

Research Progress of Pharmacological Mechanism of Cistanche in the Treatment of Vascular Dementia

Huiwen Yang, Zhiqiang Hao, Feng Miao*

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

*Correspondence Author

Abstract: *Vascular dementia is one of clinical common type of dementia, its pathogenesis is complex, the incidence of rising trend year by year, the serious influence the patient's life and health. In the category of traditional Chinese medicine, vascular dementia belongs to the category of "dementia", and its etiology and pathogenesis are mostly related to "deficiency of kidney essence". Studies have found that Cistanche deserticola is a traditional Chinese medicine with a high frequency in the treatment of vascular dementia. It has the effects of toning kidney Yang, nourishing essence blood, moistening intestine and purging, and has definite advantages in preventing vascular dementia. C. deserticola chemical composition including echinacea glycosides, mullein indican, c. deserticola total glycosides, phenylethyl alcohol glycosides, flavonoids and polysaccharides, removal of oxygen free radicals and improve antioxidant compounds with resistance to oxidative stress; It plays an anti-vascular dementia role by clearing β -amyloid protein, reducing neuronal apoptosis, protecting hippocampal neurons, and regulating neurotransmitters to protect cholinergic nerves. This article reviews the pharmacological effects of cistanche deserticola on vascular dementia. As to provide theoretical basis for the use of c. deserticola and evidence-based support.*

Keywords: Cistanche, Vascular dementia, Pharmacological effect, Oxidative stress.

1. Introduction

Vascular dementia (VaD) is an acquired dementia syndrome caused by cerebral ischemia and hypoxia caused by cerebrovascular diseases [1]. In addition to the damage of the nervous system, it is also accompanied by memory loss, cognitive dysfunction, and abnormalities in language and movement space. Nowadays, affected by aging progress faster, the total number of patients with dementia in China was also present a rising trend year by year, the current of the world about 25% of the total number of patients with dementia, is one of the highest incidence of alzheimer's disease, vascular dementia is second [2], greatly endanger the patient's quality of life, mental health, It also increases the burden on the family and society. Therefore, finding effective preventive measures and treatment methods has become an urgent problem to be solved.

Vascular dementia belongs to the category of "stupid disease" and "dementia" in traditional Chinese medicine. The etiology and pathogenesis of vascular dementia have been described as "insufficient sea of marrow" in the era of Neijing (Internal Canon of Medicine). Traditional Chinese medicine believes that the kidney contains essence, essence generates marrow, and "all the marrow belong to the brain..." The deficiency of kidney essence, the deficiency of the sea of marrow, the loss of the brain, the exhaustion of the marrow and the exhaustion of the brain, and the apnoea of kidney qi lead to cognitive impairment and even dementia syndrome. Therefore, tonifying kidney essence is an important treatment for cognitive dysfunction in traditional Chinese medicine. Li Qiang [3] et al. used the "Traditional Chinese Medicine Inheritance assistance system" to conduct data mining and analysis on the composition of prescriptions and drugs in VaD, and found that the occurrence frequency of Cistanche deserticola was high, and cistanche deserticola just happened to have the effect of toning kidney Yang, nourishment essence blood, moistening intestine and purgative, which could not be

overlooked in the treatment of VaD.

Cistanche deserticola was first recorded in Shennong Materia Medica Classic. It is used as medicine with fleshy stems with scaly leaves, which has the functions of tonifying kidney-yang, nourishing essence and blood, moistening intestines and relaxing bowels. Its nature is sweet, salty and warm, and it belongs to kidney and large intestine meridian [4]. It is mainly produced in Inner Mongolia, Xinjiang, Gansu and Ningxia. Because it grows in the desert and has good medicinal value, it is known as "desert ginseng". Modern pharmacological studies have found that c. deserticola chemical composition is complicated, mainly including echinacea glycosides, mullein indican, c. deserticola total glycosides, phenylethyl alcohol glycosides, flavonoids and polysaccharides, has extensive pharmacological effects, including antioxidant, protecting nerve and improve the learning and memory, anti-inflammatory, anti-tumor, protect liver, etc. [5]. Therefore, this paper summarized the progress on pharmacological mechanism of c. deserticola vascular dementia resistant, as to provide theoretical basis for the clinical use of the c. deserticola and evidence-based support.

