BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
© / ISSN 0717 7917 / www.blacpma.ms-editions.cl

Articulo Original / Original Article

Alleviative effect of dihydroquercetin on chronic heart failure in rats and its impact on inflammatory response, oxidative stress and cardiac myocyte apoptosis

[Efecto aliviador de la dihidroquercetina en la insuficiencia cardíaca crónica en ratas y su impacto en la respuesta inflamatoria, el estrés oxidativo y la apoptosis de miocitos cardíacos]

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Section Biological activity

Received: 11 January 2025
Accepted: 15 March 2025
Accepted corrected: 10 May 2025
Published: 30 September 2025

Citation:
Li Z, Chen J, Zhai N, Xu W, Yin L. Alleviative effect of dihydroquercetin on chronic heart failure in rats and its impact on inflammatory response, oxidative stress and cardiac myocyte apoptosis
Bol Latinoam Caribe Plant Med Aromat
24 (5): 815 - 824 (2025)
https://doi.org/10.37360/blacpma.25.24.5.56

Abstract: To investigate the alleviative effect of dihydroquercetin on chronic heart failure (CHF) in rats and the mechanisms. Thirty rats were randomly divided into sham, model and treatment groups. The CHF model was established in model and treatment groups. The treatment group was treated with 50 μg/kg dihydroquercetin for four weeks. After treatment, compared with model group, in treatment group the cardiac structure and function indexes were improved, the serum creatine kinase, lactate dehydrogenase, cardiac troponin I, tumor necrosis factor α, interleukin 6 and malondialdehyde levels decreased, the serum superoxide dismutase level increased, the myocardial B-cell lymphoma 2, nuclear factor-erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1) protein levels increased, and the myocardial Bax protein level decreased (all $p<0.05$). In conclusion, dihydroquercetin may alleviate CHF in rats by resisting inflammatory response and oxidative stress, reducing cardiac myocyte apoptosis and activating Nrf2/HO-1 signaling pathway.

Keywords: Dihydroquercetin; Chronic heart failure; Oxidative stress; Nrf2; HO-1.

Resumen: Este estudio investigó el efecto aliviador de la dihidroquercetina en la insuficiencia cardíaca crónica (ICC) en ratas y sus mecanismos. Treinta ratas fueron divididas aleatoriamente en grupos simulado, modelo y tratamiento. El modelo de ICC se estableció en los grupos modelo y tratamiento. El grupo tratamiento recibió 50 μg/kg de dihidroquercetina durante cuatro semanas. Tras el tratamiento, en comparación con el grupo modelo, el grupo tratamiento mostró mejoras en los índices de estructura y función cardíaca, disminución de los niveles séricos de creatina quinasa, lactato deshidrogenasa, troponina I cardíaca, factor de necrosis tumoral α, interleucina 6 y malondialdehído, aumento del nivel sérico de superóxido dismutasa, incremento en los niveles de proteínas Bcl-2, Nrf2 y HO-1 en el miocardio, y disminución del nivel de proteína Bax en el miocardio (todos $p<0.05$). En conclusión, la dihidroquercetina puede aliviar la ICC en ratas al resistir la respuesta inflamatoria y el estrés oxidativo, reducir la apoptosis de miocitos cardíacos y activar la vía de señalización Nrf2/HO-1.

Palabras clave: Dihidroquercetina; Insuficiencia cardíaca crónica; estrés oxidativo; Nrf2; HO-1

INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome with reduced cardiac output due to the abnormalities in the structure and/or function of heart (Hoffman, 2016). At present, it is believed that the main causes of CHF include the intrinsic myocardial diseases and heart overload diseases. The former includes coronary artery atherosclerotic heart disease, myocardial infarction, myocarditis, and dilated cardiomyopathy. The latter includes hypertension, heart valve stenosis and regurgitation, chronic anemia, and hyperthyroidism (Miller, 2016; Pagliaro *et al*., 2020). The molecular mechanisms of CHF include the over-activation of neuroendocrine system (Jiang *et al*., 2023), apoptosis and necrosis of myocardial cells (Gao *et al*., 2020), inflammation and cytokine activation (Murphy *et al*., 2020), oxidative stress (van der Pol *et al*., 2019). It has been estimated that the prevalence of CHF is 0.9%, and the mortality is 19.5% annually in China (Li, 2019). CHF will lead to multiple organ involvement and damage, and is often accompanied by clinical manifestations such as dyspnea, fatigue, fluid retention and decreased activity tolerance (Skrzypek *et al*., 2018). The myocardial injury, irreversible remodeling of cardiac structure, abnormal cardiac systolic and diastolic function and hemodynamic disorders are the driving factors that promote the development of this disease (Triposkiadis *et al*., 2022).

Dihydroquercetin (Figure No. 1), also named taxifolin, is a typical flavonoid component commonly found in pine plants such as *Pseudotsuga menziesii* (Mirb.) Franco mainly distributed in North American area and *Cedrus deodara* (Roxb. ex D. Don) G. Don. mainly distributed in Western Asia area. It has a series of biological activities in the antioxidant, anti-inflammatory and anti-tumor aspects (Lee *et al*., 2012; Zhang *et al*., 2017). Dihydroquercetin can protect the myocardial ischemia-reperfusion injury by inhibiting oxidative stress and regulating endoplasmic reticulum stress and mitochondrial apoptosis (Shu *et al*., 2019). It can also improve the myocardial hypertrophy and myocardial fibrosis after pressure overload by reducing mitochondrial dysfunction and glucose metabolism disorder (Sun *et al*., 2014; Guo *et al*., 2015). However, there are few reports on the effect of dihydroquercetin for CHF. It is hypothesized that dihydroquercetin can protect the CHF. Therefore, the purpose of this study is to investigate the alleviative effect of dihydroquercetin on CHF in rats and the related action mechanisms.

