

# Application Progress of Traditional Chinese Medicine as an Adjuvant Therapy for Cardiovascular and Cerebrovascular Diseases

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**Abstract.** At present, CVDs are a crucial problem that has puzzled many researchers for a long period. It has a high fatality rate because it will cause many complications and adverse effects on metabolism. Many side effects of pharmaceutical drugs are very serious because the majority of medicine that treat CVDs are western medicines. Pathogenic factors could not be inhibited effectively and the appropriate target spot was not discovered. However, more and more new technologies and drugs have developed and improved in treating this disease. The combination of TCM and WM has profound prospects. Especially in the clinical treatments of CVDs, TCMs play a role as adjunctive drugs by promoting blood circulation and removing blood stasis. And it can be used for reducing the toxic and side effects of chemical medicines. This integrated method not only maintains the traditional theory and drugs such as herbal, animal and mineral materials but also improves therapeutic effects by combining WM and using advanced devices, artificial intelligence and Western dosage forms. These integrative methods can effectively improve the therapeutic effects and reduce the frequency of adverse effects. Scientists made great progress and achievements in this field. However, the specific mechanism of action of the compounds still needs to be explained deeply.

**Keywords:** Traditional Chinese medicine, cardiovascular and cerebrovascular disease, adjuvant therapy.

## 1. Introduction

At present, Cardio-cerebrovascular disease (CVD) is the most tough system with high incidence and mortality in the world. Especially for elder people cardiovascular and cerebrovascular diseases are difficult to treat and have no effective access to resolve this problem due to its complex pathogenesis. The common diseases include atherosclerosis, coronary heart disease, angina pectoris, cerebral infarction [1,2], which can significantly affect people's physical system. The pathogenesis of different types is complex. Therefore, the therapies of these diseases need to be constantly explored through extensive experiments. These also significantly cause metabolic problems and result more side effects due to slow blood flow which causes the lack of oxygen and nutrients in brain cells and myocardial cell such as cerebral infarction and the formation of thrombosis [1]. At present, the treatments of these diseases are mainly western medicine (WM). For example, coronary heart disease and angina pectoris can be treated by calcium antagonists, nitrates, and other drugs [1]. Although these medical methods can effectively resolve problems and obtain good results, many adverse effects like thrombus even threat the patient's life and severely affect the quality of life. Therefore, the between WM and traditional Chinese medicine (TCM) is a promising coping strategy to resolve side effects. This integrative treatment can effectively improve the cure rate of cardiovascular and cerebrovascular diseases by up to 90%. Compared to WM, majority people believe the therapeutic methods of TCM are simple, and cannot meet the demands of treatment [3]. Even some people think that the TCM treatment method is not rigorous, which means TCM is still discriminated. Nevertheless, TCM as an ancient and complete medical system is still well persevered and constantly breaks through under the leadership of many researchers. Nowadays, the integration of TCM and WM is popular and is widely

used in clinical studies with diverse forms of application. This applicable system greatly improves the drug efficacy and prognosis, which has made contributions on human medicine and health. As an important system, many common side effects what are caused by western drugs can be resolved, including gastrointestinal adverse reactions, allergic reactions etc.

TCM lacks substantial pharmacological studies, and the components of TCM are complex with poor stability. However, it doesn't have too much severe side effects compared with WM. Its innovation potential is still very huge. Therefore, many clinical studies are essential for identification of mechanism, safety and efficacy [4]. At present integrative therapy between TCM and WM is widely used in the treatments of various diseases like CVDs, diabetes, constipation and other chronic diseases. A large number of clinic studies confirmed the clinical efficacy and many results are enough to identify the profound possibility of integrative Chinese and WM. The combination of TCM and WM to treat cardiovascular and cerebrovascular diseases will be introduced in this essay. They are called the rhizome of chuanxiong (CX) and danshen respectively, as well as other kinds of drugs. Both of them have the function of promoting blood circulation to arrest pain. These two drugs can also be combined to treat CVDs. As for this paper, we mainly discussed the combination of TCM and WM to treat cardiovascular and cerebrovascular diseases.

In order to reduce the certain toxicity with long-term treatment integrative therapy can need to develop to improve disease control and prognosis guarantee. A lot of WMs include statins, beta blocker, ACE inhibitors need long-term use, which means the tendency of many adverse actions is on the increase. In addition, studies have shown that the safety of drugs is related to factors such as age, gender. The ideal effects can be achieved in the short term by WM, but the long-term use will cause many negative effects [5]. In particular, the pharmacokinetics of drug treatments for elder people would be changeable. The changes in metabolism and body distribution occur with age, this phenomenon will cause side effects include cognitive impairment, muscle damage etc [6]. Thereby, in order to avoid adverse actions and poor prognosis researchers focus more on integrative methods between TCM and WM on clinical application.