2. Modern Pharmacological Effects of Cistanche

2.1 Cistanche has the Effect of Antioxidant

Oxidative stress is a state in which the cells of the body are affected by the external environment and the oxidation and antioxidation are unbalanced. In the stress state, the active oxygen (Reactive oxygen species, ROS) level of generated more than the body's own antioxidant system of ROS removal force, make the ROS in the body, in the produce free radicals produce oxidative damage to cells, tissues, And then accelerate the progress of chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases, cancer

and other chronic diseases [6]. Cerebral oxidative stress caused by cerebral ischemia and hypoxia is the most dangerous factor in the pathogenesis of VaD [7]. Therefore, scavenging oxygen free radicals is the main way to achieve anti-oxidative stress and prevent VaD. Benzene ethanol glycosides and polysaccharide composition of *C. deserticola* is agreed that the antioxidant activity of components. Phenethyl alcohol glycoside of structure with multiple phenolic hydroxyl, to free radicals, thereby avoiding of a large number of free radicals in the body. Li liang [8] and also through the animal experiments show that *C. deserticola* phenethyl alcohol glycoside can effectively protect the brain oxidative stress reaction, midrib occlusion rats had the potential to improve nerve function and its mechanism may be related to the activation of antioxidant system. *C. deserticola* polysaccharide has been proved to be anti-aging effect, a lot of and still for its anti-aging effect and implementation by oxidation [9]. In addition, the total glycosides of *Cistanche* can be directly involved in scavenging free radicals or blocking their occurrence. The total glycosides of *Cistanche deserticola* have obvious scavenging effect on O₂, OH, H₂O₂, O₂⁻ and other reactive oxygen free radicals generated in the metabolism of oxygen molecules, especially can protect DNA oxidative damage caused by OH [10]. Wu [11] etc. The results showed that *C. deserticola* total glycosides can obviously improve the subacute aging mice activity of superoxide dismutase (SOD), decrease the lipid peroxide content in brain tissue and liver. Luo LAN et al. showed that the total glycosides of *cistanche deserche* could enhance the activities of SOD and glutathione Px (GSH-Px) in brain tissue by establishing a dementia model of rats with bilateral common carotid artery ligation, and play a role in improving the learning and memory ability of cerebral ischemia rats.

In conclusion, *Cistanche* is capable of maintaining the stability of the antioxidant system by scavenging free radicals, reducing peroxide levels, and enhancing SOD activity, thereby mitigating oxidative damage in the brain and preventing VaD.

2.2 *Cistanche* has the Effect of Improving Cognitive Function

Cognitive dysfunction is a degenerative disease of the central nervous system, mainly manifested as memory impairment, calculation impairment, visuospatial impairment, executive dysfunction, apraxia, aphasia, agnosia, etc. In the process of nervous system development, nerve cells play an important role, nerve cells once apoptosis, resulting in neuronal cell dysfunction, leading to cognitive dysfunction. Therefore, the ultimate goal of prevention and treatment of cognitive impairment is to protect nerve cells and delay neuronal death. Apoptosis of neurons mainly includes oxidative stress and decrease of mitochondrial membrane potential. At the same time, it has also been proved [12] that neuronal apoptosis and ischemic brain injury caused by cerebrovascular dysfunction can reduce the clearance ability of β -amyloid protein (A β), increase extracellular A β deposition, and lead to cognitive impairment. A large number of previous literature has proved that *Cistanche deserticola* has antioxidant effect. CAI Kerui et al. [13] found in the experiment of dementia model mice that the polysaccharide group of *cistanche deserticola* can improve the activities of superoxide dismutase (SOD) and glutathione