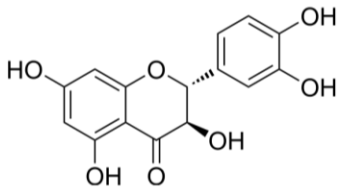

Figure No. 1
Chemical structure of dihydroquercetin

MATERIALS AND METHODS

Animal grouping and modeling

Thirty SPF-grade male SD rats (250-280 g; Shanghai Slake Laboratory Animal Co., Ltd., Shanghai, China) were adaptively fed for one week, and then were randomly divided into sham, model and treatment groups, with 10 rats in each group. The CHF model was established in model and treatment groups using the abdominal aortic constriction method (Mou *et al*., 2022). The rats were anesthetized by intraperitoneal injection of 3% pentobarbital sodium, and then the endotracheal intubation was performed. The thoracic cavity was opened, and the heart was exposed. The anterior descending branch of the left coronary artery was ligated at the position 2-3 mm below the left auricle. The T elevation and even fusion of QRS and T waves in the electrocardiogram indicated the successful ligation. After four weeks, when the left ventricular ejection fraction was below 40%, it is indicated that the CHF model was successfully established. In sham group, the thoracic cavity was opened, but the coronary artery was not ligated. No rat died during the modeling in each group. All experimental procedures were performed in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of our hospital.

Treatment
After the CHF model was successfully established, the rats in the model group were treated with dihydroquercetin by intragastrical administration, with dosage of 50 μg/kg (based on the pre-experiment). The administration was performed once a day, for eight weeks. The rats in sham group and model group were intragastrically administrated with equal volume of normal saline for four weeks.

Cardiac structure and function test
At the end of treatment, the cardiac structure and function of rats were detected by echocardiography. The left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVIDs), LVEF and left ventricular fractional shortening (LVFS) were measured.

Determination of blood indicators
Abdominal aorta blood was collected from the rats. After centrifuging, the serum was obtained. The myocardial injury indicators including creatine kinase (CK), lactate dehydrogenase (LDH) and cardiac troponin I (cTnI), inflammatory response indexes including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) and oxidative stress indexes including superoxide dismutase (SOD) and malondialdehyde (MDA) were determined using enzyme linked immunosorbent assay.

Detection of myocardial related protein expressions
Myocardial tissues were taken from the rats and were fully homogenized with precooled lysate. After centrifuging at 3000 rpm and 4°C for 10 min, the supernatant was obtained. The total protein concentration in supernatant was detected by BCA method, and the target proteins were isolated using SDS-PAGE. The isolated proteins were transferred to the PVDF membranes. After blocking with 5% skimmed milk powder for 2 h, the membranes were incubated with the primary antibody for B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-2 associated X (Bax), nuclear factor-erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1), respectively, at 4°C overnight. Then, the membranes were incubated with the secondary antibody at 37°C for 1 h. The enhanced chemiluminescence solution was dripped on the front of the membranes for reaction for 10 min. The membranes were placed in the gel imaging system for scan imaging. The optical density of the bands was measured using the Quantity One image analysis software. The optical density ratio of target band to β-actin presented the relative expression of target protein.

Statistical analysis
Statistical analysis was performed using SPSS 20.0 software. Each determination was repeated three times. The data were presented as mean±standard deviation. The comparison among the three groups was made by one-way Analysis of Variance followed by LSD-t test. $p<0.05$ was considered as significant.

RESULTS

Cardiac structure and function indexes
At the end of treatment, compared with sham group, in model and treatment groups the LVIDd and LVIDs were significantly increased, respectively ($p<0.05$), and the LVEF and FS were significantly decreased, respectively ($p<0.05$). Compared with model group, in treatment group the LVIDd and LVIDs were significantly decreased, respectively ($p<0.05$), and the LVEF and FS were significantly increased, respectively ($p<0.05$) (Figure No. 1).

Myocardial injury indicators
As shown in Figure No. 2, after treatment the serum CK, LDH and cTnI levels in model and treatment groups were significantly higher than those in sham groups, respectively ($p<0.05$). Compared with model group, each index in treatment group was significantly decreased ($p<0.05$).

Inflammatory response indexes
After treatment, compared with sham group, the serum TNF-α and IL-6 levels in model and treatment groups were significantly increased, respectively ($p<0.05$). Compared with model group, each index in treatment group was significantly decreased ($p<0.05$) (Figure No. 3).

Oxidative stress indexes
As shown in Figure No. 4, after treatment the serum SOD level in model and treatment groups was significantly lower than that in sham group, respectively ($p<0.05$), and the serum MDA level in model and treatment groups was significantly higher than that in sham group, respectively ($p<0.05$). Compared with model group, in treatment group the SOD level was significantly increased ($p<0.05$), and the MDA level was significantly decreased ($p<0.05$).

