BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
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Articulo Original / Original Article

Therapeutic effect of cirsimaritin on heart failure in rats and the underlying mechanisms

[Efecto terapéutico del cirsimaritina en la insuficiencia cardíaca en ratas y los mecanismos subyacentes]

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Section Biological activity

Received: 11 October 2024
Accepted: 11 January 2025
Accepted corrected: 26 April 2025
Published: 30 September 2025

Citation:
Chen J, Xu W, Li Z, Zhai N
Therapeutic effect of cirsimaritin on heart failure in rats and the underlying mechanisms
Bol Latinoam Caribe Plant Med Aromat
24 (5): 765 - 771 (2025)
https://doi.org/10.37360/blacpma.25.24.5.53

Abstract: To explore the effect on cirsimaritin on heart failure in rats and the mechanisms. The heart failure model with coronary artery ligation was established in 40 rats, which were then randomly divided into model and low-, middle- and high-dose cirsimaritin groups, 10 rats in each group. The 10 rats without coronary artery ligation were set as sham-operated group. The low-, middle- and high-dose cirsimaritin groups were treated with 20, 40 and 80 μg/kg cirsimaritin for one month, respectively. After treatment, compared with model group, in middle-dose cirsimaritin group the cardiac function indexes, heart and left ventricular indexes, myocardial injury indicators, and oxidative stress and inflammatory response indexes were significantly improved (all p<0.05). In conclusion, cirsimaritin has obvious therapeutic effect on heart failure in rats. It can effectively improve the cardiac function of rats, alleviate the myocardial injury, reduce the oxidative stress and decrease the inflammatory response.

Keywords: Cirsimaritin; Heart failure; Myocardial injury; Oxidative stress; Inflammatory response.

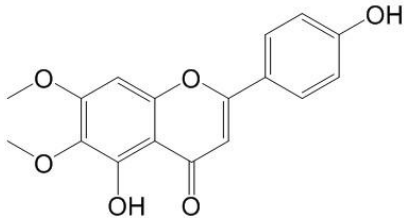
Resumen: Este estudio tuvo como objetivo explorar el efecto del cirsimaritina en la insuficiencia cardíaca en ratas y sus mecanismos. Se estableció un modelo de insuficiencia cardíaca mediante ligadura de la arteria coronaria en 40 ratas, las cuales se dividieron aleatoriamente en grupos modelo, cirsimaritina a dosis baja, media y alta, con 10 ratas por grupo. Un grupo adicional de 10 ratas sin ligadura se designó como grupo de simulación. Los grupos de dosis baja, media y alta de cirsimaritina recibieron un tratamiento de 20, 40 y 80 μg/kg de cirsimaritina, respectivamente, durante un mes. Tras el tratamiento, en comparación con el grupo modelo, el grupo de dosis media mostró mejoras significativas en los índices de función cardíaca, parámetros del corazón y ventrículo izquierdo, marcadores de lesión miocárdica, estrés oxidativo y respuesta inflamatoria (todos p<0,05). En conclusión, el cirsimaritina posee un efecto terapéutico evidente en la insuficiencia cardíaca en ratas, mejorando la función cardíaca, reduciendo la lesión miocárdica, el estrés oxidativo y la respuesta inflamatoria.

Palabras clave: Cirsimaritina; Insuficiencia cardíaca; Lesión miocárdica; Estrés oxidativo; Respuesta inflamatoria.

INTRODUCTION

Heart failure is a syndrome with symptoms and signs due to changes in myocardial structure and function, resulting in ventricular congestion and ejection disorders (Mosterd & Hoes, 2007). Heart failure affects about 40 million people worldwide. It can be caused by many things, but the most common risk factors are high blood pressure, coronary artery disease (blockages in the arteries of the heart), diabetes, obesity, smoking, and genetics (Baman & Ahmad, 2020). Heart failure can lead to myocardial ischemia, severe damage to myocardial cells, decreased levels of oxidative phosphorylation, and accumulation of reactive oxygen species (Dietl & Maack, 2017). The conversion of polyunsaturated fatty acids into lipid peroxides increases the production of malondialdehyde (MDA), leading to an imbalance in the antioxidant system and the occurrence of oxidative stress. Therefore, oxidative stress is closely related to the occurrence and development of heart failure (Tsutsui *et al.*, 2011; van der Pol *et al.*, 2019). In addition, the inflammation and heart failure are closely related to each other (Adamo *et al.*, 2020). Flavonoids are found in the roots, stems, leaves, and fruits of many plant taxa. They are related to plant growth and development, pigment formation, and protection against environmental stress. They are the potential therapeutic agents for cardiovascular disease (Liu *et al.*, 2024; Zheng *et al.*, 2024). It is found that, the flavonoids play an important role in alleviating the heart failure in animals. For example, luteolin can improve the cardiac dysfunction in heart failure rats by regulating sarcoplasmic reticulum Ca^{2+}-ATPase 2a (Hu *et al.*, 2017); hyperoside can protect against heart failure-induced liver fibrosis in rats by suppressing TGF-β1-mediated hepatic stellate cell activation (Guo *et al.*, 2019); butein can inhibit the oxidative stress injury in rats with chronic heart failure via ERK/Nrf2 signaling (Liu *et al.*, 2022). Cirsimaritin (molecular formula: $C_{17}H_{14}O_6$; molecular weight: 314.29) (Figure No. 1) is a natural flavonoid compound which is present in *Ocimum sanctum*, *Microtea debilis*, *Artemisia judaica*, *Cirsium japonicum*, and *Lithocarpus dealbatus* (Pathak *et al.*, 2021). Cirsimaritin has various biological activities in antiviral (Yan *et al.*, 2018), anti-inflammatory (Shin *et al.*, 2017), antioxidant (Quan *et al.*, 2010), anti-tumor (Szoka *et al.*, 2021), and other aspects, and has high clinical application value. In this study, we attempted to investigate the therapeutic effect of cirsimaritin on heart failure in rats and the mechanisms.