This paper will mainly discuss how the two Chinese medicine monomers function in treating CVDs and their effects. In addition, the therapeutic effects and application of the combination of two drugs and western drugs were also analyzed, as well as other methods of collaboration. The relevant pharmacological activity and effective constituent will be further explained. The team members analyzed the relevant clinical research cases from various CVDs and compared the pathogenesis of cardiovascular and cerebrovascular diseases. Focused on influences about human metabolism, the current drug development process, and the case of integrated TCM and WM based on substantial experimental results and discussion

## **2. Pathogenesis**

### **2.1. Atherosclerosis**

There are two related doctrines: one is about protein, and the other one is about RNA. For the first one, some inflammatory factors such as cholesterol are involved in the formation and development of atherosclerosis through mutual excitation and synergistic action. Appearance of Hippo regulating cytokine expression can increase the expression of inflammatory factors. Activation of YAP / TAZ protein (A pair of homologous proteins) will enhance the activity of YAP / TAZ-JNK and enhance the phosphorylation degree of JNK, leading to the abnormal expression of the Hippo pathway[7]. For the second one, circRNA (circular RNAs) and RBP (RNA binding proteins) can regulate rRNA maturation, which in turn regulates angiogenesis and cardiomyocyte regeneration. Interaction between the circular RNA and RBP can interfere with ribosome biogenesis[7]. The Pes 1 nucleolar proteins make up PeBow, and PeBow plays an important role in the development of ribosomal organisms. In addition, Can inhibit rRNA maturation by deleting the Pes 1 c-terminal domain and stabilize the pro-apoptotic protein p53.

## **2.2. Coronary Heart Disease**

As an endogenous miR-939 sponge, circ-SATB 2 has the ability to adsorb miR-939 and upregulate STIM 1 expression, which can increase the expression of proliferative VSMC and enhance the risk of coronary heart disease[7]. About protein, The expression of proteins such as P2Y12, RIAM could activate the platelet integrin signaling pathway and promote platelet aggregation activation[7]. If platelet aggregation activation and other platelet functions are abnormal, it is highly likely to cause thrombosis.

## **2.3. Heart Failure**

circFndc3b is a cirRNA that has been demonstrated can decrease VEGF levels, which leads to myocardial infarction. Besides, Autophagy dysregulation is also greatly associated with myocardial infarction. The DNA methylation of the Pink1 promoter is blocked upon binding of circ-aCR[7]. In this way, it will phosphorylate FAM65B and increase Pink1 to achieve the effect of inhibiting autophagy. Hypoxic glycolysis, inhibition of oxidative metabolism, and cellular remodeling are able to change related gene expression. KL15, a regulatory factor of gene expression about ischemic cardiomyopathy, is controlled by EZH2.

## **2.4. Myocardial Infarction**

Diabetic cardiomyopathy is early characterized by myocardial fibrosis and cardiac stiffness, leading to diastolic dysfunction, progressing as cardiomyocyte apoptosis increases, further exacerbating myocardial fibrosis. Mitochondrial dysfunction and caspase molecules activate PAR 4, a pro-apoptotic protein that is also an important target of a tiny RNA, causing brain cell apoptosis, which then triggers ischemic damage.

From these examples, it can be seen that most of these diseases have a connection with genetic material such as DNA or RNA. They control the expression of transcription factors, and control proteins' expression. If this part loses its control, it will possibly lead to angiemphraxis, thus leading to cardiovascular and cerebrovascular disease.

## **3. Metabolic Mechanism**

### **3.1. Lipid Metabolism**

The lipid metabolism involves the following elements: in atherosclerosis, macrophages uptake oxidized low-density lipoprotein (oxLDL) through CD36 (Also known as fatty acid translocase (FAT), glycoprotein IIIb (GPIIb), or glycoprotein IV) to form foam cells, which is a key process in atherosclerosis. CVDs are often accompanied by disturbances in lipid metabolism, including abnormal increases in triglyceride and cholesterol levels. These lipids can be deposited in the heart and vascular tissues, leading to dysfunction[8]. Last, the occurrence of diabetic cardiomyopathy is associated with alterations in cardiac energy metabolism. In the hyperglycemic environment, glucose uptake and utilization of cardiomyocytes are impaired and mitochondrial function decreases, resulting in insufficient energy supply of cardiomyocytes and impaired myocardial contraction and diastolic function.

### **3.2. Proteometabolism**

Then, about proteometabolism, the part of the pathogenesis of CVDs regarding protein metabolism is just like this: For example, in CVDs, such as diabetic cardiomyopathy, the activity of metabolic regulatory proteins such as peroxisome proliferator-activated receptors (PPARs) may increase, promote the expression of genes involved in fatty acid oxidation, but may also lead to the accumulation of lipids in cardiomyocytes.