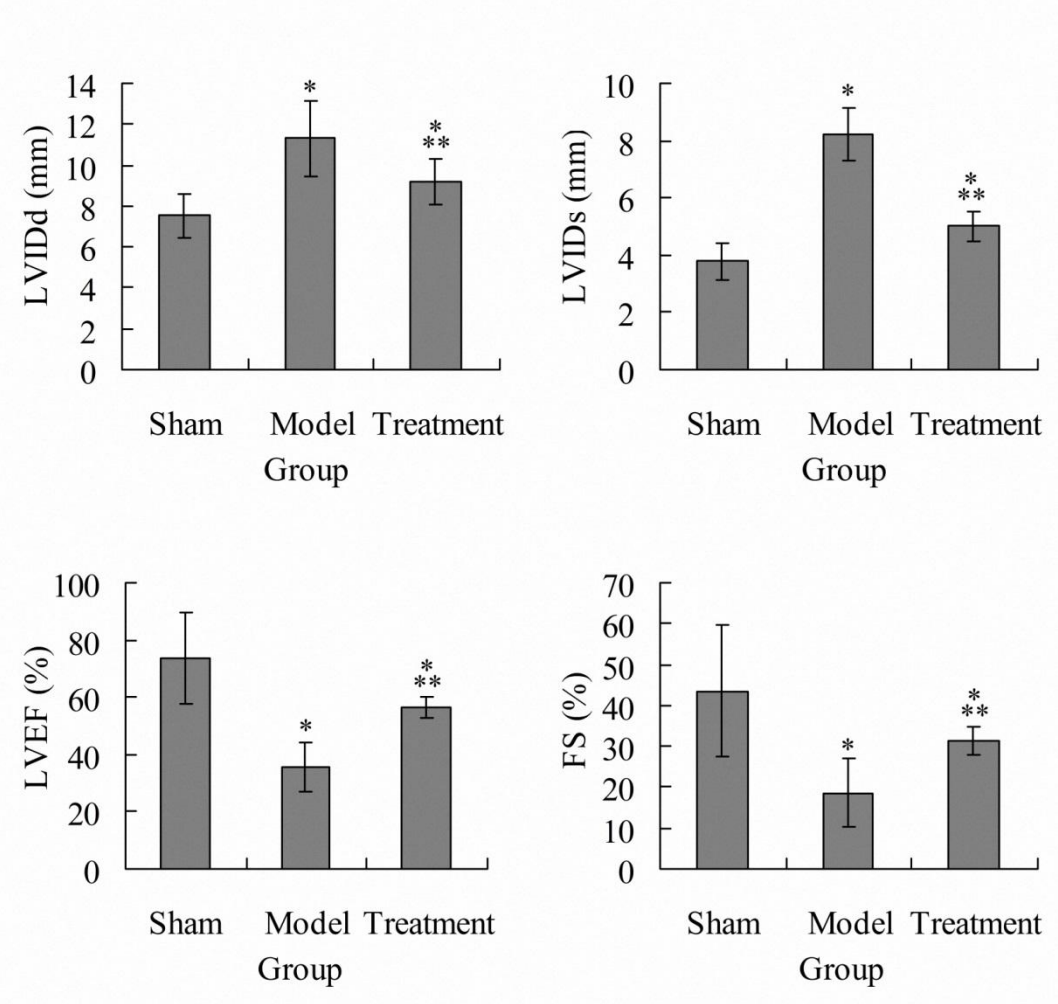

Figure No. 1
Cardiac structure and function indexes in three groups (n=10 for each group) (LVIDd: F=18.557, *p*<0.001; LVIDs: F=104.656, *p*<0.001; LVEF: F=31.330, *p*<0.001; FS: F=13.545, *p*<0.001). **p*<0.05 compared with sham group; ***p*<0.05 compared with model group. LVIDd, left ventricular end diastolic diameter; LVIDs, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening

