

## Research Article

# The Review: Current Situation of Exosomes of Traditional Chinese Medicine in Treating Coronary Atherosclerotic Heart Disease

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**Abstract**

Traditional Chinese medicine can be used to treat cardiovascular diseases. It is unique in that they have nano-sized vesicles with a size between 30-100  $\mu\text{m}$ , a bimolecular phospholipid structure, similar to a tea tray, and contain a variety of biologically active ingredients, such as DNA, RNA ( sRNA, miRNA, circRNA ), protein and lipid. Their structure is very stable, wide range of applications, can be treated for the cause, and no toxic side effects. Although in recent years, the research of exosomes has achieved certain results, it can be directly ingested into the human body, and has good absorption, transfer, storage, transmission, metabolism and other characteristics. It also has anti-inflammatory, regulating the immune system, and has the effect of promoting thorough tissue repair. However, due to the incomplete understanding of its mechanism and efficacy, there are still some difficulties in its practical application.

**INTRODUCTION**

Coronary atherosclerotic heart disease, referred to as coronary heart disease, is a serious threat to human life. Although public health has realized the risk factors of coronary heart disease, such as smoking, obesity, and high-fat diet, the mortality rate caused by coronary heart disease is increasing year by year in the world [1]. The existing treatment of coronary heart disease includes basic drug therapy, interventional therapy and surgical treatment. The concept of " interventional non-implantation " has been deeply rooted in the hearts of medical workers and the majority of cardiovascular diseases, and it is also the mainstream idea of interventional therapy for cardiovascular diseases [2]. Studies have found that myocardial exosomes are more effective than intracoronary administration [3]. In recent years, scientific research has found that the size of exosomes has become smaller and smaller. They not only appear in the body fluids of mammals, such as fresh blood, cerebrospinal fluid, urine, saliva, milk and ascites, but also are considered to survive in plants [5]. At the same time, they are used to treat various diseases, such as tumors, neurological disorders, mental illness, heart disease, liver and kidney, and have achieved good results. Traditional Chinese medicine has been used for thousands of years in China. It is also becoming more and more popular around the world, especially in the treatment of cardiovascular diseases. Modern

pharmacological studies have shown that many Chinese herbal extracts protect the development of cardiovascular diseases through antioxidant effects [4]. Exosomes extracted from riboflavin, ginger, salvia miltiorrhiza, honeysuckle, peony bark, and Buyang Huaiwu Decoction have made great progress.

**Brief introduction of Chinese medicine exosomes**

In 1983, scientists found exosomes in sheep reticulocytes. Exosomes are mainly released by the fusion of multivesicular bodies and cell membranes after the formation of multivesicular bodies by endosomes. They contain DNA, RNA, proteins, lipids and other bioactive substances, which are bimolecular phospholipid structures. Exosomes [5], were isolated by centrifugation and purification ; centrifugation methods include ultracentrifugation, density gradient centrifugation, exosome extraction kit, immunomagnetic beads, molecular exclusion, and membrane separation. Exosomes were purified by suspending them in phosphate buffered saline (PBS) and transferring them to discontinuous sucrose gradients (8 %, 30 %, 45 % and 60 %), followed by ultracentrifugation at 1500000 g for 1 h. After that, the Bio-Rad protein quantitative determination kit was used to quantify the obtained exosome concentration according to the protein concentration. The commonly used methods for identifying exosomes are : transmission electron

microscopy, nano-ion tracking analysis, Western Blot detection, and flow analysis. In 2009, the secretion of exosome vesicles in plants (sunflower seeds) was first reported [6]. Compared with mammalian exosomes, plant exosomes have unique advantages, including not being monitored by the immune system, higher bioavailability and harmlessness [7]. Plant exosomes were observed 60 years ago, but less attention has been paid to this field [8]. Compared with free or protein-related miRNAs, plant exosomes have better bioavailability [9]. Plant exosomes have been shown to be stable in the gastrointestinal tract. Some studies have shown that plant exosomes can be used to treat gastrointestinal diseases by oral or intranasal administration [10-12]. Compared with natural products, plant exosomes can target specific organs, have higher solubility, higher permeability to blood, lower solubility in blood, and less side effects. Plant exosomes are stable and can exist in the body for a long time without being destroyed, which can be used as a carrier of drugs. At the same time, it can bind to target cells and regulate a variety of physiological or pathological reactions, and it can also affect gene transcription and translation, cell differentiation, metabolic regulation, angiogenesis, tumor cell invasion and metastasis, and immune response *in vivo*.

