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Exploration on the Research Progress of Traditional Chinese Medicine in Treating Uremic Cardiomyopathy based on Cardiomyocyte Protection

Ximeng Yao, Xiaohui Li*, Liming Chen, Jie Qu

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Uremic cardiomyopathy is an important complication that affects the quality of life and prognosis of patients with chronic kidney disease. The damage to myocardial cells is a major pathological mechanism of uremic cardiomyopathy. Traditional Chinese medicine (TCM) can promote the elimination of uremic toxins, improve the renal and cardiac function of chronic kidney disease patients, and alleviate renal anemia. At the same time, TCM can regulate relevant signaling pathways and gene expressions through multiple targets, reduce oxidative stress and inflammatory responses in myocardial cells, inhibit apoptosis of myocardial cells, and improve left ventricular hypertrophy and myocardial fibrosis. This ultimately enhances cardiac function and delays the progression of uremic patients and the development of uremic cardiomyopathy. In this paper, the author aims to review recent experimental research advances in TCM for the treatment of uremic cardiomyopathy from the perspective of protecting damaged myocardial cells. The goal is to explore the strategies and methods of TCM in treating uremic cardiomyopathy, providing references and evidence for clinical TCM treatment of this condition.***

Keywords: Uremic cardiomyopathy, Myocardial cells, Traditional Chinese medicine compound formula**.**

1. Overview of Uremic Cardiomyopathy

Uremic cardiomyopathy (UCM) is a form of uremia, which is a cardiac complication of uremia due to chronic kidney disease (chronic kidney disease (CKD)), and is mainly manifested by left ventricular hypertrophy, reduced capillary density, fibrosis and ventricular remodelling, which can lead to arrhythmias and heart failure, etc. Sudden death can even occur in severe cases and is a major cause of morbidity and mortality in patients with CKD [1, 2]. UCM occurs mainly in patients with renal failure, especially in patients with advanced CKD or end-stage renal disease, and usually requires haemodialysis or kidney transplantation for life support, yet haemodialysis, although it is the first choice of treatment for uremic cardiomyopathy, does not seem to be an adequate treatment because cardiac insufficiency or uremic cardiomyopathy often persists despite haemodialysis treatment [3]. Moreover, the pathogenesis of cardiovascular injury in patients with CRF is much more complex than in the general population, and their unique haemodynamic and metabolic risk factors further increase cardiovascular risk [4]; approximately 90% of patients die due to cardiovascular complications before their renal disease progresses to end-stage. Therefore, UCM is a global public health problem, especially in developing and developed countries, where its prevalence has increased significantly due to the increase in chronic diseases such as diabetes mellitus and hypertension, which not only threaten the health of the individual but also represent a public health challenge. Currently, Western medical treatment for UCM is mostly based on symptomatic treatments such as controlling blood pressure, correcting anaemia and improving hypoproteinaemia without specific drugs, however, many previous studies and clinical practices have shown that traditional Chinese medicine (TCM) plays its own unique role in UCM, which is worth exploring further. Nowadays, it is usually believed that the progression of UCM is closely related to cardiomyocyte damage, which includes uremic toxins, inflammation and oxidative stress, cardiac fibrosis and left ventricular hypertrophy [5], among which, left ventricular hypertrophy and myocardial fibrosis are the main pathological manifestations of its cardiac damage. Meanwhile, previous studies have found that the main mechanisms of action of TCM against UCM include removal of uremic toxins, inhibition of inflammatory response, reduction of oxidative stress, alleviation of cardiac fibrosis and left ventricular hypertrophy, inhibition of apoptosis, etc., and modulation of related signalling pathways. Therefore, further research on the progress of TCM in protecting cardiomyocyte damage and preventing UCM is of great practical significance for further elucidating the pathogenesis of UCM.

2. Chinese Medicine's Understanding of Uremic Cardiomyopathy

The etiology and pathogenesis of UCM have not yet established an independent and systematic cognition in Chinese medicine, as its onset is usually co-occurring with CRF. In TCM theory, there exists a certain unity and continuity in the pathogenesis of the two [6]. Discussions of their clinical manifestations and pathomechanisms can be found in ancient medical classics, and Huang Chunlin et al. [7] considered "turbid toxin, " "blood stasis, " and "qi deficiency" to be the main etiological and pathological mechanisms of UCM in TCM; its The root of the disease lies in the impaired function of the lungs, spleen and kidneys, which leads to the gradual decline of positive qi, qi imbalance, and internal stagnation of turbid toxin, blood stasis and phlegm-dampness, affecting qi, blood, yin and yang, as well as the functions of the internal organs. Kidneys main qi clear and urinate turbid,

