Therapeutic Effect of Intragastric Administration of Jiangtang Shuxin Recipe Suspension on Diabetic Heart Failure in Rats and Its Mechanism

Xiaofeng JIANG[1], Jiajun CHEN[1], Guangming HUANG[2], Yaya SHEN[1], Xianzhao FU[3]*

1. Clinical Medical College, Youjiang Medical University for Nationalities, Baise 533000, China; 2. Department of Rehabilitation Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, China; 3. Department of Traditional Chinese Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, China

Abstract [**Objectives**] To observe the therapeutic effect of intragastric administration of Jiangtang Shuxin recipe on diabetic heart failure (DHF) in rats and to explore its mechanism. [**Methods**] Fifty SD rats were randomly divided into five groups, with 10 rats in each group. DHF models were prepared in the low-dose group, high-dose group, Western medicine group, and model group except the control group. Rats in the low-dose and high-dose groups were given 1.0 and 1.5 g/(kg · d) Jiangtang Shuxin recipe suspension by gavage, respectively. Rats in the Western medicine group were given gliquidone and benazepril by gavage for 2 months, and were fed with high-fat diet. Rats in the control group were fed with ordinary diet. Fasting blood glucose (FBG), serum triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), pathological morphology of myocardial tissue, NF-κB p65 protein and IκBα protein were compared among groups. [**Results**] Compared with the control group, the levels of FBG, serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH increased, while the level of serum HDL-C decreased. The myocardial tissue was seriously damaged, and the expression of NF-κB p65 protein increased, while the expression of IκBα protein decreased in the other four gruops (all $P<0.05$). Compared with the model group, the levels of FBG, serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH decreased, while the serum HDL-C level increased. The myocardial tissue damage was alleviated, and the expression of NF-κB p65 protein decreased, while the expression of IκBα protein increased in the low-dose group, high-dose group and Western medicine group (all $P<0.05$). Compared with the Western medicine group, the levels of FBG, serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH decreased, and the level of serum HDL-C increased in the high-dose group (all $P<0.05$). [**Conclusions**] Jiangtang Shuxin recipe has a therapeutic effect on DHF in rats, with the best effect in the high-dose group. It can not only alleviate high glucose and high fat state, but also reduce myocardial injury and inflammation, and improve the pathological morphology of myocardial cells. The mechanism may be related to its inhibition of NF-κB signaling pathway.

Key words Jiangtang Shuxin recipe, Diabetes complications, Heart failure, NF-κB signaling pathway

1 Introduction

Diabetes mellitus (DM) is a metabolic disease caused by genetic and environmental factors. With the change of lifestyle and the acceleration of population aging, the morbidity of DM is on the rise. According to the prediction by the World Health Organization, DM will become the seventh cause of death by 2030[1]. DM is an independent risk factor for heart failure (HF) and increases the risk of suffering HF by 2 - 5 times[2]. The etiology and pathogenesis of HF caused by DM include hyperglycemia, hyperlipidemia, inflammatory reaction, cardiac autonomic nervous disorder, *etc*[3]. At present, there is no specific drug for the treatment of diastolic heart failure (DHF). Western medicine mainly focuses on hypoglycemic treatment, and alleviates the disease by controlling blood sugar. However, Western medicine has many adverse reactions and is prone to drug dependence. Traditional Chinese medicine therapy has the advantages of multiple target spots, multiple pathways and relatively small adverse reactions, so it is of great significance to explore the treatment of DHF with traditional Chinese medicine. Jiangtang Shuxin recipe has the effect of "nourishing yin and tonifying qi, promoting blood circulation and detoxifying", and can improve metabolic disorder caused by DM, enhance anti-oxidative stress ability, relieve cardiomyocyte apoptosis by inhibiting apoptosis pathway of endoplasmic reticulum stress, and protect myocardial injury in DM rats[4]. In this paper, the therapeutic effect of Jiangtang Shuxin recipe suspension on DHF in rats was studied, and its possible mechanism was explored from July 2022 to February 2023.