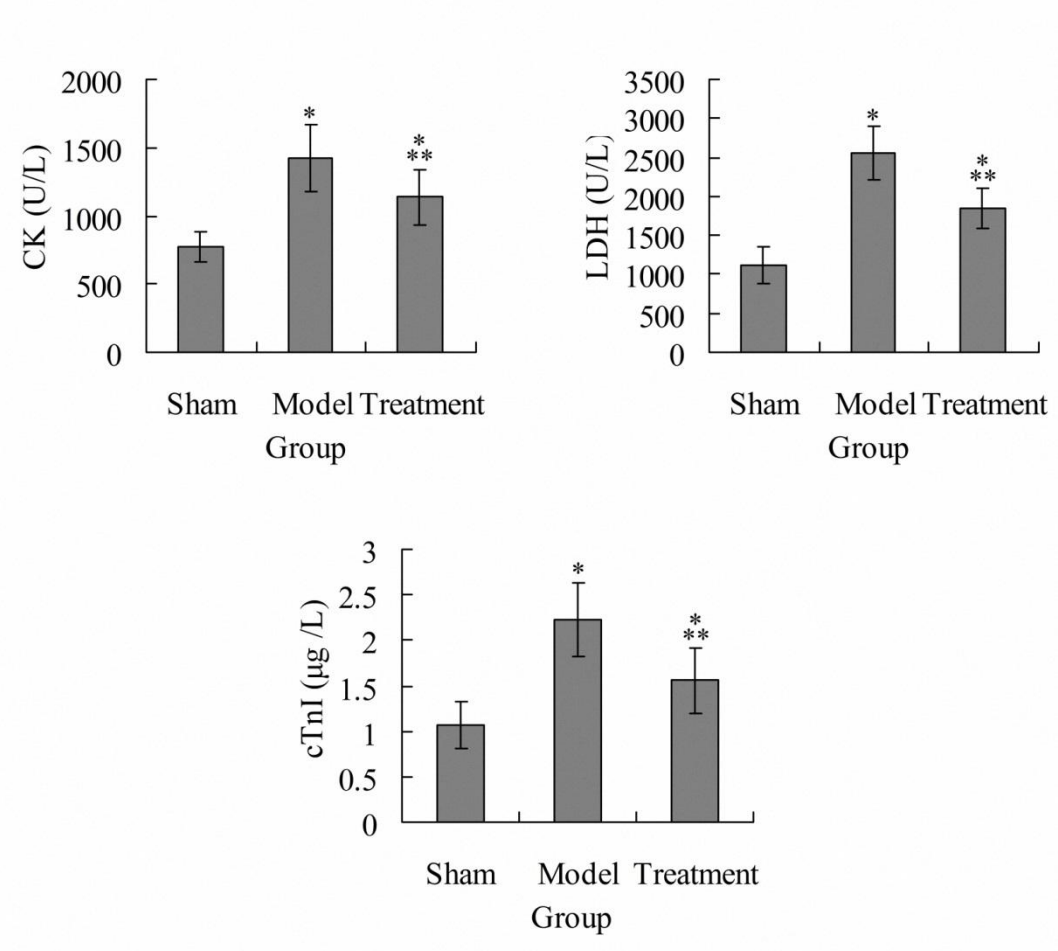

Figure No. 2
Myocardial injury indicators in three groups (n=10 for each group) (CK: F=28.071, *p*<0.001; LDH: F=63.924, *p*<0.001; cTnI: F=27.848, *p*<0.001). **p*<0.05 compared with sham group; ***p*<0.05 compared with model group. CK, creatine kinase; LDH, lactate dehydrogenase; cTnI, cardiac troponin I

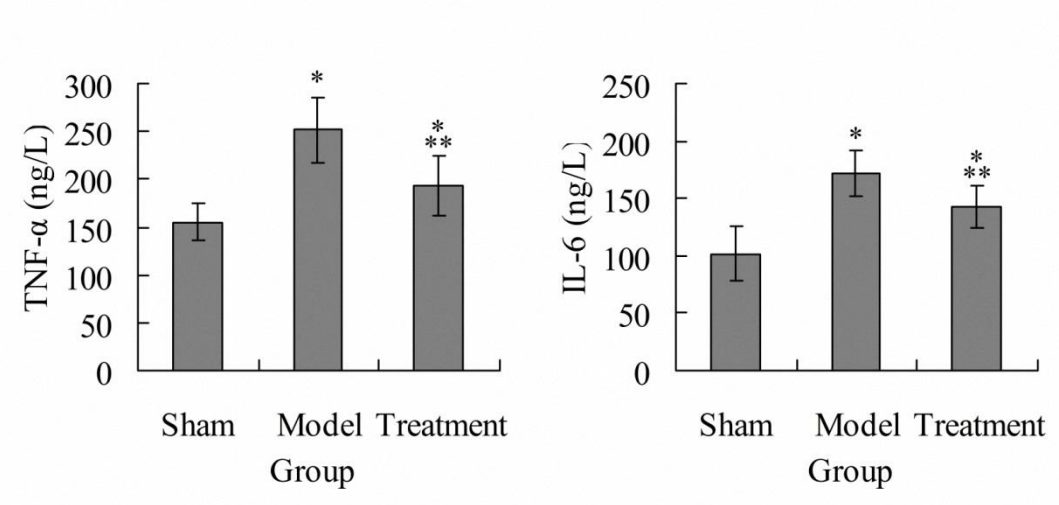

Figure No. 3
Inflammatory response indexes in three groups (n=10 for each group) (TNF-α: F=28.081, *p*<0.001; IL-6: F=29.266, *p*<0.001). *p<0.05 compared with sham group; **p<0.05 compared with model group. TNF-α, tumor necrosis factor α; IL-6, interleukin 6

