vincristine (VCR) killing this type of cells. Liu Xueqiang[38] further studied the mechanism of aconitine reversing multidrug resistance in KBv200 cells, and believed that the reversal mechanism was closely related to aconitine reducing the expression of Pgp protein, promoting apoptosis of tumor cells, and affecting MAPK signal transduction.

5 Effect of enhancing immunity

Experimental studies have shown that Aconiti Radix enhances immunity by promoting T cell proliferation[39], and T lymphocytes play an important role in cellular and humoral immune responses. Fu Wenwen *et al.*[40] studied the effect of aconite injection on the immune function of mice, and the results showed that aconite injection could significantly inhibit the transformation function of T cells in mice, and could significantly inhibit the production of monocyte-macrophage cytokine IL-1 at 1/5 and 1/10 dilution, which had a certain regulatory effect on the immune system of the body. In recent years, there are many studies on Aconiti Lateralis Radix Praeparata to improve the immune function of mice[41-42]. However, Aconiti Lateralis Radix Praeparata and Aconiti Radix are derived from the mother root and daughter root of the same plant *A. carmichaeli*, and their chemical constituents and pharmacological effects are similar[43], which also have certain mutual reference value. In addition, the statement that traditional Chinese medicine polysaccharides enhance immunity has also been confirmed by studies[44]. Polysaccharides are the main active ingredients of Aconitum plants besides diterpenoid alkaloids, and have biological activities such as enhancing immunity, lowering blood sugar, anti-inflammatory, and anti-tumor[45]. A study used cyclophosphamide (Cy) to induce immunosuppressive mice to carry out an immune test, and that result show that among the water-soluble polysaccharides extracted from *A. carmichaeli*, Aconiti Radix and Aconiti Lateralis Radix Praeparata, all non-starch polysaccharides, In particular, pectin polysaccharide components not only have obvious immunostimulatory activity, including non-specific immunity, cellular immunity and humoral immunity, but also can restore the immune function inhibited by anti-tumor drugs[20].

6 Analgesic effect

Aconitum alkaloids have shown good analgesic effects in a variety of pain models and clinical studies[46]. Clinically, *A. carmichaeli* can be used for pain caused by bone and joint pain, neuropathic pain, lumbago and leg pain, heel pain, forehead and face pain and other reasons[47]. Wang Hualing *et al.*[48] found that aconitine can relieve the pain caused by cancer, especially chronic pain, mild pain, distending pain and dull pain in the study on the therapeutic effect of morphine on cancer pain. Its analgesic effect is related to the dosage, the relief time is longer than that of morphine, and there is no drug dependence.

7 Prospects

At present, the aconitine drug BC1 has been used as an inhibitor of tumor angiogenesis by inhibiting endothelial cell proliferation. However, it is generally believed that the key issues affecting the clinical use of Aconiti Radix are its potential cardiological, neurological and other toxicities, and the safe dose range is narrow. Therefore, in future research, our team will also actively explore new methods for reducing the toxicity and increasing the efficiency of Aconiti Radix from the perspectives of processing, extraction methods, and synergistic compatibility. However, the efficacy of Aconiti Radix for different tumors may be selective, and further research and exploration are needed for the clinical use of Aconiti Radix for anti-cancer.

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