spleen main transport and ascending clear and descending turbid. When the lungs, spleen and kidneys are deficient in function, the qi function is out of order and the qi cannot rise and fall properly, resulting in the stagnation and retention of water and dampness. Turbid evils cannot be discharged and coalesce, blocking the triple jiao, and the triple jiao qi is out of order; clear qi cannot be elevated and sinks, forming turbid toxins, stasis, water-dampness, and dampness-heat, etc., which stagnate in the renal collaterals, impairing the opening and closing functions of the kidneys, affecting the qi and blood, yin and yang, and the functions of the internal organs, and resulting in the emergence of a wide range of pathologies [8]. Combined with the characteristics of UCM, modern medical doctors believe that when the lungs, spleen and kidneys are deficient, resulting in the regulation of fluid metabolism and the dysfunction of the urinary turbidity, fluid metabolism disorders, resulting in fluid internal stagnation, the formation of oedema, wheezing and fullness; stasis blockage of the heart veins, vein paralysis and obstruction, chest pain, palpitations; water and turbid and stagnant blood fight with each other, ultimately brewing turbid toxin, and then further development of turbid toxicity within the stagnation, impeding the generation of qi and blood, affecting all five viscera and six bowels, and affecting the function of the heart. This leads to heart and kidney disease, which ultimately triggers the development of UCM [9]. Combined with the theory of traditional Chinese medicine and the pathogenesis of UCM, cardiomyocytes are similar to the yang of the heart, which is the material basis for functional activities, and a deficiency of cardiac yang leads to internal stagnation of turbid toxins, which in turn leads to cardiorenal co-morbidities, as well as a decrease in the number of myocardial cells and functional decline caused by damage to myocardial cells, and damage to cardiomyocytes is the main pathogenesis of uremic cardiomyopathy.

3. Traditional Chinese Medicine for Uremic Cardiomyopathy

3.1 Removal of Uremic Toxins

The majority of UCM are untreated, prolonged, and progressive CKD, with eventual involvement of one organ and related organs or even multiple organs. In the progression of CKD, CKD-specific non-traditional cardiovascular factors, such as uremic toxin accumulation, vascular calcification, inflammation and oxidative stress, etc., which is also an important pathogenetic mechanism of UCM. The process is characterised by abnormal renal metabolism, in which large amounts of compounds accumulate in the body and cannot be excreted as uremic toxins, thus affecting the structure and function of the heart. There are three main categories of uremic toxins: small molecule water-soluble substances, protein-bound compounds, and intermediate molecules. The first category, small molecule water-soluble metabolic toxins, such as BUN, Scr, most of this type of toxin can be cleared by conventional haemodialysis; the second category, intermediate molecule toxins, such as parathyroid hormone, β2-microglobulin, conventional haemodialysis is not very good at removing intermediate molecules; and the third category of protein-bound toxins, such as indole phenol sulphate (indoxyl sulphate, IS), p-cresyl sulphate (The third group of protein-bound toxins, such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), have high cardiovascular and nephrotoxicity, and are difficult to be removed by haemodialysis. IS is a product of the intestinal catabolism of tryptophan, and high levels of which may be detrimental to cardiomyocytes through a variety of mechanisms, which are mainly caused by damage to the cellular antioxidant system, and which has a direct pro-fibrotic, pro-hypertrophic, and other cardiac remodeling effects on cardiomyocytes and fibroblasts. PCS is an intestinal catabolite of tyrosine and alanine, etc. Similar to IS, PCS exerts prorenal fibrotic effects by inducing oxidative stress and inflammation, and can induce cardiomyocyte cellular demodulation and lead to impaired cardiac diastolic function, reduced spontaneous contraction rate of cardiomyocytes, and disruption of the structure and function of the inter-cardiomyocyte gap junctions. However, the retention of toxins in uremia is equivalent to the "turbid toxins within" in Chinese medicine, and Chinese medicine adopts the basic treatment principle of draining turbid and detoxification. Zhang Qian et al. [10] applied renal failure enema formula, which can effectively remove uremic toxins from CKD patients, improve patients' symptoms, effectively protect patients' renal function, and reduce atherosclerotic lipid accumulation caused by protein-bound toxins, meanwhile, the effectiveness and safety of clinical use are high, and it can be used as the main treatment method before renal replacement therapy, which can give full play to the characteristics and advantages of Chinese medicine in the treatment of CKD. Fang Lugui et al. [11] found that the addition of slow decay formula can reduce the serum IS, PCS, Scr, BUN levels of peritoneal dialysis patients, improve the clinical symptoms of the patients, and alleviate the damage of uremic toxins to the heart, brain and other organs. Wang Yingyi et al. [12] found that wasabulet can directly act on intestinal bacteria, regulate the synthesis of urotoxin precursors in the intestine, and ultimately inhibit the accumulation of urotoxins in the body, which can help to slow down the progression of CKD.