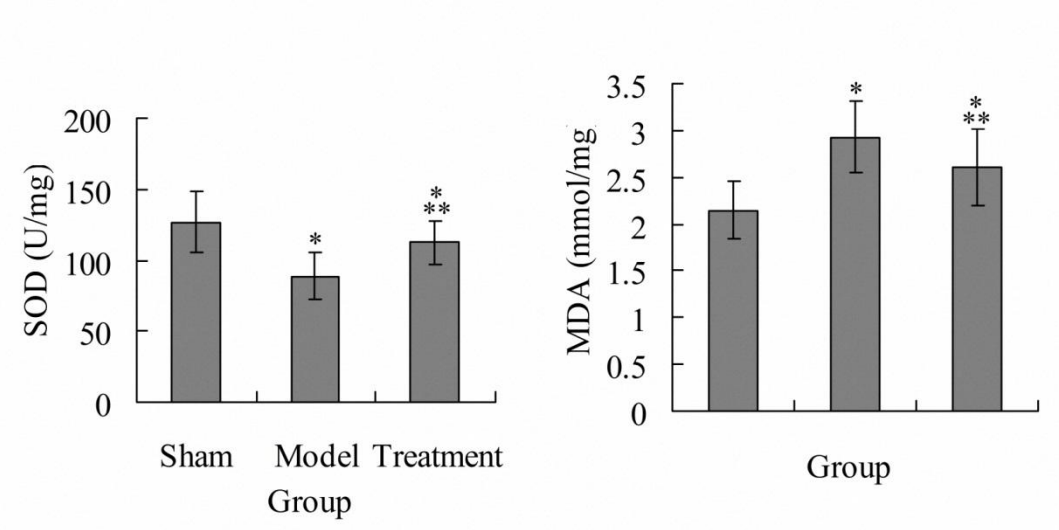

Figure No. 4
Oxidative stress indexes in three groups (n=10 for each group) (SOD: F=10.914, *p*<0.001; MDA: F=11.287, *p*<0.001). *p<0.05 compared with sham group; **p<0.05 compared with model group. SOD, superoxide dismutase; MDA, malondialdehyde

Myocardial Bcl-2 and Bax protein expressions

After treatment, compared with sham group, in model and treatment groups the myocardial Bcl-2 protein expression level was significantly decreased, respectively (p<0.05), and the Bax protein expression level was significantly increased, respectively (p<0.05). Compared with model group, in treatment group the Bcl-2 protein level was significantly increased (p<0.05), and the Bax protein level was significantly decreased (p<0.05) (Figure No. 5).

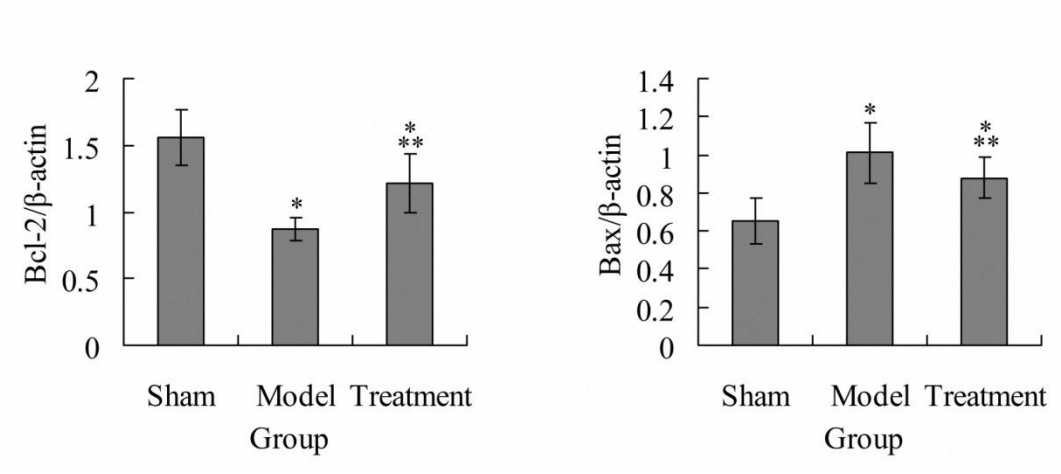

Figure No. 5

Myocardial Bcl-2 and Bax protein expressions in three groups (n=10 for each group) (Bcl-2/β-actin: F=35.497, p<0.001; Bax/β-actin: F=19.136, p<0.001). *P<0.05 compared with sham group; **P<0.05 compared with model group. Bcl-2, B-cell lymphoma 2; Bax, B-cell lymphoma-2 associated X.

Myocardial Nrf2 and HO-1 protein expressions

As shown in Figure No. 6, after treatment the myocardial Nrf2 and HO-1 protein expression levels in model group were significantly lower than those in sham group, respectively (p<0.05). Compared with model group, each index in treatment group significantly increased (p<0.05).

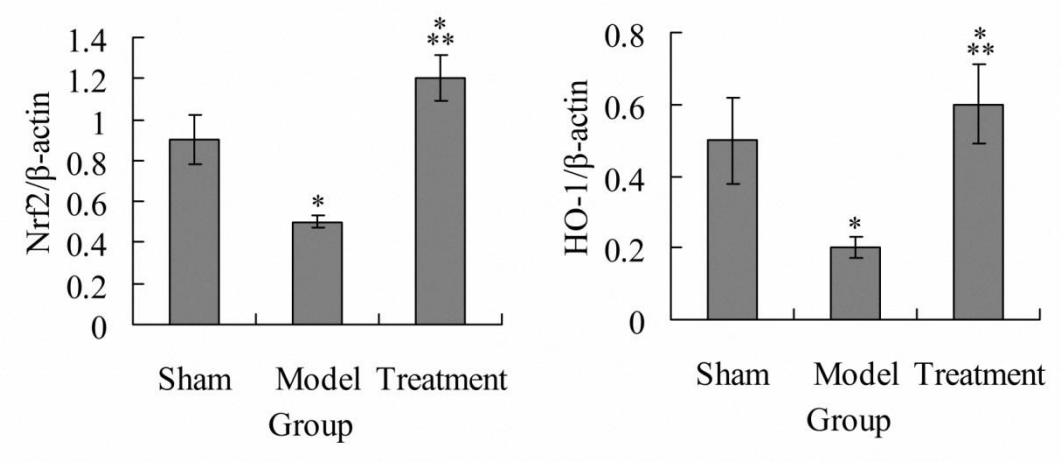

Figure No. 6

Myocardial Nrf2 and HO-1 protein expressions in three groups (n=10 for each group) (Nrf2/β-actin: F=135.036, p<0.001; HO-1/β-actin: F=47.445, p<0.001). *p<0.05 compared with sham group; **p<0.05 compared with model group. Nrf2, nuclear factor-erythroid 2-related factor 2; HO-1, heme oxygenase 1