peroxidase (GSH) in serum, and at the same time, the DNA damage of nerve cells can be repair to a certain extent, and the cognitive function can be improved. Phenylethanoside, as an active component of *Cistanche deserticola*, can block A β deposition, Increasing the expression of acetylcholine (Ach) and Choline acetyltransferase (ChAT) and restoring the function of hippocampal dopamine neurons can improve the learning and cognitive function of dementia model rats [14-16]. After brain injury, it is related to the accumulation of reactive oxygen species and intracellular calcium overload. Studies have shown that echinoside in *Cistanche* can inhibit the accumulation of a large amount of intracellular free calcium caused by reactive oxygen species, thus playing a neuroprotective role to improve cognitive function [17]. Luo LAN [18] et al., through the experiment of dementia model rats, found that the total glycosides of *cistanche deserche* can reduce the pathological state of the damaged nerve cells in the hippocampal CA1 region of the experimental model rats, and reduce the damage of the ultrastructure of hippocampal neurons, thus improving the cognitive function. Song Qingqing conducted a water maze experiment on the rat model of bilateral common carotid artery nodes. This model was easy to cause damage to neurons in the hippocampus of rats. After the administration of *cistanche deserticola*, HE staining and Nissl staining were used, and the results were found. There is no obvious damage to neuronal cells after administration of *cistanches*, which further proves that *cistanches* has a neuroprotective effect, thereby improving learning and memory ability.

In conclusion, *Cistanche* exerts neuroprotective effects by blocking A β deposition, increasing neurotransmitter activity, inhibiting reactive oxygen species and free calcium accumulation, and reducing the damage of hippocampal neuronal ultrastructure, thereby improving cognitive function and preventing VaD.

2.3 *Cistanche* has an Anti-inflammatory Effects

An inflammatory response is a series of defensive responses to injury in the body. Studies have shown that a large number of inflammatory factors can be infiltrated after brain tissue injury, mainly including leukocytes, microglia and astrocytes as effector cells, and a large number of inflammatory factors are released, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis- α factors- α), a large accumulation of inflammatory factors can cause a cascade reaction, promote the inflammatory response of the central nervous system, accelerate the death of nerve cells, and lead to VaD symptoms [19]. Studies have shown that several compounds in *Cistanche* have anti-inflammatory effects. Xie Qian [20] found in cell experiments that the microglia activated by lipopolysaccharide promoted the expression of inflammatory factors (IL-1 β , COX-2) to cause an inflammatory storm, and the expression of IL-1 β and COX-2 could be significantly reduced after the intervention of *cistanche* total glycosides, indicating that *Cistanche* total glycosides could inhibit the expression of lipopolysaccharide-activated microglial inflammatory factors and exert anti-inflammatory effects. Through in vitro experiments, Wang Chunhui found that *Cistanche* phenylethanol glycosides, verbascosides and echinacosides regulated the transcriptional events of NF- κ Bp65 on

inflammatory factors by inhibiting the TLR4/NF κ B transduction pathway, thereby reducing neuroinflammation and delaying the progression of dementia.

In conclusion, the active ingredients of *cistanche deserticola* play an anti-inflammatory role by inhibiting the expression of inflammatory factors or inhibiting the signaling pathway of inflammatory factors, and delay the occurrence and development of dementia.

2.4 Cistanche has the Effect of Regulating Neurotransmitters to Protect Cholinergic Nerves

Acetylcholine (acetylcholine, ACh) is the central nervous system line excitatory neurotransmitter, most closely relationship with learning and memory. The continuous release of ACh is an important neurotransmitter to maintain learning and memory and delay the decline of learning and memory function in aging. ACh by acetylcholine transferase (acetylcholinesterase, AChE) catalytic synthesis, after transport vesicles released by cholinesterase (cholinesterase, ChAT) hydrolyzed into choline, acetic acid, etc. Studies have found that there is significant damage to the cholinergic system in the brain and cerebrospinal fluid of VaD patients. The activities of AChE and ChAT are decreased, ACh synthesis is decreased, and serotonergic and dopaminergic systems are also affected. Therefore, neurotransmitter system, especially the central cholinergic system may be targets for the treatment of VaD. Hai-yan xing [21] in vitro experiment found that *c. deserticola* mullein sugar active ingredients can reduce AChE model cell activity, reduce the decomposition of ACh, also can improve the content of ACh of synaptic cleft, prolong the effect of ACh affect the ability of learning and memory. The total glycosides of *Cistanche deserticola* can reduce the activity of AChE in the hippocampus of rats, maintain the normal level of acetylcholine (ACh) in the brain, and improve the learning and memory ability of rats.