## THE ROLE AND FUNCTION OF CHINESE MEDICINE EXOSOMES

### Drug carriers

Traditional Chinese medicines have a wide range of applications in today's research field. They can be accepted by people in various ways and in a targeted manner. Although they have a complete theoretical framework and have made great progress in practical applications, most of them are decoctions, pills or powders. These methods have poor solubility of active ingredients, poor bioavailability to human body, long treatment cycle and slow effect. Plant exosomes are nanoparticles with a double-layer phospholipid structure that can be used as a carrier for anti-inflammatory drugs. Curcumin [13], is considered to be a powerful anti-cancer, anti-inflammatory, regulating the nervous system function of the compound, its pharmacological function has also been widely recognized. A recent study showed that the use of its exosomes for treatment can greatly enhance its mechanical absorption capacity, and it is safe without any side effects. Some studies have suggested that the nutritional uptake of plant-derived nanovesicles has a variety of functions, which can bring health benefits. At the same time, it also has great potential for effective delivery of therapeutic drugs without causing inflammatory reactions [14]. Curcumin exosomes loaded with infliximab by oral administration have gastrointestinal stability, colon-targeted delivery, high intestinal epithelial permeability, and the efficacy of colitis is better than that of intravenous administration of infliximab [15]. Plant exosomes are harmless non-immunogenic nanoparticles that have higher uptake in human cells than other artificial nanoparticles used for drug delivery [16]. Studies have shown that a variety of chemical substances and nucleic acid drugs can be effectively delivered to the site of intestinal inflammation through plant-

derived exosomes, thereby reducing inflammation or inhibiting gene expression [17]. This new drug delivery method has been shown to have a good therapeutic effect on intestinal inflammation [18]. In the current study, a variety of nanocarriers have been invented to load drugs for the treatment of intestinal inflammation [19]. Grapefruit-derived nanovesicles were coupled with immunosuppressant and anti-inflammatory drug methotrexate, and then administered orally. The extracellular microenvironment of tumor cells was acidic ( pH 6.5 ~ 6.9 ), and the release performance of grapefruit-derived nanovesicles was detected by biological model. The experimental results show that grapefruit-derived nanovesicles can stably release drugs at a pH of about 6.5, which indicates that grapefruit-derived nanovesicles can release drugs faster at an acidic pH close to the tumor microenvironment [20]. Plant exosomes also have good drug loading capacity and can effectively load chemicals, nucleic acids and peptides [21]. Plant exosomes can be loaded with different drugs, and their biological effects *in vivo* will not change, which is an important aspect of improving the transport of hydrophobic drugs [22,23]. Although the loading and release capacity of exosomes may vary from different types of reagents, existing experiments have shown that this is a very effective, stable and safe delivery method.

### Anti-fibrosis effect

Pulmonary fibrosis, including idiopathic pulmonary fibrosis, is a refractory disease with irreversible dysfunction of the respiratory system. Its pathogenesis involves the excessive production of fibroblast extracellular matrix induced by transforming factor  $\beta$  (TGF $\beta$ ). Kumazoe [24], found that plant-derived miRNA osa-miR17 d-5p is an effective anti-fibrotic miRNA ; osa-miR17 d-5p inhibits TGF- $\beta$ -activated kinase (MAP3k7) binding protein ( Tab1 ) gene expression, and it also inhibits TGF- $\beta$ -induced fibrosis gene expression in human lung fibroblasts. In conclusion, osa-miR17 d-5p may be an effective candidate drug for the treatment of pulmonary fibrosis. Plant exosomes have a regulatory effect on tissue regeneration. Sahin et al., reported that wheat-derived exosomes promote type I collagen production, proliferation, and fibroblast migration. Wheat-derived exosomes have anti-apoptotic activity in human dermal fibroblasts, human keratinocytes and human keratinocytes [25].

