Pharmacological Action and Mechanism of Dendrobine

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Abstract Dendrobine, an alkaloid extracted from the stem of *Dendrobium nobile* Lindl., has many biological activities such as anti-cancer effect, anti-inflammation effect, anti-influenza A virus effect, treatment of leukemia, treatment of Parkinson's disease, protection of internal organs and promotion of cell maturation. In this paper, the related research progress of pharmacological action and molecular mechanism of dendrobine will be reviewed in order to provide a theoretical basis for further research and drug development of dendrobine.

Key words Dendrobine, Anti-cancer, Anti-inflammation, Anti-influenza A virus, Leukemia treatment

1 Introduction

Dendrobium nobile Lindl. is also known as Diaolanhua, Bianhuangcao and so on. *D. nobile* Lindl. has pharmacological effects such as anti-tumor effect, nerve protection effect, and effect of promoting blood circulation and removing blood stasis. According to *Chinese Pharmacopoeia*, dendrobine is one of the main active components of *D. nobile* Lindl., and the content of dendrobine is used as an index to judge the quality of *D. nobile* Lindl.[1] Its molecular formula is $C_{16}H_{25}NO_2$, and it is white or white-like powder, easily soluble in ether, chloroform and other organic solvents, but insoluble in ethanol and water. A large number of studies have shown that dendrobine has many pharmacological activities such as anti-cancer effect, anti-inflammation effect, anti-influenza A virus effect and leukemia treatment. This article reviews the progress of pharmacological action and mechanism of dendrobine in order to provide a theoretical basis for further study of dendrobine.

2 Pharmacological action and mechanism of dendrobine

2.1 Anti-cancer effect Cancer is a disease caused by the loss of normal regulation and excessive proliferation of cell growth. Generally, it can refer to all malignant tumors[2], with the characteristics of invasion and metastasis. At present, cancer is one of the important factors leading to the increase of human mortality, and it seriously threatens human life and health[3]. Studies have found that dendrobine has good anti-cancer effect.

Liu Zhoujiang *et al.*[4] detected the inhibitory effect of dendrobine on proliferation of lung cancer A549 cells by MTT and cell cloning assay. The results showed that dendrobine inhibited the proliferation of A549 cells in a dose-dependent manner (0, 125, 250, 500 μmol/mL). The effects of dendrobine on migration and invasion of A549 cells were detected by Transwell test. The results showed that with the increase of dendrobine concentration, the number of A549 cell-penetrating membranes decreased gradually. Furthermore, the effect of dendrobine on the expression of proliferation-related proteins in A549 cells was detected by real-time quantitative PCR and Western blotting. The results showed that the mRNA and protein expression levels of tet methylcytosine dioxygenase-1 (tet-1) and tumor suppressor factor (p53) in A549 cells increased significantly after treatment with dendrobine. These results suggest that dendrobine can significantly inhibit the proliferation and invasion of lung cancer A549 cells by regulating the expression of proliferation-related proteins, and induce apoptosis of lung cancer A549 cells, thus exerting anti-cancer effect.

2.2 Anti-inflammation effect Inflammation is a defensive response caused by infection or injury, characterized by redness, fever and pain. On the one hand, inflammatory reaction can help the body play its immune function and reduce the damage to the body; on the other hand, inflammation will attack tissues, resulting in imbalance of internal environment homeostasis and other diseases[5]. Studies have found that dendrobine has good anti-inflammatory effect.

Fan Xiaobao *et al.*[6] detected the effect of dendrobine on the expression level of pro-inflammatory factors in serum of diabetic nephropathy model rats by ELISA. The results showed that dendrobine decreased the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in serum in a concentration-dependent manner (0, 2, 4, 8 mg/mL). The effect of dendrobine on the expression of inflammation-related proteins was further detected by Western blotting. The results showed that the protein expression levels of phosphatidylinositol 3-kinase (P13K), protein kinase B (Akt) and rapamycin (mTOR) increased significantly with the increase of dendrobine concentration. These results indicated that dendrobine could activate P13K/Akt/mTOR signaling pathway by regulating the expression of pro-inflammatory factors in serum, thus exerting anti-inflammatory effect and improving kidney injury in diabetic nephropathy model rats.

2.3 Anti-influenza A virus effect Virus is a kind of self-replicating and intracellular parasitic non-cellular organism, which has the characteristics of high tolerance and strong infectivity. People infected with influenza A virus will have symptoms such as

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high fever, pneumonia and various organ failure. Studies have shown that dendrobine has a good anti-influenza A virus effect.