3.2 Suppression of the Inflammatory Response

The inflammatory response is a dynamic process of inflammatory factor release in the body, which disrupts normal cellular function and leads to tissue damage, with pro-inflammatory cytokines such as tumour necrosis factor (TNF-α), interleukin (IL-1β) and vascular endothelial growth factor (VEGF) playing a central role. Moreover, the most studied inflammatory mediator in the development of UCM is the NLRP3 inflammasome. The activation of NLRP3 inflammasome is mainly in monocytes and macrophages, but can also be widely activated in endothelial, epithelial, and mesenchymal cells; the NLRP3 inflammasome and its downstream inflammatory factors are involved in the pathogenesis and progression of UCM, and play an important role; therefore, inflammatory responses play an important role in UCM through Multiple mechanisms and pathways cause damage to the patient's cardiovascular system, which is highly related to the development of UCM. Duan Xuefeng et al. [13] found that the accumulation of p-cresol sulphate and indolylphenol sulphate in uremic patients not only accelerates renal fibrosis, but also increases reactive oxygen species in endothelial cells, activates the NF-κB pathway, and leads to inflammation; and the combination of rhubarb with samples of samples of samples of samples of rats with UCM injection

reduces the generation and release of TNF-α and inhibits the over-activation of the NF-κB signalling pathway to remove oxygen free radicals and alleviate the inflammatory response. free radicals, and alleviate the inflammatory response. Yang Huawei et al. [14] found that the treatment of septic cardiomyopathy with the addition and subtraction of Broken Heart Soup could regulate the left ventricular ejection fraction of the treatment group, reduce the levels of pro-BNP, ultrasensitive troponin I, leukocyte count, and C-reactive protein, which could effectively reduce the inflammatory reaction of septic cardiomyopathy patients, help to alleviate the secondary injuries, protect the target organs and tissues, reduce the risk of organ failure, and promote the disease regression of the patients. It can help reduce secondary damage, protect target organs and tissues, reduce the risk of organ failure, and promote the regression of patients. Guo Yining et al. [15] found that the use of cardiomyocyte HL-1 injury model and the treatment of heart failure with Xin Yang tablet-containing serum at the same time, found that different dosages of Xin Yang tablet-containing serum can over-regulate the NLRP3/IL-1β signalling pathway, inhibit inflammation, reduce cell death, alleviate myocardial injury, and improve cardiac function.

3.3 Anti-oxidative Stress

Oxidative stress, as one of the important mechanisms in the development of UCM, refers to an imbalance between oxidation and antioxidation in the body, an increase in the generation of intracellular oxygen free radicals, such as the excessive production of reactive oxygen radicals (ROS) and reactive nitrogen radicals (RNS), and an oxidation that exceeds the scavenging of oxidants, which can lead to tissue damage [16], as a result of which, the reactive oxygen species (ROS) accumulates in the body or in the cells and cannot be degraded and induces a series of cytotoxic processes. Oxidative stress can lead to glutathione depletion, lipid peroxidation, membrane damage, and DNA strand breaks, as well as activation of proteases, nucleases, and protein kinases [17], which can lead to body damage and disease. Moreover, a large number of studies have found that oxidative stress can directly or indirectly induce the occurrence and development of UCM, therefore, in-depth research on oxidative stress seems to be very necessary. Liu Guang et al. [18, 19] used indolephenol sulfate-induced H9c2 cardiomyocyte injury to establish a model of uremic cardiomyopathy, and used rhodopsin for treatment, which showed that rhodopsin could reduce the level of ROS in H9c2 cardiomyocytes, and inhibit apoptosis of cardiomyocytes by resisting oxidative stress; at the same time, the study also found that rhodopsin was able to lower serum creatinine urea nitrogen level, also increased the serum superoxide dismutase level and reduced malondialdehyde level, thus reducing myocardial injury and cardiomyocyte H9C2 injury in uremic rat model.