Figure No. 1
Chemical structure of cirsimaritin



MATERIALS AND METHODS

Establishment of heart failure model

Heart failure model was established in SD rats (250-280 g; Shanghai Slake Laboratory Animal Co., Ltd., Shanghai, China). According to the reported method (Goldman & Raya, 1995) with some modification, the rats were intraperitoneally injected with 3% pentobarbital sodium, followed by endotracheal intubation. The electrocardiogram of rats was monitored using the biological function experiment system. The abdominal skin was cut open. The thoracic cavity was opened to expose the heart completely. The anterior descending branch of 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 heart failure model was successfully established in 40 rats. In other 10 rats only the thoracic cavity was opened, without coronary artery ligation. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol has been reviewed and approved by the Institutional Animal Care and Use Committee of the First Affiliated Hospital of Shihezi University.

Grouping and treatment

Forty modeled rats were randomly divided into the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups, 10 rats in each group. The 10 rats without coronary artery ligation were selected as the sham-operated group. The rats in low-dose cirsimaritin, middle-dose cirsimaritin and middle-dose cirsimaritin groups were treated with 20, 40 and 80 μg/kg cirsimaritin by intragastrical administration, respectively. The sham-operated and model groups were treated with equal volume of normal saline. The treatment was also performed once per day, for one month. No rat died in the treatment period.

Cardiac function test

At the end of treatment, the rats in each group were anesthetized with 3% pentobarbital sodium. The left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVIDd), left ventricular end systolic diameter (LVIDs) and left ventricular fractional shortening (LVFS) were measured by color Doppler ultrasound.

Determination of blood indexes

After the cardiac function test was conducted, the blood was collected from the abdominal aorta of rats. The blood was centrifuged at 3000 rpm for 15 min, and the serum was obtained. The myocardial injury indicators including creatine kinas (CK), lactate dehydrogenase (LDH) and cardiac troponin I (cTnI), oxidative stress indexes including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde and inflammatory response indexes including C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) were determined using enzyme linked immunosorbent assay.

Measurement of heart index and left ventricular index

After the blood collection, the heart of rats was taken, and weighed. The left ventricle was isolated, and weighed. The heart index (ratio of heart weight to body weight) and left ventricular index (ratio of left ventricle weight to body weight) were calculated.

Statistical analysis

Data were expressed as the mean±standard deviation, and were processed using SPSS 22.0 software. For a statistical analysis of the data, the group means were compared by one-way Analysis of Variance followed by LSD-t test. $p<0.05$ was considered as statistically significant.

RESULTS

Effect of cirsimaritin on cardiac function of rats with heart failure

After treatment, compared to the sham-operated group, in the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups the LVEF and LVFS were significantly decreased, respectively ($p<0.05$), and the LVIDd and LVIDs were increased, respectively ($p<0.05$). Compared with the model group, the LVEF in the middle-dose cirsimaritin and high-dose cirsimaritin groups and the LVFS in the high-dose cirsimaritin group were significantly increased, respectively ($p<0.05$), and the LVIDd and LVIDs in the middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly decreased, respectively (Table No. 1).

Effect of cirsimaritin on heart index and left ventricular index of rats with heart failure

Table No. 2 showed that, after one month of treatment, the heart index and left ventricular index in the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly increased, respectively ($p<0.05$). Compared with model group, each index in the low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups was significantly decreased, respectively ($p<0.05$).