DISCUSSION

CHF develops from almost all cardiovascular diseases, with common clinical causes including myocardial infarction, hypertension, cardiomyopathy, etc.. It is found that a series of progressive pathological changes occur in the heart during CHF occurrence, which can exacerbate the myocardial damage and lead to the decline in heart function (Dharmarajan & Rich, 2017). Dihydroquercetin has received special attention due to its pharmacological activity demonstrated in diseases such as inflammation, microbial infections, tumors, and liver (Orlova *et al*., 2022). In this study, the CHF model of rats was established, and the alleviative effect of dihydroquercetin on CHF was investigated. Results showed that, after treatment, compared with model group, in treatment group the LVIDd and LVIDs were significantly decreased, the LVEF and FS were significantly increased, and serum CK, LDH and cTnI levels were significantly decreased. This indicates that, dihydroquercetin can improve the cardiac structure and function and alleviate myocardial injury in rats with CHF. Previous study has found that dihydroquercetin can enhance the cardiac function of diabetic cardiomyopathy mice (Sun *et al*., 2014) and reduce the myocardial injury in rats (Tang *et al*., 2019). These are basically consistent with the results of this study.

It is found that, the occurrence of CHF is closely related to the inflammatory response (Dick & Epelman, 2016). TNF-α is an anti-tumor cytokine, which is produced after stimulation by lipopolysaccharide and viruses. When the CHF occurs, the hemodynamics is abnormal and left ventricular end-diastolic pressure is increased, which results in stimulation of myocardial cells by stretch and production of TNF-α (Sinagra *et al*., 2013). IL-6 is mainly produced by monocytes and vascular endothelial cells and participates in the regulation of cardiac dysfunction (Xu *et al*., 2018). The level of IL-6 increases in the condition of CHF (Korotaeva *et al*., 2023). Our study showed that, after treatment, compared with the sham group, in the model group the serum TNF-α and IL-6 levels were significantly increased. Compared with the model group, each index in the treatment group was significantly decreased. This suggests that the alleviation of CHF in rats by dihydroquercetin may be closed with its reduction of inflammatory response. It is shown that dihydroquercetin has obvious anti-inflammatory effect (Iwasa *et al*., 2023), which further confirms the anti-inflammatory mechanism of dihydroquercetin for alleviation of CHF.

Oxidative stress refers to the process of oxidative damage caused by the imbalance between oxidative and antioxidant systems due to the excessive production of oxygen free radicals in the body (Sies, 2015). Recent research has shown that, in animal model of CHF, there is significant increase in oxygen free radicals and a decrease in the ability to resist oxidation (Linke *et al*., 2005). SOD is the important antioxidant enzymes in myocardial tissue (Peoples *et al*., 2019). MDA is the main end product of lipid peroxidation. When the myocardial injury occurs, the MDA level increases (Zheng *et al*., 2017). Dihydroquercetin is a good antioxidant (Zhang *et al*., 2017). Results of our study showed that, after treatment, compared with the sham group, in the model group the serum SOD level was significantly decreased, and the MDA level was significantly increased. This confirms that oxidative stress is involved in the occurrence of CHF in rats. Compared with the model group, in the treatment group the SOD level was significantly increased, and the MDA level was significantly decreased. This suggests that dihydroquercetin can reduce the oxidative stress, thereby alleviating the CHF in rats.

Inflammation and oxidative stress can lead to structural damage and functional abnormalities in myocardial cells, which results in increased cardiac myocyte apoptosis and cardiac dysfunction, leading to the CHF (Garg *et al*., 2005). The occurrence of apoptosis is regulated by apoptotic proteins. Bcl-2 and Bax belong to the same family of Bcl-2 genes. The members of Bcl-2 gene family can form dimers or polymers and regulate the cell survival or apoptosis through interaction. Bcl-2 inhibits the cardiac myocyte apoptosis, while Bax antagonizes Bcl-2 and promotes cardiac myocyte apoptosis (Dong *et al*., 2003). Results of our study showed that, after treatment, compared with sham group, in model group the myocardial Bcl-2 protein expression level was significantly decreased, and the Bax protein expression level was significantly increased. Compared with model group, in treatment group the Bcl-2 protein level was significantly increased, and the Bax protein level was significantly decreased. This indicates that, the cardiac myocyte apoptosis is involved in the process of CHF in rats, and dihydroquercetin can alleviate the cardiac myocyte apoptosis, thus protecting the cardiac structure and function of rats. This is basically consistent with the conclusion that dihydroquercetin can decrease the cardiac myocyte apoptosis in previous study (Sun *et al*., 2014).