3.4 Improvement of Left Ventricular Hypertrophy and Myocardial Fibrosis

Under the influence of various pathogenic factors, patients with CKD progressively exhibit LVH, decreased cardiac diastolic and/or systolic function, coronary atherosclerosis, arrhythmias, heart failure, and SCD. Cardiac diastolic dysfunction tends to precede systolic dysfunction because of reduced ventricular compliance due to LV myocardial hypertrophy. The presence of diastolic dysfunction in patients with UCM may be associated with interstitial fibrosis and myocardial calcification. Later diastolic insufficiency may be associated with interstitial fibrosis and myocardial calcification. Patients with UCM are prone to various types of arrhythmias, which may be a manifestation of their cardiac dysfunction as well as due to electrolyte alterations and disturbances in acid-base balance. Then again, haemodialysis itself can induce arrhythmias. In contrast to other cardiovascular complications, UCM is most predominantly manifested by LVH and LVH is an independent predictor of cardiac death in dialysis patients. LVH consists of cardiomyocyte hypertrophy and myocardial interstitial fibrosis. Myocardial hypertrophy is a compensatory mechanism of the heart in response to various physiological or pathological stimuli, of which the physiological stimuli are mainly exercise, and the pathological stimuli include hypertension and valvular disease. At first, cardiac hypertrophy can play a compensatory role, but if the etiology persists it can lead to loss of compensation and even cause cardiac insufficiency. Cardiac hypertrophy is manifested by hypertrophy of cardiomyocytes, increased protein synthesis and activation of several embryonic genes, such as A-type brain natriuretic peptide, B-type brain natriuretic peptide, and heavy chain myosin gene. Chen Qi et al. [20] applied most of the nephrectomy can deteriorate the renal function of mice, followed by cardiomyocyte hypertrophy, left ventricular hypertrophy and other simulated uremic cardiomyopathy manifestations, and then applied Zhenwu Tang to intervene in the UCM mice, and found that Zhenwu Tang was able to inhibit cardiac hypertrophy in mice via the AMPK-mTOR signalling pathway. Lai Jun et al. [21] applied Zhenwu Tang to intervene in UCM mice, and found that Zhenwu Tang was able to reduce plasma IS levels and improve cardiac and renal function in patients with cardiorenal syndrome. Meanwhile, in vitro experiments found that Zhenwu Tang was able to reduce plasma IS levels, inhibit hypertrophy and fibrosis of rat myocardial tissue, and delay ventricular remodelling in UCM rats.

3.5 Regulation of Apoptosis-related Genes in Cardiomyocytes by Chinese Medicine

Apoptosis usually occurs during development and aging and serves as a homeostatic mechanism to maintain cell populations in tissues, and its dynamic balance with cell proliferation maintains homeostasis in the body's internal environment, and disruption of the balance by excessive apoptosis can lead to a number of pathological conditions such as carcinogenesis, autoimmune disorders, neurodegenerative disorders, and ischemia-related injuries [22, 23]. As a major pathological feature in the pathogenesis of UCM, excessive apoptosis of cardiomyocytes leads to structural and functional damage of cardiac tissue, which in turn affects the overall contraction and pumping function of the heart. And studies have shown that cardiomyocyte apoptosis is involved in a variety of cardiac pathophysiological processes [24]. Therefore, stopping cardiomyocyte apoptosis and improving cardiac function have become one of the important research directions for the treatment of UCM. Tong Mengyao et al. [25] used 5/6 nephrectomy to establish a mouse model of UCM, while in

vitro experiments were conducted by isolating mouse peripheral blood exosomes and co-culturing them with primary mouse cardiomyocytes, and it was found that the traditional Chinese medicine compound of the Beneficial Kidney Detoxification Method could prevent and control cardiac dysfunction, cardiac morphology changes and remodeling of UCM mice by interfering with the miR-30 transport in the peripheral blood exosomes, and improve the cardiac function and cardiomyocyte remodeling of UCM cardiac function and myocardial structure in UCM mice; it also reduced serum CK-MB and LDH levels, inhibited apoptosis of cardiomyocytes in UCM mice, and suppressed autophagic vesicle formation and the expression of autophagy marker protein LC3.