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* Corresponding author. E-mail: 1620100638@qq.com

2 Materials and methods

2.1 Experimental animals Firstly, 50 SD male rats with body weight of (230 ± 10) g were purchased from Laboratory Animal Center of Guangxi Medical University, with the license number of SCXK (Gui) 2014-002. The animals were fed in the Animal Experimental Center of Youjiang Medical University for Nationalities, where temperature was (23 ± 2) ℃, and humidity was 45% - 60%. Light or dark time was 12 h, and adaptive feeding was conducted for 7 d.

2.2 Main reagents and instruments Main reagents and instruments included streptozotocin (Beijing Huachioyang Biological Co., Ltd.), blood glucose tester (Shanghai Yuyan Scientific Instrument Co., Ltd.), high-fat feed (Jiangsu Xietong Bioengineering Co., Ltd.), glequiqualone (Beijing Wanhui Shuanghe Pharmaceutical Co., Ltd.), Benazepil (Beijing Novartis Pharmaceutical Co., Ltd.), CRP, IL-6, and TNF-α kits (Wuhan Bode Bioengineering Co., Ltd.), LDH and CK-MB detection kits (Nanjing Jiancheng Technology Co., Ltd.), HE staining kits (Biyun-

tian Biotechnology Co., Ltd.), Western blot kits (Wuhan Sanying Co., Ltd.), automatic biochemical instrument (Shenzhen Mindray Bio-medical Electronics Co., Ltd.), enzyme label instrument (Shenzhen Huisong Technology Development Co., Ltd.), optical microscope (Japan Olympus Corporation), and gel imaging system (Guangzhou Kezhilan Instrument Co., Ltd.).

2.3 Preparation of Jiangtang Shuxin recipe extract Firstly, 10 g of ginseng, 12 g of *Ophiopogon japonicus*, 10 g of *Schisandra chinensis*, 18 g of *Astragalus membranaceus*, 15 g of *Rehmannia glutinosa*, 15 g of yam, 10 g of dogwood, 5 g of *Rheum officinale*, 8 g of *Coptis chinensis*, and 12 g of *Salvia miltiorrhiza* were soaked for half an hour and decocted for 1.5 h. Afterwards, the concentrated liquid was transferred to a drying box, and dried at 90 ℃ for 36 h to make extract. Each 1 g of the extract was equivalent to 10 g of raw drug. After sterilization, it was sealed with plastic wrap and stored in a refrigerator at −20 ℃.

2.4 Grouping of experimental animals, preparation of DHF model and intragastric administration of Jiangtang Shuxin recipe suspension At first, 50 SD rats were randomly divided into 5 groups, with 10 rats in each group. DHF models were prepared in the low-dose group, high-dose group, Western medicine group, and model group except the control group. Methods for the preparation of DHF models: the rats in the low-dose group, high-dose group, Western medicine group and model group were injected with 50 mg/kg streptozotocin once intraperitoneally, and their fasting blood glucose value was detected 72 h later. FBG ≥ 16.7 mmol/L for two consecutive times indicated that the models of DM rats were successfully established. Subsequently, DM rats fasted for 12 h and could not refrain from water. The modeling method of HF was referred to reference[5]. DM rats were anesthetized by injecting 2 mL/kg 8% pentobarbital sodium into the abdomen, and the abdominal cavity was opened to expose the abdominal aorta. No. 7 needle was placed on the abdominal aorta, and the abdominal aorta and No. 7 needle were ligated with surgical thread. Afterwards, the needle was pulled out to narrow the abdominal aorta by 60% − 70%, and then intraperitoneal injection of penicillin was performed for 3 d after the operation. After 8 weeks, the left ventricular ejection fraction (LVEF) of the rats was examined by ultrasound. If LVEF was less than 45%, DHF models were established successfully. The extract was thawed at room temperature, placed in an EP tube, added with normal saline, and prepared into 2 mL suspension by vortex oscillation. The rates in the low-dose group were given 1.0 g/(kg · d) of Jiangtang Shuxin recipe suspension by gavage, while the rates in the high-dose group were given 1.5 g/(kg · d) of Jiangtang Shuxin recipe suspension by gavage, and the rats in the Western medicine group was given galiquazone and benazepril (two drugs combined into an equivalent volume solution) by gavage. Continuous gavage was conducted for 2 months, and they were fed with high-fat diet for 2 months. The rats in the control group was fed with ordinary diet.