### Regulation of Cholesterol

Willeit et al. [26], have shown that miR-148a-3p is a drug that regulates cholesterol, which can negatively regulate the activity of low-density lipoprotein receptor and ABCA1, thereby reducing the number of LDL-cholesterol and also increasing the number of HDL-cholesterol. The expression of MiR-148a-3p is very significant. It can not only regulate the performance of ABCA1, but also regulate the metabolism of cholesterol, and its specific location can be found. These specific single nucleotide polymorphisms can affect the level of abnormal circulating total cholesterol, TG or LDL-cholesterol. Therefore, the metabolic genetic determinants of lipoproteins and liver and / or other tissues may affect the expression of miR-148a-3p.

## Antibacterial activity

Through the experiment of Teng et al., [27]. It was found that the exogenous granules of ginger had antibacterial activity. They were absorbed by the lipid-dependent absorption of Lactobacillus, and also included IL targeting Lactobacillus. They had the characteristics of promoting antibacterial activity, thus improving the antibacterial effect. In addition, they also have antibacterial activity. Through the mechanism of antibacterial activity, they can reduce liver damage and reduce the damage of dextran sodium sulfate to the liver. Pulmonary macrophages activated by exosomes nsp12nsp13 induce tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL) -6 and IL-1 $\beta$ , which help to induce apoptosis of lung epithelial cells. Ginger exosome-like nanoparticles (GELN) microRNA (miRNA aly-miR396a-5p) can eliminate nsp13-mediated exosome nsp12 nsp13-mediated lung inflammation. GELN aly-miR396a-5p and rlc-mir11-28-3p mediated the inhibition of Nsp12 and spike gene expression, respectively, further confirming the role of GELN in inhibiting SARS-cov-2-induced cytopathic effect (CPE) [28]. Exosomes from edible plants such as grapefruit, tomato, blueberry, and mushroom have anti-inflammatory functions [29].

## The role of repair treatment

As one of the most common diseases in modern society, low back pain and neck and shoulder pain seriously affect people's quality of life. At present, the main etiological studies on low back pain and neck and shoulder pain show that more than 40 % of patients with low back pain and 20 % of patients with neck and shoulder pain are mainly caused by intervertebral disc lesions and a series of lesions secondary to intervertebral disc lesions. Xu et al. [30], found that MSC-derived exosomes may promote the repair of intervertebral discs by activating the expression of CHSY, an enzyme related to ECM synthesis in nucleus pulposus cells.

## Anti-tumor effect

The evidence of exosome-mediated intercellular antigen transfer was found by Thery and his colleagues [31]. EB virus-transformed B cells release exosomes containing major histocompatibility complex (MHC)-II, which can activate CD4 + T cells, while exosomes secreted by dendritic cells express MHC-I, which can activate CD8 + T cells in vitro. Through immune checkpoint therapy, we found that the immune imbalance of several cancer types has been effectively solved, which provides a new opportunity for us to further study the tumor immune mechanism. Citrus and lemon exosomes have antioxidant and anti-tumor effects [32-34].

## RESEARCH PROGRESS OF TRADITIONAL CHINESE MEDICINE EXOSOMES IN CARDIOVASCULAR AND CEREBROVASCULAR DISEASES

### Peripheral vascular disease

Often refers to limb arteries or veins due to wall lesions,

thrombosis, embolism and other causes of vascular stenosis or obstruction caused by ischemia or blood stasis swelling and other related symptoms of the disease. For the treatment of such diseases, conservative treatment alone has great limitations, and it is difficult to be effective in the short term. Surgical treatment often loses a lot, and there are many restrictions on the choice of cases. Interventional therapy has gradually become the mainstream treatment choice. However, there are many types of peripheral vascular diseases, the pathogenic factors are complex, and the individual differences are huge. Interventional therapy often only improves the patency of some blood vessels, and it is difficult to restore normal vascular lesions of large segments or extensive whole body. The acute re occlusion after interventional therapy and the recurrence of deep vein thrombosis after interventional therapy are also a difficult problem. In these aspects, the theory of traditional Chinese medicine may play a key role. In the study, Wang Fang jun [35], and others found that by combining TCM syndrome differentiation with external application of Shuangbai powder honey, it can effectively treat occlusive diseases of lower extremity arteries and veins, and achieve good curative effect. The intravascular application of traditional Chinese medicine decoction is in addition to internal and external application. The results suggest that it can improve the short-term efficacy of deep venous thrombosis of lower extremities and prevent the recurrence of thrombosis. Studies in the nervous system have found that dendritic cells [36], may interact with cells by transmitting miRNAs through exosomes. MiRNAs such as miR-3 in macrophages [37], can be transmitted to other cells by exosomes to exert corresponding biological functions. Exosomes secreted by monocytes [38], are rich in miR-150, which can be transported to endothelial cells to promote neovascularization of endothelial cells. Wheat-derived exosomes can induce angiogenesis in human umbilical vein endothelial cells [39].