In conclusion, *Cistanche* protects cholinergic nerves by regulating the neurotransmitter (ACh) or AChE, promotes cholinergic function, and improves the cognitive function of VaD.

2.5 Cistanche has Immunomodulatory Effects

The immune system can not only resist the invasion of foreign substances, but also accurately identify and remove adverse substances in the body in time, so as to maintain the stability of the body. For the mutation of cells in the body and the immune system can also specificity recognition, in order to prevent the body produce canceration. *Cistanche deserticola* is rich in chemical components, which can significantly improve the immune function of the body. Zhi-qin liu [22], etc. Based on H22 tumor-burdened experimental mice model, can find *c. deserticola* against chemotherapy drugs 5 - fluorouracil (5 - Fu) caused by white blood cells (WBC), platelet (PLT), bone marrow nucleated cells and the DNA of the bone marrow, The spleen index, thymus index, splenic lymphocyte proliferation and natural killer cell (NK) activity of chemotherapeutic tumor-bearing mice were improved. These results indicated that *Cistanche deserticola* could protect the hematopoietic and immune functions of chemotherapy-bearing mice.

2.6 Cistanche has the Effect of Protecting the Liver

Liver is an important organ for the metabolism and biotransformation of substances in the body, so the health of the body is of great significance. Studies have found [23] that the total glycosides of *cistanche deserticola* can activate Nrf-2/Keap-1 signaling pathway in liver tissue, inhibit liver cell apoptosis, and improve liver pathological tissue and intestinal pathological morphology and intestinal wall permeability by reducing liver coefficient, liver tissue lipid deposition, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in mice. In treatment of alcoholic liver injury in order to achieve the role of liver protection. You Shuping [24] et al found that the phenylethanoides of *cistanche deserticola* acted on rats with immune liver fibrosis induced by bovine serum albumin, serum albumin increased, serum total bilirubin and serum direct bilirubin decreased, and serum hyaluronic acid, laminin, type III procollagen and type IV collagen decreased significantly. The expression of TGF- β 1 protein was also significantly inhibited, and the contents of ALT and AST were decreased, thus playing a role in protecting hepatocytes and preventing liver fibrosis.

2.7 Other Potential Effects of Cistanche

With the in-depth study of *cistanche*, it has been revealed that *cistanche* has the following potential effects in animal studies and preclinical studies. 1) Reverse bone loss and increase bone mineral density [25]; 2) improve blood glucose and blood lipid levels [26, 27]; 3) improve reproductive function [28]; 4) ease constipation [29], etc. *Cistanche deserticola* contains rich chemical components, and its pharmacological effects still need to be further studied.

3. Cistanche and Vascular Dementia

VaD is caused by cerebrovascular disease caused by brain ischemia, hypoxia and high intelligence and acquired cognitive impairment to dementia syndrome, its pathogenesis may be related to ischemia hypoxia, cerebral blood flow perfusion inadequacy, nerve cells apoptosis, oxidative stress, nerve inflammation, injury related to cholinergic system. In conclusion, *C. deserticola* could prevent oxidative stress by scavenging oxygen free radicals and increasing antioxidant substances. Clearing beta-amyloid, reduce nerve cells apoptosis, protect hippocampal neurons and regulate neurotransmitters in order to protect the cholinergic nerve, multi-channel, multiple targets, multiple pathways involved in VaD pathophysiological process of each link, and then play puzzle, brain protection. Not only provide theoretical basis for treatment of VaD, more VaD provide direction for new drug development. In clinical practice, compound *Cistanche Yizhi* capsule has been widely used in the long-term and synergistic treatment of VaD, and its curative effect is significant, which is recommended by many guidelines, consensus and series.

4. The Summary and Prospect

Cistanche deserticola, as one of the traditional Chinese tonic medicines, has a wide range of biological activities and high medicinal value. It not only shows a good application prospect in nervous system diseases, especially VaD, but also plays an

important role in immune, reproductive and endocrine systems. It has a variety of pharmacological effects such as anti-oxidation, anti-inflammation, improving cognition, regulating neurotransmitters, preventing and treating osteoporosis, regulating immunity, protecting liver, improving reproductive function, and so on. It has a good application prospect. However, the exact mechanism of *cistanche deserticola*'s pharmacological action has not been fully clarified. Therefore, further in-depth research is needed to clarify the specific mechanism of its pharmacological action, so as to lay a good theoretical foundation for the development of traditional Chinese medicine and the application of *cistanche* in central nervous system diseases.