2.5 Detection of FBG and serum TG, LDL-C, HDL-C, CRP, IL-6, TNF-α, CK-MB, and LDH in rats Ten rats were taken from each group, and fasted for 12 h after the last administration, but could drink water. The rats were anesthetized with 2 mL/kg 8% pentobarbital sodium, and abdominal aorta blood was drawn with a syringe. After being placed at 4 ℃, it was centrifuged for 15 min at a rotating speed of 3 000 r/min, and the supernatant was taken. It was packed, labeled and then stored in a refrigerator at −80 ℃. Blood glucose tester was used to detect FBG, and serum TG, LDL-C and HDL-C were determined by automatic biochemical analyzer. Serum CK-MB, LDH, CRP, IL-6 and TNF-α were detected according to the instructions of ELISA kits.

2.6 Observation of pathological morphology of myocardium in rats HE staining method was used. The rats in Section **2.5** were killed after blood collection, and the hearts were quickly sampled on ice. They were rinsed with 0.9% sodium chloride solution, and after the blood was washed, they were dried with filter paper. Part of them was used for HE staining, and the myocardial tissue was fixed with 4% paraformaldehyde to made paraffin sections with a thickness of 4 μm. After the sections were treated with xylene, anhydrous ethanol and 95%, 80%, and 70% ethanol in turn, they were soaked with hematoxylin dye for 5 min, rinsed with tap water for 1 − 2 min, differentiated with 1% HCI solution for 10 s, rinsed with tap water for 10 − 30 min, and dyed with eosin for 2 − 5 min. The gradient alcohol and xylene were dehydrated and transparent again, and they were finally sealed with neutral gum. Three sections were taken from each rat, and 5 fields were randomly selected from each section to be observed under the microscope. The nucleus was blue, and the cytoplasm, muscle fibers, and collagen fibers were different shades of red. For the other part, the myocardium was broken up with an ophthalmic scissor, and the protein was extracted with RIPA cracking solution. After being quantified, packaged and labeled, they were stored in a refrigerator at −80 ℃ for the determination of protein.

2.7 Detection of NF-κBp65 and IκBα proteins in rat myocardium Western blot was adopted. Another part of the myocardial tissue in Section **2.6** was taken. After the homogenate was fully split, it was placed on ice for 0.5 h, and centrifuged for 15 min at a speed of 12 000 r/min. After the supernatant was taken, the protein standard was prepared, and the BCA working fluid was prepared for the determination of protein content. The 50 μg of each protein sample was used for SDS-PAGE electrophoresis and film transfer. After they were sealed with 5% skim milk powder for 1 h, primary antibody incubation was conducted overnight at 4 ℃, and they were washed 3 times with TBST. Secondary antibody incubation was conducted for 1 − 2 h, and then they were washed 3 times with TBST. Hereafter, they were developed with ECL developer. GAPDH was used as the internal reference, and Image J software was used to analyze the relative expression of target proteins on the membrane.

2.8 Statistical method SPSS 24.0 statistical software was adopted. Measurement data conforming to normal distribution

were expressed as $\bar{x} \pm s$, and one-way ANOVA was used for multi-group comparison. LSD-*t* test was used for the comparison between two groups. $P < 0.05$ means the difference was statistically significant.

3 Results and analysis

3.1 Comparison of FBG and serum TG, LDL-C and HDL-C levels of rats in each group The comparison of FBG and serum TG, LDL-C and HDL-C levels of rats is shown in Table 1.