### Viral myocarditis

Viral myocarditis is considered to be a life-threatening disease, but there is no complete cure strategy. However, the results of Li et al. [40], showed that CPCs-Ex can provide a new, safe and efficient means of heart disease prevention and control. It can not only inhibit the invasion of viruses, but also stimulate the proliferation of bacteria, thus significantly improving the symptoms of children.

### Cerebral vascular disease

Buyang Huanwu Decoction (BYHWD) has been used to treat paralysis and stroke for centuries. Yang [41], found that BYHWD combined with mesenchymal stem cell (MSC), transplantation partially alleviated ischemic injury by up-regulating angiogenesis, and the purified exosomes could activate the expression of vascular endothelial growth factor (VEGF) in endothelial cells (ECs). In addition, exosomes from MSCs and BYHWD-treated MSCs induced increased microRNA (miRNA)-16 expression and decreased miR-1 and miR-expression. In mesenchymal stem cells, this ability of exosomes can be eliminated by the destruction

of dicer (an enzyme responsible for miRNA maturation) by pretreatment with dicer small interfering RNA (siRNA) or RNase. In addition, BYHWD-treated MSCs exosomes promoted the expression of VEGF and Ki-67 in the brain of rats after bilateral carotid artery ligation and increased vascular density. BYHWD exposure enhanced the expression of angiogenic miRNAs and VEGF in exosomes secreted by MSCs, and promoted rat cerebral angiogenesis. Based on the great potential of G-Exos in stimulating neural differentiation, development and sensory function of bone marrow mesenchymal stem cells, g-e-mir is transferred to mammalian cells to initiate nerve repair. PI3K signaling pathway may be a possible signaling pathway for G-Exos to induce neural differentiation of bone marrow mesenchymal stem cells [42].

## CURRENT RESEARCH STATUS ON THE RELATIONSHIP BETWEEN TRADITIONAL CHINESE MEDICINE EXOSOMES AND CORONARY HEART DISEASE

Cardiovascular disease has become the world's leading cause of death. Cardiovascular disease is most commonly caused by atherosclerosis (AS). The core event of AS is the formation of plaque in the intima of arteries. The mortality and recurrence rate of coronary atherosclerotic heart are high, and traditional Chinese medicine classifies it as "chest obstruction", "sudden heart pain", and "jue heart pain", with the primary cause being "heart pulse obstruction". The development of translational medicine, evidence-based medicine, and individualized medicine has necessitated TCM to interpret the mechanism of TCM syndrome in an objective and quantitative manner, due to modern medicine's conviction that coronary heart disease is associated with pathological processes such as endothelial dysfunction, lipid infiltration, and macrophage inflammatory response. In spite of 90% of human genes being transcribed, only 1% of them encode proteins, a great number of which are regulated by RNA encoding. MiRNA belongs to non coding RNA and is a highly conserved single stranded RNA. miRNAs in exosomes have more potential as biomarkers than free miRNAs. The clinical importance of investigating the action of extracellular miRNAs from various cell origins in cardiovascular diseases, examining the pathological and physiological processes of cardiovascular diseases, and furnishing theoretical backing for comprehending the emergence, growth trends, and prevention and treatment of coronary heart disease is immense.