Nrf2/HO-1 signaling pathway is one of the

most important endogenous antioxidant stress pathways. Many antioxidant enzymes in the body contain a common promoter sequence - antioxidant response element (ARE). Among the various transcription factors that bind to ARE, Nrf2 is currently considered to play a key role and can be induced by external factors. When the oxidative stress or other chemical stimuli occur, Nrf2 is phosphorylated and decoupled from Keap1, activating Nrf2 to enter the nucleus and bind to ARE specific sites, thereby inducing downstream expression of a series of endogenous protective genes (Ndisang, 2017). HO-1 is an important downstream target gene of Nrf2 and a novel cardioprotective factor (Cheng *et al*., 2022). In our study, after treatment the myocardial Nrf2 and HO-1expression levels in model group were significantly lower than those in sham group. Compared with model group, each index in treatment group was significantly increased. This suggests that the Nrf2/HO-1 signaling pathway is involved in the CHF in rats, and dihydroquercetin can activate this signaling pathway, thus alleviating the CHF.

CONCLUSIONS

Dihydroquercetin can alleviate CHF in rats. The action mechanisms may be related to its resistance of inflammatory response and oxidative stress, reduction of cardiac myocyte apoptosis and activation of Nrf2/HO-1 signaling pathway. This study has provided an experimental evidence for the development and clinical application of dihydroquercetin-related drugs.

REFERENCES

Cheng Y, Wu X, Nie X, Wu Y, Zhang C, Lee SM, Lv K, Leung GP, Fu C, Zhang J, Li J. 2022. Natural compound glycyrrhetinic acid protects against doxorubicin-induced cardiotoxicity by activating the Nrf2/HO-1 signaling pathway. **Phytomedicine** 106: 154407. **https://doi.org/10.1016/j.phymed.2022.154407**

Dharmarajan K, Rich MW. 2017. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. **Heart Fail Clin** 13: 417 - 426. **https://doi.org/10.1016/j.hfc.2017.02.001**

Dick SA, Epelman S. 2016. Chronic heart failure and inflammation: what do we really know? **Circ Res** 119: 159 - 176. **https://doi.org/10.1161/CIRCRESAHA**

Dong JW, Zhu HF, Zhu WZ, Ding HL, Ma TM, Zhou ZN. 2003. Intermittent hypoxia attenuates ischemia/reperfusion induced apoptosis in cardiac myocytes via regulating Bcl-2/Bax expression. **Cell Res** 13: 385 - 391. **https://doi.org/10.1038/sj.cr.7290184**

Gao G, Chen W, Yan M, Liu J, Luo H, Wang C, Yang P. 2020. Rapamycin regulates the balance between cardiomyocyte apoptosis and autophagy in chronic heart failure by inhibiting mTOR signaling. **Int J Mol Med** 45: 195 - 209. **https://doi.org/10.3892/ijmm.2019.4407**

Garg S, Narula J, Chandrashekhar Y. 2005. Apoptosis and heart failure: clinical relevance and therapeutic target. **J Mol Cell Cardiol** 38: 73 - 79. **https://doi.org/10.1016/j.yjmcc.2004.11.006**

Guo H, Zhang X, Cui Y, Zhou H, Xu D, Shan T, Zhang F, Guo Y, Chen Y, Wu D. 2015. Taxifolin protects against cardiac hypertrophy and fibrosis during biomechanical stress of pressure overload. **Toxicol Appl Pharmacol** 287: 168 - 177. **https://doi.org/10.1016/j.taap.2015.06.002**

Hoffman TM. 2016. Chronic heart failure. **Pediatr Crit Care Med** 17: S119 - S123. **https://doi.org/10.1097/PCC.0000000000000755**

Iwasa M, Kato H, Iwashita K, Yamakage H, Kato S, Saito S, Ihara M, Nishimura H, Kawamoto A, Suganami T, Tanaka M, Satoh-Asahara N. 2023. Taxifolin suppresses inflammatory responses of high-glucose-stimulated mouse microglia by attenuating the TXNIP-NLRP3 axis. **Nutrients** 15: 2738. **https://doi.org/10.3390/nu15122738**

Jiang H, Fang T, Cheng Z. 2023. Mechanism of heart failure after myocardial infarction. **J Int Med Res** 51: 3000605231202573. **https://doi.org/10.1177/03000605231202573**

Korotaeva AA, Samoilova EV, Zhirov IV, Mindzaev DR, Nasonova SN, Tereschenko SN. 2023. Dynamics of the levels of interleukin 6, its soluble receptor, and soluble glycoprotein 130 in patients with chronic heart failure and preserved or reduced ejection fraction. **Bull Exp Biol Med** 174: 666 - 669. **https://doi.org/10.1007/s10517-023-05765-7**

Lee CW, Park NH, Kim JW, Um BH, Shpatov AV, Shults EE, Sorokina IV, Popov SA. 2012. Study of skin anti-ageing and anti-inflammatory effects of dihydroquercetin, natural triterpenoids, and their synthetic derivatives. **Bioorg Khim** 38: 374 - 381. **https://doi.org/10.1134/s1068162012030028**

Li XQ. 2019. Effects of high-quality nursing care on psychological outcomes in patients with chronic heart failure.