Table 1 FBG and serum TG, LDL-C and HDL-C levels of rats in each group (mmol/L, $\bar{x} \pm s$, $n = 10$)

Group	FBG	TG	LDL-C	HDL-C
High-dose group	9.57 ± 2.45^{abc}	1.60 ± 0.16^{abc}	1.71 ± 0.21^{abc}	0.79 ± 0.08^{abc}
Low-dose group	10.79 ± 3.35^{ab}	1.65 ± 0.12^{ab}	1.82 ± 0.26^{ab}	0.71 ± 0.09^{ab}
Western medicine group	11.01 ± 3.32^{ab}	1.76 ± 0.15^{ab}	1.95 ± 0.25^{ab}	0.65 ± 0.08^{ab}
Model group	16.90 ± 4.81^{a}	2.45 ± 0.26^{a}	2.45 ± 0.65^{a}	0.52 ± 0.03^{a}
Control group	5.62 ± 0.78	1.01 ± 0.09	0.82 ± 0.07	0.96 ± 0.04

NOTE Compared with the control group, $^{a}P < 0.05$; compared with the model group, $^{b}P < 0.05$; compared with western medicine group, $^{c}P < 0.05$. The same below.

3.2 Comparison of serum CRP, TNF-α and IL-6 levels of rats in each group The comparison of serum CRP, TNF-α and IL-6 levels of rats is shown in Table 2.

Table 2 Serum CRP, TNF-α and IL-6 levels of rats in each group ($\bar{x} \pm s$, $n = 10$)

Group	CRP//mg/L	TNF-α//ng/L	IL-6//ng/L
High-dose group	8.08 ± 2.31^{abc}	110.63 ± 45.67^{abc}	52.31 ± 5.52^{abc}
Low-dose group	9.48 ± 2.15^{ab}	130.56 ± 51.43^{ab}	59.45 ± 5.67^{ab}
Western medicine group	11.18 ± 2.24^{ab}	142.54 ± 42.34^{ab}	61.23 ± 6.67^{ab}
Model group	15.69 ± 3.52^{a}	375.00 ± 52.56^{a}	85.62 ± 7.69^{a}
Control group	7.52 ± 1.52	60.75 ± 3.52	18.02 ± 3.31

3.3 Comparison of serum CK-MB and LDH levels of rats in each group The comparison of serum CK-MB and LDH levels of rats is shown in Table 3.

3.4 Comparison of pathological morphology of myocardial tissue of rats in each group In the control group, the myocardium cells had normal morphology, neat arrangement, normal cell space, clear boundary, no obvious inflammatory cells and fibrosis.

Table 3 Serum CK-MB and LDH levels of rats in each group (U/L, $\bar{x} \pm s$, $n = 10$)

Group	CK-MB	LDH
High-dose group	67.84 ± 9.91^{abc}	97.58 ± 11.66^{abc}
Low-dose group	71.14 ± 9.23^{abc}	106.24 ± 11.83^{abc}
Western medicine group	87.46 ± 10.32^{ab}	137.44 ± 15.36^{ab}
Model group	113.27 ± 13.85^{a}	194.65 ± 23.41^{a}
Control group	39.52 ± 5.68	59.32 ± 7.73

Compared with the control group, the myocardial tissue of rats in the model group was seriously damaged, and the arrangement of myocardium cells was disordered. The cells were swollen and necrotic, and the space was blurred. Some inflammatory cells were gathered. Compared with the model group, the myocardial damage of rats in the low-dose group, high-dose group and Western medicine group was alleviated to different degrees. The myocardial damage of rats in the high-dose group was significantly reduced, and the morphology of myocardial cells was more normal. The infiltration of inflammatory cells was significantly reduced, and the myocardial cells were arranged more neatly (Fig. 1).