References

- [1] Wang Jiaying, Nie Jiao. Progress in Traditional Chinese Medicine Research on Vascular Dementia [J]. Inner Mongolia Journal of Traditional Chinese Medicine, 2023, 42 (02): 140-143.
- [2] Yu Wenxiao, Wang Yanjiang. Epidemiological Status and Development Trends of Vascular Cognitive Impairment in Asia [J]. Chinese Journal of Frontiers in Medicine (Electronic Edition), 2020, 12 (10): 1-8.
- [3] Li Qiang, Geng Xiuchao, Yu Wentao, et al. Literature study on the composition rules of vascular dementia prescriptions based on data mining [J]. Clinical Research of Traditional Chinese Medicine, 2018, 10 (06): 34-37.
- [4] Tu Pengfei, Jiang Yong. Re examination of the Materia Medica of *Cistanche deserticola* [J]. Chinese Journal of Traditional Chinese Medicine, 2022, 47 (20): 5670-5679 DOI: 10.19540/j.cnki.cjcm.20220711.101.Fu Z, Fan X, Wang X, et al. *Cistanche* Herba: an overview of its chemistry, pharmacology, and pharmacokinetics property [J]. Journal of Ethnopharmacology, 2018, 219: 233-247.
- [5] Forman H J, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy [J]. Nature Reviews Drug Discovery, 2021, 20(9): 689-709.
- [6] Zhao R, Xu F, Xu X, et al. Effects of alpha-lipoic acid on spatial learning and memory, oxidative stress, and central cholinergic system in a rat model of vascular dementia [J]. Neuroscience letters, 2015, 587: 113-119.
- [7] Li Liang, Jiang Xiaofan, Li Xia, et al. Experimental study on the regulation of GSK3 β /Nrf2/ARE pathway by *Cistanche deserticola* phenylethanolic glycoside to alleviate oxidative stress injury in rats with middle cerebral artery infarction [J]. Shaanxi Medical Journal, 2023, 52 (06): 660-665.
- [8] Cui Bingbing, Li Ji, Zhu Juanjuan, et al. Research progress on the anti-aging mechanism of traditional Chinese medicine polysaccharides [J]. Grassroots Traditional Chinese Medicine, 2023, 2 (10): 143-148 DOI:10.20065/j.cnki.bcm.20230233.
- [9] Wang Xiaowen, Jiang Xiaoyan, Wu Liya Yiming, et al. In vitro clearance of free radicals and protective effect on DNA damage induced by OH \cdot by total glycosides of *Cistanche deserticola* [J]. Chinese Journal of Pharmacy, 2001, (01): 29-32.
- [10] Wu Bo, Fu Yumei. Study on the anti lipid peroxidation effect of total glycosides of *Cistanche deserticola* on subacute aging mice [J]. Chinese Pharmacological Bulletin, 2005, (05): 639.
- [11] Meng Shengxi, Huo Qingping. Research progress on the effects of active ingredients in *Cistanche deserticola* on the nervous system [J]. Chinese Journal of Traditional Chinese Medicine Information, 2016, 23 (10): 123-126.
- [12] Cai Krei, Liu Zhixin, Sun Xiaodong, et al. Protective effects and mechanisms of polysaccharides from *Cistanche deserticola* on brain neurons in D-galactose-induced aging mice [J]. Chinese Journal of Gerontology, 2018, 38 (19): 4732-4734.
- [13] Jia J, Yan X, Cai Z, et al. The effects of phenylethanoid glycosides, derived from *Herba cistanche*, on cognitive deficits and antioxidant activities in male SAMP8 mice [J]. Journal of Toxicology and Environmental Health, Part A, 2017, 80(22): 1180-1186.
- [14] Jia J, Yan X, Song W, et al. The protective mechanism underlying phenylethanoid glycosides (PHG) actions on synaptic plasticity in rat Alzheimer's disease model induced by beta amyloid 1-42 [J]. Journal of Toxicology and Environmental Health, Part A, 2018, 81(21): 1098-1107.
- [15] Zhu K, Meng Z, Tian Y, et al. Hypoglycemic and hypolipidemic effects of total glycosides of *Cistanche tubulosa* in diet/streptozotocin-induced diabetic rats [J]. Journal of ethnopharmacology, 2021, 276: 113991.
- [16] Wu C R, Lin H C, Su M H. Reversal by aqueous extracts of *Cistanche tubulosa* from behavioral deficits in Alzheimer's disease-like rat model: relevance for amyloid deposition and central neurotransmitter function [J]. BMC complementary and alternative medicine, 2014, 14: 1-11.
- [17] Roland, Wang Xiaowen, Shi Kourong, et al. Preliminary study on the effect of total glycosides of *Cistanche deserticola* on the pathological morphology of hippocampal CA1 region in experimental AD rats induced by β - amyloid protein [J]. Journal of North Sichuan Medical College, 2020, 35 (06): 947-951.
- [18] Li Guangzong, Li Jing, Zhu Chen, et al. Risk factors for vascular dementia after cerebral infarction and early predictive value of serum VEGF and MMP-9 [J]. Journal of Integrated Traditional Chinese and Western Medicine in Cardiovascular and Cerebrovascular Diseases, 2021, 19 (05): 836-839.
- [19] Xie Qian. Protective effect of total glycosides of *Cistanche deserticola* on lipopolysaccharide induced inflammation in microglia [D]. Xinjiang Medical University, 2021
- [20] Xing Haiyan. Molecular mechanism of Mongolian medicine *Cistanche deserticola* and verbascoside promoting neurotransmitter acetylcholine release [D]. Inner Mongolia Medical University, 2020.
- [21] Liu Zhiqin, Chen Queting, Li Yan, et al. Effects of *Cistanche deserticola* on hematopoietic and immune function in chemotherapy induced tumor bearing mice [J]. Journal of Beijing University of Traditional Chinese Medicine, 2010, 33 (11): 758-761.
- [22] Wang Fujiang, Tu Pengfei, Zeng Kewu, et al. Study on the protective effect of total glycosides of *Cistanche deserticola* on alcoholic liver injury in mice [J]. Acta Pharmaceutica Sinica, 2021, 56 (09): 2528-2535.
- [23] Shuping, Zhao Jun, Mukremu Tudimaiti, et al. Effects of phenylethanoid glycosides from *Cistanche deserticola*