Minlin Zheng [26, 27] et al. found that Beneficial Kidney Lowering and Chong Chong Chong, which reused raw Astragalus, Radix et Rhizoma Ginseng, Rhizoma Atractylodis Macrocephalae, and Poria, by the method of cultivating soil and making water, was able to alleviate the cardiac pathological changes in rats with uremic cardiomyopathy, improve the levels of urea nitrogen, creatinine, creatine kinase isoforms, and lactic acid dehydrogenase, increase the content of ATP in cardiac tissues, and decrease the expression of CytochromeC, Caspase 3, and Caspase 9 proteins; and protect mitochondria, decrease the expression of free radicals, and reduce the apoptosis rate of cardiac cells. CytochromeC, Caspase-3, Caspase-9 protein expression, inhibit mitochondrial pathway apoptosis, and reduce the apoptosis rate of cardiomyocytes; at the same time, it protects the mitochondria and reduces the production of free radicals, so as to achieve the dual effect of protecting the tubules of the residual renal units and attenuating the myocardial mitochondrial damage caused by uremic toxins. Liu Shujuan [28] applied 3% adenine to model UCM rats and found that Toxin Naiqing Granule is to benefit qi and tonify the kidney, activate blood circulation and eliminate blood stasis, and pass through the internal organs and drain the turbid as the rule of thumb, which can effectively reduce the blood BUN and Scr levels in UCM rats, and alleviate the myocardial remodelling by inhibiting the blood and myocardium of the local renin-angiotensin-aldosterone (RAS) system. Thus, it effectively inhibited myocardial cell apoptosis in UCM, increased myocardial contractile functional units, and improved myocardial ultrastructure. Han Baojuan et al. [29] selected 40 cases of UCM patients in the clinic to treat UCM patients with Reducing Toxin Nourishing Heart Soup, which has the efficacy of benefiting qi and warming yang, nourishing yin and activating blood, and inducing diuresis to pass the internal organs, and the treatment can significantly reduce the patient's blood creatinine and urea nitrogen, improve the patient's left ventricular mass fraction and cardiac structure, and improve the patient's left ventricular ejection fraction.

3.6 Other Roles

In addition to the protective effects of TCM on myocardial tissue or uremic toxin-induced cardiomyocyte injury in UCM rats through the five mechanisms mentioned above, TCM can also protect myocardial tissue by regulating mitochondrial energy metabolism, regulating intestinal flora, improving cardiomyocyte pyrokinesis and modulating autophagy to prevent and control the injury of UCM. Moreover, the combination of TCM and Western medicine is an important idea that should not be ignored in the prevention and treatment of UCM. Wang Xuemin et al.[30] through clinical observation of 64 cases of uremic cardiomyopathy patients found that the application of the dialysis alone is easy to make the patients have insufficient qi and blood biochemistry phenomenon, the emergence of ultrafiltration and dehydration, angelica blood replenishment soup has the effect of eliminating blood stasis and generating new blood, benefiting the qi and generating blood, and the effect of the combination of dialysis with adjustable sodium curve in the treatment of patients with uremic cardiomyopathy is significant, and it can effectively improve the phenomenon of patients with hypotension, promote the microcirculation of kidneys, and reduce the degree of damage. Degree.

4. Summary and Outlook

In summary, a series of risk factors and signalling pathways are closely involved in the process of myocardial injury in uremic cardiomyopathy. Therefore, it is important to find therapeutic approaches that target cellular and molecular mechanisms to prevent or even reverse myocardial injury. Experimental studies have shown that reducing myocardial cell injury is one of the targets of TCM in the treatment of uremic cardiomyopathy in order to slow down the disease progression. With the further clarification of the pathogenesis of this disease and the in-depth development of experimental research, the mechanism of TCM effect can be clarified from different levels, such as cytology and molecular, so as to obtain more basis for the use of medicine. Chinese medicine has the two advantages of holistic concept and evidence-based treatment, which can combine the three aspects of "disease identification - evidence identification - symptom identification", and there are differences in the use of medicines for different types of the same disease in the clinic, so the same traditional Chinese medicine used in the same disease model may have different effects and mechanisms of efficacy, which are issues of more far-reaching significance. In addition, Chinese medicine treatment also includes external treatments such as Chinese medicine enema, medicinal bath, external application, ionic introduction and so on. On the basis of the existing research results, we should continue to study how to better integrate the identification and administration of drugs into disease models and how to apply the research results of animal and cellular experiments to the clinic, so as to reflect the clinical value of experimental research on TCM and provide new targets for the protection and treatment of UCM.

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