Li Richan[7] detected the effect of dendrobine on the activity of renal MDCK cells infected with influenza A virus by MTT assay. The results showed that dendrobine inhibited the proliferation of MDCK cells in a concentration-dependent manner (0, 6.25, 12.5, 25, 50 μg/mL). Immunofluorescence assay and Western blot assay were used to detect the effect of dendrobine on the expression of virus-related proteins. The results showed that the expression level of viral hemagglutinin (HA) protein decreased gradually with the increase of dendrobine concentration. These results indicate that dendrobine can inhibit the proliferation of infected cells by regulating the expression level of HA protein, thus playing an anti-influenza A virus role.

2.4 Therapeutic effect on leukemia Acute T lymphocytic leukemia is a tumor disease caused by malignant proliferation of T cells derived from lymphocytes[8]. The increase in peripheral blood leukocyte count and anemia were the main clinical features. In the course of treatment, the side effects were great, the disease progressed rapidly, and the survival rate was less than 50%[9]. Studies have shown that dendrobine has a good therapeutic effect on acute T-lymphocytic leukemia.

Guo Tao *et al.*[10] detected the inhibitory effect of dendrobine on proliferation of human cutaneous T-cell lymphoma Hut-78 cells by CCK-8 experiment. The results showed that dendrobine inhibited the proliferation of Hut-78 cells in a dose-dependent manner (0, 2.5, 5, 10, 25, 50 μg/mL). The apoptosis of Hut-78 cells and the expression of apoptosis-related proteins were detected by flow cytometry and Western blotting. The results showed that the apoptosis rate of Hut-78 cells increased gradually with the increase of dendrobine concentration, and the expression levels of pro-apoptosis protein (Bax), cle-caspase-3, cle-caspase-9, Cyto-c increased significantly, while the expression level of anti-apoptosis protein (Bcl-2) decreased significantly. Transwell assay and Western blotting assay were used to detect the effect of dendrobine on the invasion of HuT-78 cells and the expression level of invasion-related proteins. The results showed that after treatment with dendrobine, the number of HuT-78 cells decreased significantly, and the expression levels of mesenchymal marker protein (N-cadherin), zinc finger transcription factor (Snail), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) decreased significantly, while the expression level of epithelial marker protein (E-cadherin) increased significantly. The effect of dendrobine on the expression of proliferation-related proteins in HuT-78 cells was further detected by Western blotting. The results showed that the expression levels of phosphorylated c-Jun amino-terminal kinase (p-JNK) and phosphorylated tyrosine phosphoprotein kinase (p-p38) increased significantly after treatment with dendrobine. These results suggest that dendrobine can inhibit proliferation and invasion of leukemia cells by regulating JNK signaling pathway.

2.5 Therapeutic effect on Parkinson's disease Parkinson's disease is a disease caused by degeneration and loss of dopaminergic neurons in substantia nigra of mesencephalon[11], which reduces the level of inhibitory neurotransmitters and then destroys the level of excitatory neurotransmitters. The main clinical features include muscle stiffness and autonomic nerve dysfunction[12]. Studies have shown that dendrobine has a good delaying effect on Parkinson's disease.

Su Shuangqiao[13] detected the effect of dendrobine on the activity of human neuroblastoma SH-SY5Y cells by MTT, CCK-8 and LDH assay. The results showed that dendrobine increased the activity of SH-SY5Y cells in a concentration-dependent manner (0, 1, 5, 10 μM). The apoptosis of SH-SY5Y cells induced by dendrobine and the expression of apoptosis-related proteins were detected by Hoechst/PI double staining assay and Western blotting assay. The results showed that the apoptosis rate of SH-SY5Y cells decreased gradually with the increase of dendrobine concentration, and the expression levels of cle-caspase-3, heavy chain binding protein (BIP), phosphorylated eukaryotic translation initiation factor e IF2α (p-e IF2α), activated transcription factor 4 (ATF4), activated transcription factor 6 (ATF6), X-Box binding protein 1 (XBP1S) and C/Ebp homologous protein (CHOP) decreased significantly. The effect of dendrobine on the expression of neural related factor protein was detected by real-time quantitative PCR and Western blotting. The results showed that the expression levels of astrocyte-derived neurotrophic factor (MANF) mRNA and MANF protein were significantly increased after treatment with dendrobine. These results suggest that dendrobine can promote the secretion of MANF and inhibit the apoptosis of nerve cells by regulating the expression of apoptosis-related proteins, thus playing a role in delaying Parkinson's disease.

2.6 Protection of internal organs Internal organs are the general name of various organs located in the body cavity and connected with the body outside, mainly including heart, liver, gastrointestinal tract and other organs, playing a leading role in the life activities of the body. Insufficiency or loss of internal organs can lead to shock and even death. Studies have shown that dendrobine has a good protective effect on internal organs.