Studies have shown that curcumin can reduce lipopolysaccharide (LPS) -induced inflammatory injury by increasing the viability of VSMC, reducing apoptosis and inhibiting the release of inflammatory factors. In addition, curcumin increased the expression of toll-like receptor 4 (TLR4) in LPS-treated smooth muscle cells (VSMCs). Curcumin can reduce LPS-induced VSMCs injury by inhibiting NF- $\kappa$ B and JNK signaling pathways. Curcumin can protect VSMCs from LPS-induced inflammatory injury, which may be related to blocking NF- $\kappa$ B and JNK signaling pathways. Therefore, curcumin may be a potential therapy for the treatment of atherosclerosis [43].

Paeonol is the extract of Cortex Moutan, which has the effect of anti atherosclerosis and is commonly used to treat cardiovascular diseases. Liu [44], and other studies showed that the number of atherosclerotic plaques in the aorta of high-fat ApoE  $-/-$  mice who took paeonol orally was significantly lower than that of the control group (high-fat ApoE  $-/-$  mice who did not take paeonol orally). Studies have demonstrated that paeonol can not only diminish inflammation in rat aortic endothelial cells, but also act as an anti-atherosclerosis agent by augmenting miR-3 expression in hyperlipidemic rats' plasma exosomes, hindering the inflammatory body signal pathway of downstream nucleotide binding oligomeric domain such as receptor protein 3, and diminishing the inflammation of rat aortic endothelial cells. Danshen is a representative medicine for promoting blood circulation and resolving blood stasis. It has a bitter taste, a slightly cold nature, and is beneficial for regulating the heart, pericardium, and liver meridians. The effects of this are manifold: it encourages blood flow and meridians, relieves stasis and agony in the blood, clears the heart of any issues, and cools the blood to alleviate carbuncle. Modern pharmacological research has shown that Danshen can prevent and treat myocardial IR injury by clearing free radicals, reducing calcium overload, improving microvascular function, inhibiting white blood cell activation, and reducing cell apoptosis. Widely employed in the clinical prevention and treatment of cardiovascular diseases, drugs containing Danshen are a common component. Tanshinone IIA (TSA) is a lipid soluble component in *Salvia miltiorrhiza*. Researchers Li [45], and others discovered that MSCexo, extracted from mesenchymal stem cells, can enhance myocardial ischemia-reperfusion injury, impede monocyte infiltration, and stimulate angiogenesis. TSA MSCexo enhances the protective effect of MSCexo on the heart. It was found that miR-3-5p played a key role in TSA MSCexo improving cardiac function after myocardial ischemia/reperfusion, regulating monocyte infiltration and angiogenesis. Ji et al. [46], studied that extracellular miRNA-3 derived from cardiac progenitor cells promotes neovascularization in necrotic regions by regulating the upregulation of the Nox ROS signaling axis.

## SUMMARY AND OUTLOOK

Modern research on coronary heart disease increasingly needs specific indicators to evaluate the occurrence, development and outcome of disease. Both single and compound Chinese medicines are involved in disease treatment with multiple targets and pathways. Exosomes can participate in the occurrence of atherosclerosis by regulating inflammatory reaction, endothelial cell apoptosis, macrophage polarization, vascular smooth muscle phenotype transformation and platelet activity. The donor cells of exosomes mainly include mesenchymal stem cells, bone marrow mesenchymal stem cells, macrophages, etc. The clinical studies involved include coronary heart disease, rheumatoid arthritis, polycystic ovary syndrome, tumors, atherosclerosis, etc; Exosome-derived miRNAs have high specificity. Carriers of miRNAs and proteins, exosomes are involved in cellular communication and the pathological and physiological processes of coronary heart disease, as evidenced by the exosome-derived

miRNA pathway, which is of great clinical importance. And there is a correlation between the material foundation of traditional Chinese medicine theory and exosomes. Traditional Chinese medicine theory can provide clear direction for exosomes research and play a preventive and therapeutic role in disease evolution and transmission. Currently, the mechanism of action of traditional Chinese medicine on exosomes miRNA is still in the preliminary stage. How to determine the optimal drug incubation method, determine the optimal reaction dose of drugs on exosomes miRNA, and determine the role of multiple sites of traditional Chinese medicine The interaction between multiple cells will be a research hotspot.

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