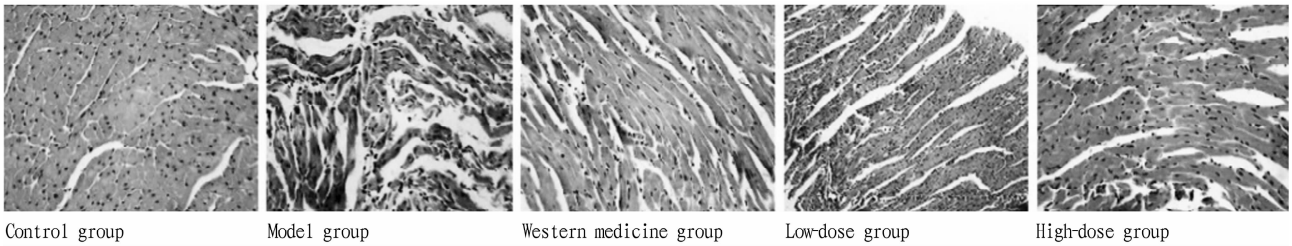

Fig. 1 Comparison of pathological morphology of myocardial tissue of rats in each group (×400)

3.5 Comparison of NF-κB p65 and IκBα protein expression in the myocardial tissue of rats in each group The comparison of NF-κB p65 and IκBα protein expression in the myocardial tissue of rats is shown in Table 4.

Table 4 NF-κB p65 and IκBα protein expression in the myocardial tissue of rats in all groups ($\bar{x} \pm s$, $n = 10$)

Group	NF-κB p65	IκBα
High-dose group	0.65 ± 0.07^{ab}	0.62 ± 0.04^{ab}
Low-dose group	0.79 ± 0.04^{ab}	0.53 ± 0.07^{ab}
Western medicine group	0.85 ± 0.06^{ab}	0.46 ± 0.06^{ab}
Model group	1.15 ± 0.12^{a}	0.32 ± 0.03^{a}
Control group	0.45 ± 0.03	0.74 ± 0.05

4 Discussion

Studies have shown that DM increases the risk of suffering cardiovascular disease by about 2.5 times that of people without DM[6]. HF is one of the cardiovascular complications of DM. It is a group of complex clinical syndromes caused by abnormal changes in cardiac structure and (or) function caused by a variety of reasons, so that ventricular contraction and (or) diastolic function occur. It

represents the final stage of most cardiovascular diseases, and the main manifestations are dyspnea, fatigue, and fluid retention (pulmonary congestion, systemic congestion, and peripheral edema)[7]. It is found that the myocardial damage caused by DM leads to the occurrence of HF, which includes three stages. In the first stage, there is no obvious clinical symptoms, and the characteristics include impaired metabolic signal transmission and changes in heart energy utilization; in the second stage, the remodeling of myocardia can be found by clinical imaging examination, such as left ventricular hypertrophy and myocardial fibrosis, and there is no without typical HF symptoms; systolic dysfunction and obvious symptoms of heart failure occur in the third stage[8]. At present, hypoglycemic drugs such as thiazolidinediones, sulfonylureas and insulin used in the treatment of DHF can reduce blood sugar, but can trigger and aggravate the development of HF[9], which indicates the limitations of Western medicine intervention in DHF. Under the guidance of traditional Chinese medicine theory, traditional Chinese medicine has a multi-faceted and multi-level regulating effect, so it is of great significance to explore the treatment of DHF by traditional Chinese medicine.