### 3.3. Hormone Metabolism

The hormone metabolism leads to CVDs are most related to insulin. The diabetic state, insulin resistance not only affects the regulation of blood sugar but also affects the normal function of cardiomyocytes[7], leading to metabolic disorders of the heart. Then, in a state of diabetes, there is activation of the renin-angiotensin-aldosterone system (RAAS) throughout the body and the heart, leading to vasoconstriction, water and sodium retention, and myocardial fibrosis. Last, hyperglycemia and insulin resistance can impair vascular endothelial function, reduce the production of nitric oxide (NO), and increase endothelin production, leading to vascular stiffness and infiltration of inflammatory cells.

Many cardiovascular and cerebrovascular diseases are caused by the blockage of blood vessels in the heart and brain parts, and most of these obstructions are lipids. Then the metabolism of sugars and lipids is an important part of the study of the causes of cardiovascular and cerebrovascular diseases, which involves the metabolic mechanism of a series of substances such as hormones and proteins.

## 4. Effect and Application of TCM Monomer Components on CVDs

### 4.1. Tetramethylpyrazine (TMPZ)

TMPZ which belongs to the class of amide alkaloids is the most active compound among the components of CX. Scientists found it has the function of protecting endothelial cells, antioxidant, anti-platelet aggregation and so on, which are related to CVDs.

For instance, oxidative stress (OS) greatly leads to endothelium dysfunction and increase the risk of cardiovascular and cerebrovascular events. Excessive reactive oxygen species (ROS) which have already become the key mediators of the pathogenesis of vascular disease are its direct primers. ROS is produced by the highly activated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mostly under the induction of cerebral ischemia. Excessive ROS will damage the normal function of cells and organs severely, as well as influence the redox equilibrium in our body. However, TMPZ is a kind of antioxidant which has the ability of eliminating ROS or inhibiting activity of NADPH. It plays an antioxidant role by these abilities. In addition, TMPZ can decline the expression of ROS by inhibiting a certain gene [9].

### 4.2. Tanshinones

Tanshinones come from a medicinal plant that is called danshen (DS). It generally contains o-quinone and para-quinone structures. In recent years, the pharmacological activities of tanshinones in cardiovascular and cerebrovascular aspects have attracted extensive research and attention. Researchers have discovered that Tanshinones have the function of anti-myocardial ischemia, anti-atherosclerosis, anti-inflammatory, etc.

Atherosclerosis (AS) is one of the important pathological bases of CVDs. If AS can be treated in early stage, it is important to regulate lipid metabolism. This is because the primary factor of causing AS is hyperlipidemia and dysregulation of lipid metabolism, especially the lipid peroxidation. Tanshinones can decline the content of oxidized low-density lipoprotein(ox-LDL) and ROS in the serum of the atherosclerosis model, and increase the level of superoxide dismutase (SOD) at the same time. In addition, Tanshinones also have the function of decreasing apolipoprotein B, inhibiting lipid peroxidation in macrophages, reducing the level of low density lipoprotein cholesterol (LDL-C), which means it can regulate lipid metabolism in different methods to achieve anti-atherosclerosis action[10].

### 4.3. The Function of DS-CX

The two important factors that will cause CVDs have been mentioned now. However, inflammatory response is one of the factors of vascular endothelial injury. It is accompanied by a variety of CVDs.

Both DS and CX can inhibit inflammatory reactions by regulating factors or restraining certain signal paths. If they were combined in specified ratio, anti-inflammatory action will be displayed much better compared with individual medication. What's more, thrombus is the pathological basis of many kinds of CVDs. The signal path of mitogen-activated protein kinase (MAPK) is the major method of platelet activation, which can be activated by collagen and thrombin, resulting in platelet deformation, adhesion and aggregation. This kind of combination will inhibit the phosphorylation level of the kinase and other kinases in MAPK so the platelet aggregation will be inhibited and antithrombotic effect can be shown better [11].

#### **4.4. The Combination of DS and WM**

Antiplatelet drugs can inhibit platelet adhesion, activation and aggregation, and reduce cardiovascular and cerebrovascular events. Researchers tried to combine compound DS tablet with clopidogrel to treat platelet activation hyperlipidemia. They discovered that compound DS tablet can increase the effect of clopidogrel on reducing activated platelet ratio and platelet aggregation rate remarkably. This combination will enhance the function of antiplatelet and antithrombotic. Moreover, scientists explored the clinical effectiveness of the combination of DS and aspirin which is used to treat coronary heart disease that also belongs to CVDs. The results showed that the platelet mass aggregation rate was reduced effectively compared with using aspirin alone. The maximum platelet aggregation rate (PAGM) and thromboxane B<sub>2</sub> (TXB<sub>2</sub>) level declined remarkably in the patients who accepted this treatment [12]. Of course, there are also some other Chinese medicine that can be combined with WM to treat CVDs such as ShuXueNing which has the components of ginkgo leaf and Naoxintong capsule. All in all, the combination of DS and WM is capable of antiplatelet therapy for CVDs.