- on the expression of transforming growth factor β 1 in BSA induced liver fibrosis rats [J]. *Carcinogenesis, Aberration, and Mutation*, 2015, 27 (06): 409-414.
- [24] Zhang Yuequan, Zheng Danhong, Xu Jianfeng, et al. Effects of Desert Cistanche on BMP-2 Protein Expression in Rapidly Aging Osteoporosis Mice [J]. *Ningxia Medical Journal*, 2014, 36 (12): 1114-1116.
- [25] Yang L, Zhang X, Liao M, et al. RETRACTED: Echinacoside improves diabetic liver injury by regulating the AMPK/SIRT1 signaling pathway in db/db mice [J]. 2021.
- [26] Zhu K, Meng Z, Tian Y, et al. Hypoglycemic and hypolipidemic effects of total glycosides of *Cistanche tubulosa* in diet/streptozotocin-induced diabetic rats [J]. *Journal of ethnopharmacology*, 2021, 276: 113991.
- [27] Zhao Donghai, Zhang Lei, Zhang Yan, et al. The therapeutic effect and mechanism of *Cistanche deserticola* phenylethanolic glycoside on cyclophosphamide induced spermatogenic disorders in mice [J]. *Journal of Jilin University (Medical Edition)*, 2014, 40 (03): 612-615.
- [28] Fan Yanan, Huang Yuqiu, Jia Tianzhu, et al. The catharsis effect of *Cistanche deserticola* on constipation rats before and after processing [J]. *traditional Chinese patent medicines and simple preparations*, 2016, 38 (12): 2684-2687.