Jiangtang Shuxin recipe is composed of *A. membranaceus*, ginseng, *R. glutinosa*, *O. japonicus*, dogwood, *S. miltiorrhiza*, *R. officinale*, *C. chinensis*, *S. chinensis*, and yam, among which ginseng, *O. japonicus*, and *S. chinensis* are components of Shengmai Powder, and yam, dogwood and *R. glutinosa* are components of Zuogui Pill. Both of them are tonifying prescriptions, and have the functions of tonifying kidney yin, tonifying heart qi, nourishing yin and promoting the secretion of saliva or body fluid. *R. officinale* and *C. chinensis* are the main components of Xiexin Decoction, and have the effect of clearing heat and detoxifying. *S. miltiorrhiza* has the functions of clearing away the heart fire, relieving restlessness, promoting blood circulation and removing blood stasis, and *A. membranaceus* has the functions of tonifying spleen and invigorating qi and securing the exterior. The whole recipe has the effect of nourishing yin and benefiting qi, promoting blood circulation and detoxifying, strengthening body resistance and eliminating evil, tonification and purgation in combination[10]. In the condition of DM, hyperglycemia and hyperlipemia may occur. In this study, it is found that FBG, TG and LDL-C levels in the model group increased, while HDL-C level decreased, which was consistent with the general manifestations of DM. It has been reported that CRP, IL-6 and TNF-α inflammatory factors reflect the level of inflammation in the body, and the increase of the level can induce and reflect myocardial injury in DM rats[11-12]. CK-MB and LDH are markers of myocardial injury, and are positively correlated with myocardial injury[13].

In this study, compared with the control group, FBG and serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH levels in the other 4 groups increased, while serum HDL-C level declined, and the myocardial tissue was seriously damaged. Compared with the model group, FBG and serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH levels in the low-dose group, high-dose group and Western medicine group decreased, while serum HDL-C level rose, and the damage of the myocardial tissue was alleviated. Compared with the Western medicine group, FBG and serum TG, LDL-C, CRP, IL-6, TNF-α, CK-MB and LDH levels in the high-dose group reduced, while serum HDL-C level increased, and the damage of the myocardial tissue was alleviated. The results showed that Jiangtang Shuxin recipe could improve the status of high glucose and high fat, reduce inflammation and alleviate myocardial damage in DHF rats, and the therapeutic effect of the high-dose group was better than that of Western medicine group.

The nuclear transcription factor NF-κB, composed of two subunits p50 and p65, is a key mediator of inflammatory response. In the resting state, IκB protein tightly binds to the dimer NF-κB, preventing NF-κB from binding to DNA and causing it to be inactivated[14-15]. Studies have shown that hyperglycemia, hyperlipidemia, advanced glycation end products, oxidative stress and inflammatory factors in the condition of DM can activate the NF-κB signaling pathway through classical and non-classical pathways, and the activation of NF-κB can induce endothelial dysfunction, myocardial fibrosis, hypertrophy and apoptosis, and promote the occurrence of diabetic cardiomyopathy (DCM)[16]. WANG *et al.*[17] conducted RNA sequencing and KEGG enrichment analysis of the heart tissues of type 1 diabetes (T1DM) mice, and found that NF-κB signaling pathway was up-regulated in the T1DM model. Based on these results, Western blot analysis was used to detect the expression of NF-κB P65 and IκBα in mouse heart tissues. The results indicated that the expression of NF-κB P65 increased, and the expression of IκBα decreased. The activation of NF-κB signaling pathway was inhibited to reduce the inflammatory response and the cardiac hypertrophy and fibrosis of DCM. The same results were confirmed in high-fat fed models of type 2 diabetes and high-sugar treated H9c2 cells. Zhang Chi *et al.*[18] also confirmed *in vivo* and *in vitro* experiments that irisin can play a role in protecting myocardial damage in DM by inhibiting the activation of NF-κB signaling pathway. It can be seen that NF-κB signaling plays an important role in DM heart disease. In this study, compared with the control group, the expression of NF-κB p65 protein increased, and the expression of IκBα protein decreased. Compared with the model group, the expression of NF-κB p65 protein declined, and the expression of IκBα protein increased in the low-dose, high-dose and Western drug groups. These results indicated that Jiangtang Shuxin recipe could inhibit NF-κB signaling pathway and then improve myocardial injury in DHF rats.

In conclusion, Jiangtang Shuxin recipe can reduce glucose, lipid, and inflammation, improve myocardial injury, and has the therapeutic effect on DHF. The mechanism may be related to the inhibition of NF-κB signaling pathway.

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grading of China's planting industry, create new employment opportunities, especially increase the income of the agricultural population.

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