Medicine 98: e17351. **https://doi.org/10.1097/MD.0000000000017351**

Linke A, Adams V, Schulze PC, Erbs S, Gielen S, Fiehn E, Möbius-Winkler S, Schubert A, Schuler G, Hambrecht R. 2005. Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. **Circulation** 111: 1763 - 1770. **https://doi.org/10.1161/01.CIR.0000165503.08661.E5**

Miller WL. 2016. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. **Circ Heart Fail** 9: e002922. **https://doi.org/10.1161/CIRCHEARTFAILURE.115.002922**

Mou Q, Jia Z, Luo M, Liu L, Huang X, Quan J, Tian J. 2022. Epigallocatechin-3-gallate exerts cardioprotective effects related to energy metabolism in pressure overload-induced cardiac dysfunction. **Arch Biochem Biophys** 723: 109217. **https://doi.org/10.1016/j.abb.2022.109217**

Murphy SP, Kakkar R, McCarthy CP, Januzzi JL. 2020. Inflammation in heart failure: JACC state-of-the-art review. **J Am Coll Cardiol** 75: 1324 - 1340. **https://doi.org/10.1016/j.jacc.2020.01.014**

Ndisang JF. 2017. Synergistic interaction between heme oxygenase (HO) and nuclear-factor E2-related factor-2 (Nrf2) against oxidative stress in cardiovascular related diseases. **Curr Pharm Des** 23: 1465 - 1470. **https://doi.org/10.2174/1381612823666170113153818**

Orlova SV, Tatarinov VV, Nikitina EA, Sheremeta AV, Ivlev VA, Vasil'ev VG, Paliy KV, Goryainov SV. 2022. Bioavailability and safety of dihydroquercetin (review). **Pharm Chem J** 55: 1133 - 1137. **https://doi.org/10.1007/s11094-022-02548-8**

Pagliaro BR, Cannata F, Stefanini GG, Bolognese L. 2020. Myocardial ischemia and coronary disease in heart failure. **Heart Fail Rev** 25: 53 - 65. **https://doi.org/10.1007/s10741-019-09831-z**

Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. 2019. Mitochondrial dysfunction and oxidative stress in heart disease. **Exp Mol Med** 51: 1 - 13. **https://doi.org/10.1038/s12276-019-0355-7**

Shu Z, Yang Y, Yang L, Jiang H, Yu X, Wang Y. 2019. Cardioprotective effects of dihydroquercetin against ischemia reperfusion injury by inhibiting oxidative stress and endoplasmic reticulum stress-induced apoptosis via the PI3K/Akt pathway. **Food Funct** 10: 203 - 215. **https://doi.org/10.1039/c8fo01256c**

Sies H. 2015. Oxidative stress: A concept in redox biology and medicine. **Redox Biol** 4: 180 - 183. **https://doi.org/10.1016/j.redox.2015.01.002**

Sinagra E, Perricone G, Romano C, Cottone M. 2013. Heart failure and anti tumor necrosis factor-alpha in systemic chronic inflammatory diseases. **Eur J Intern Med** 24: 385 - 392. **https://doi.org/10.1016/j.ejim.2012.12.015**

Skrzypek A, Mostowik M, Szeliga M, Wilczyńska-Golonka M, Dębicka-Dąbrowska D, Nessler J. 2018. Chronic heart failure in the elderly: still a current medical problem. **Folia Med Cracov** 58: 47 - 56.

Sun X, Chen RC, Yang ZH, Sun GB, Wang M, Ma XJ, Yang LJ, Sun XB. 2014. Taxifolin prevents diabetic cardiomyopathy *in vivo* and *in vitro* by inhibition of oxidative stress and cell apoptosis. **Food Chem Toxicol** 63: 221 - 232. **https://doi.org/10.1016/j.fct.2013.11.013**

Tang Z, Yang C, Zuo B, Zhang Y, Wu G, Wang Y, Wang Z. 2019. Taxifolin protects rat against myocardial ischemia/reperfusion injury by modulating the mitochondrial apoptosis pathway. **Peer J** 7: e6383. **https://doi.org/10.7717/peerj.6383**

Triposkiadis F, Xanthopoulos A, Parissis J, Butler J, Farmakis D. 2022. Pathogenesis of chronic heart failure: cardiovascular aging, risk factors, comorbidities, and disease modifiers. **Heart Fail Rev** 27: 337 - 344. **https://doi.org/10.1007/s10741-020-09987-z**

van der Pol A, van Gilst WH, Voors AA, van der Meer P. 2019. Treating oxidative stress in heart failure: past, present and future. **Eur J Heart Fail** 21: 425 - 435. **https://doi.org/10.1002/ejhf.1320**

Xu Y, Zhang Y, Ye J. 2018. IL-6: a potential role in cardiac metabolic homeostasis. **Int J Mol Sci** 19: 2474. **https://doi.org/10.3390/ijms19092474**

Zhang Y, Yu J, Dong XD, Ji HY. 2017. Research on characteristics, antioxidant and antitumor activities of dihydroquercetin and its complexes. **Molecules** 23: 20. **https://doi.org/10.3390/molecules23010020**

Zheng P, Xie Z, Yuan Y, Sui W, Wang C, Gao X, Zhao Y, Zhang F, Gu Y, Hu P, Ye J, Feng X, Zhang L. 2017. Plin5 alleviates myocardial ischaemia/reperfusion injury by reducing oxidative stress through inhibiting the lipolysis of lipid droplets. **Sci Rep** 7: 42574. **https://doi.org/10.1038/srep42574**