### **5. Clinical Discipline of Chinese and Western Integrative Medicine**

Combining TCM and WM is a novel method for the treatment of clinical diseases and common symptoms. This combination is also an important individualized therapy. In ancient times, WM was introduced in China, majority of people began to admire WM because of its better therapeutic effects and diverse therapeutic methods. However, a large number of researchers still preserve TCM and constantly explore the development of Chinese herbal medicine (CHM) and novel integration between WM and TCM. At present, the combination of WM and TCM has many huge breakthroughs in clinical therapy. Especially for the treatments of some tenacious diseases like cere-CVD, gastrointestinal disease, diabetes and cancer, this integration showed considerably obvious effects and higher prognostic indexes. With the further development of TCM and further validation of molecular mechanism, the combination of WM and TCM can generally become a more effective therapy. WM and TCM need to constantly integrate to dig new therapeutic prospects. At present, TCM was proved can be an important component of contemporary and alternative medicine (CAM). Although the mechanisms of TCM are uncertain, a lot of studies and clinical studies can prove its therapeutic improvements and prognosis. ZihanWang et al. combined adjunctive herbal medicines with beta- receptor blockers and other WMs for heart failure [13]. Through the clinical trial and data showed the combination of WM and TCM has long-term clinical effects for patients, which indicates long-term therapeutic effects can be improved if people constantly promote the expansion of integrative therapy. Weiquan Ren et al. used Meta-analysis to prove the antihypertensive efficacy of CHM plus antihypertensive drugs (CPAD) is better than regular WM [14]. Many clinical data also determined integrative therapy would be more effective in lowering blood pressure, improving vascular endothelial function, regulate blood lipids and inhibiting inflammatory reaction. Yu-Chen Cheng et al made a prescription by TCM and western medicine for different strokes [15]. Compared to WM therapy, integrative therapy can reduce the risks of ischemic stroke and acute hemorrhagic stroke because of the effect of promoting blood circulation and removing blood stasis.

## 6. Innovative Dosage of Integrative Therapy

Nowadays, TCM has different forms of treatment, including the combination of CHM and chemical drugs for CVDs, acupuncture and Western medicine for hypertension and coronary heart diseases. Therefore, TCM can be used to treat adverse effects by relieving aches and improving the outcomes of prognosis. However, in recent years, with the constant development of research and exploration, more novel forms of TCM and novel therapies are generally emerging. In particular, Chinese herbal injection (CHI) is the most emerging example of the combining form. CHI as a novel drug delivery modality integrates modern medical pattern with TCM liquid, which can effectively prevent the first pass effect of liver and gastrointestinal absorption to keep high usage of medicine. These dosage forms also resolve the difficulty of taking medicine by resolving the bitter character of Chinese herbal drugs. Currently, CHIs on the market like Puerarin [15] injection can improve Cardiovascular endothelial function, increase blood volume, improve microcirculation and inhibit inflammatory factors to treat similar symptoms caused by abnormal blood flow. DS injection is also a popular type of CHI, which plays important roles in the treatment of Various types of atherosclerosis by controlling fat and protein content, improving microcirculation and inhibiting the action of different coagulation related factors to reduce the incidence of thrombus [16]. CHIs have effects on clinical treatment of acute and critical patients due to their prosperity of rapid action. However, CHI directly connected with blood may cause slight chemical reactions and potential risks. Moreover, at present, there are few relevant studies and reports about CHI's adverse effects. Thereby, continuously exploring is indispensable for promoting overall development of integrated TCM and WM.

## 7. Conclusion

TCM as a contemporary and alternative therapy can treat CVDs and other stubborn problems such as antithrombotic agents may cause severe risks of bleeding. Currently, many herbal drugs as adjunctive medicines have positive effects on hypertension, coronary heart disease stroke etc. But for the gaps in mechanism and side reaction still need to be replenished and improved. According to the therapy of Yin and Yang, which can achieve one prescription for various diseases. It can be sure that monomer of TCM can use personal immune to treat common aches and adverse effects with sufficient safety and convenience. Our group not only introduced typical monomers of Chinese traditional herbs but made many comparisons of CVDs' pathogenesis, effects on metabolism and the efficacy and adverse effects after the combination with TCM and WM. These studies indicated that its effects as adjunctive drugs. Therefore, the treatment of integrated TCM and WM has a wider application and developmental prospects still needs to be explored in the future.

## 8. Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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