Luo Xianghong *et al.*[14] detected the effect of dendrobine on serum related myocardial enzymes in myocardial infarction model rats through serum biochemical experiments. The results showed that dendrobine decreased the content of creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH) in rat serum in a dose-dependent manner (10, 20, 40 mg/kg). Besides, TTC test was used to detect the effect of dendrobine on myocardial infarction area in rats. The results showed that with the increase of dendrobine concentration, the myocardial infarction area of rats gradually decreased. Further, the effects of dendrobine on the expression of apoptosis-related mRNA and protein were detected by reverse transcription-PCR and Western blotting. The results showed that the expression of pro-apoptotic protein Bax, Cyto-c, cl-caspase-3 increased significantly, while the expression of Bcl-2 decreased significantly after treatment with

dendrobine. These results suggest that dendrobine plays a protective role in the heart by regulating the Bax/Cyto-c/Caspase3 signaling pathway and inhibiting the expression of serum myocardial enzymes.

Pan Xiaoou *et al.* [15] detected the effect of dendrobine on the expression level of nerve-related factors in irritable bowel syndrome model mice by ELISA. The results showed that dendrobine down-regulated the expression of serum nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial acidic fibrin factor (GFAP) at 5-hydroxytryptamine (5-HT) and substance P (SP) levels in a concentration-dependent manner (0, 3, 6, 12 mg/mL). The effect of dendrobine on the expression of nerve-related proteins in colon tissue was further detected by Western blotting. The results showed that the protein expression levels of NGF and BDNF decreased significantly after treatment with dendrobine. These results indicate that dendrobine can protect intestinal tract by down-regulating the expression of 5-HT, SP and other neurofactors.

Zhang Xiao *et al.* [16] detected the effect of dendrobine on the expression level of liver microsomes in mouse liver cells by real-time quantitative PCR. The results showed that dendrobine up-regulated the mRNA expression of cytochrome P450 isozyme (Cyp1A1) in a concentration-dependent manner (0, 0.5, 1.5, 3 mg/kg). Further, the effect of dendrobine on the expression of liver microsomal protein was detected by Western blotting. The results showed that the protein expression of cytochrome P450 isozymes (Cyp1A1, Cyp2B, Cyp2C19) increased significantly after treatment with dendrobine. Further, the effect of dendrobine on pathological changes of liver tissue in mice was detected by tissue section observation experiment. The results showed that after treatment with dendrobine, the morphology of liver tissue slices in mice was normal, and the hepatocytes were arranged neatly, without obvious cell necrosis. These results indicate that dendrobine has no side effects on liver function in mice, and can protect liver by regulating cytochrome isotype mRNA and related enzymes.

2.7 Promoting cell maturation Cell maturation is a process in which body cells evolve into specialized cell types after cell proliferation and differentiation, and produce unique functional proteins and exercise special functions. Cell maturation is of great significance to the normal development of cell function, and is closely related to the subsequent development of organisms. Studies have shown that dendrobine has a good promoting effect on cell maturation.

E Zhiqiang *et al.* [17] detected the effect of dendrobine on the expression level of oocyte proliferation-related proteins by immunofluorescence staining. The results showed that glutathione (GSH) and matrix metalloproteinase (MMP) levels increased gradually with the increase of dendrobine concentration, while reactive oxygen species (ROS) levels decreased gradually. Furthermore, the effect of dendrobine on antioxidant related enzymes in oocytes was detected by real-time quantitative PCR. The results showed that the mRNA expression levels of histone deacetylase 1 (SIRT1), histone deacetylase 2 (SIRT2) and superoxide dismutase 2 (SOD2) increased significantly after treatment with dendrobine. These results indicate that dendrobine can promote the development and maturation of mouse oocytes by regulating ROS, GSH and MMP levels.

3 Discussion

Dendrobine is an alkaloid extracted from the stem of *Dendrobium nobile* Lindl., having many pharmacological activities such as anti-cancer effect, anti-inflammation effect and anti-influenza A virus effect. It has attracted wide attention of researchers at home and abroad because of its abundant sources and low price. Although there are many studies on the biological activity of dendrobine at present, most of them stay on the pharmacological representation, lacking comprehensive and detailed mechanism research and animal experimental basis. Therefore, it is necessary to combine the knowledge of molecular biology, cell biology, experimental zoology and clinical medicine, and make more specific and in-depth research on dendrobine at molecular level, cell level and animal level, so as to provide a theoretical basis for further development and clinical application of dendrobine.

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expected to provide a theoretical basis for the discovery of new pharmaceutical active compounds.

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