Effect of cirsimaritin on heart index and left ventricular index of rats with heart failure

Myocardial injury indicators such as serum CK, LDH and cTnI in the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly higher than those in the sham-operated group, respectively ($p<0.05$). Compared with the model group, the CK and cTnI in the high-dose cirsimaritin group and the LDH in middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly decreased ($p<0.05$) (Table No. 3).

Effect of cirsimaritin on oxidative stress indexes of rats with heart failure

As shown in Table No. 4, compared with the sham-operated group, in the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups the serum SOD and GSH-Px levels were significantly decreased, respectively ($p<0.05$), and the MDA level was significantly increased ($p<0.05$).

Compared with the model group, in the SOD and GSH-Px levels in the high-dose cirsimaritin group were significantly increased, respectively (p<0.05), and the MDA level in the middle-dose cirsimaritin and high-dose cirsimaritin groups was significantly decreased, respectively (p<0.05).

Table No. 1
Cardiac function indexes in five groups (n=10)

Group	LVEF (%)	LVIDd (mm)	LVIDs (mm)	LVFS (%)
Sham-operated	74.87±10.31	5.08±1.05	3.68±0.43	46.38±5.67
Model	41.89±2.29*	7.11±1.08*	6.25±0.47*	31.39±4.31*
Low-dose cirsimaritin	44.74±3.82*	6.81±1.07*	5.89±0.55*	35.21±3.59*
Middle-dose cirsimaritin	50.38±4.20*#%	6.16±0.85*#	5.56±0.49*#	35.42±4.05*
High-dose cirsimaritin	54.48±4.34*#%	6.07±1.06*#	5.08±0.52*#%$	39.95±5.24*#%$

***p<0.05 compared with sham-operated group; #p<0.05 compared with model group; %p<0.05 compared with low-dose cirsimaritin group; $$p$<0.05 compared with middle dose cirsimaritin group. LVEF, left ventricular ejection fraction; LVIDd, left ventricular end diastolic diameter; LVIDs, left ventricular end systolic diameter; LVFS, left ventricular fractional shortening**

Table No. 2
Heart index and left ventricular index in five groups (n=10)

Group	Heart index (mg/g)	Left ventricular index (mg/g)
Sham-operated	2.19 ± 0.08	1.88 ± 0.05
Model	3.01 ± 0.09*	2.51 ± 0.08*
Low-dose cirsimaritin	2.63 ± 0.06*#	2.21 ± 0.07*#
Middle-dose cirsimaritin	2.44 ± 0.09*#%	2.16 ± 0.05*#
High-dose cirsimaritin	2.35 ± 0.07*#%$	2.07 ± 0.06*#%$

***p<0.05 compared with sham-operated group; #p<0.05 compared with model group; %p<0.05 compared with low-dose cirsimaritin group; $$p$<0.05 compared with middle dose cirsimaritin group**

Table No. 3
Myocardial injury indicators in five groups (n=10)

Group	CK (U/L)	LDH (U/L)	cTnI (μg /L)
Sham-operated	764.61 ± 112.42	1112.04±230.34	1.06±0.26
Model	1409.41 ± 243.32*	2535.90±342.21*	2.21±0.41*
Low-dose cirsimaritin	1369.43 ± 134.47*	2255.64±166.26	2.16±0.35*
Middle-dose cirsimaritin	1265.22 ± 99.00*	1871.10±198.00*#%	1.98±0.30*
High-dose cirsimaritin	1127.23 ± 199.54*#%	1823.85±260.19*#%	1.37±0.36*#%$

***p<0.05 compared with sham-operated group; #p<0.05 compared with model group; %p<0.05 compared with low-dose cirsimaritin group; $$p$<0.05 compared with middle dose cirsimaritin group. CK, creatine kinase; LDH, lactate dehydrogenase; cTnI, cardiac troponin I**

Table No. 4
Oxidative stress indexes in five groups (n=10)

Group	SOD (U/L)	GSH-Px (μmol/L)	MDA (μmol/L)
Sham-operated	65.91±4.95	71.12±8.91	8.07±0.99
Model	38.37±4.26*	44.03±7.92*	32.61±2.97*
Low-dose cirsimaritin	44.55±5.94*	44.55±7.03*	30.70±3.96*
Middle-dose cirsimaritin	46.43±8.02*	50.48±9.90*	24.75±1.98*#%
High-dose cirsimaritin	55.40±8.81*#%	63.33±9.11*#%$	15.84±1.98*#%$

***p<0.05 compared with sham-operated group; #p<0.05 compared with model group; %p<0.05 compared with low-dose cirsimaritin group; $$p$<0.05 compared with middle dose cirsimaritin group. SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde**

Effect of cirsimaritin on inflammatory response indexes of rats with heart failure

Serum CRP, TNF-α and IL-6 levels in the model, low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly higher than those in the sham-operated group, respectively (p<0.05). Compared with the model group, the CRP and IL-6 levels in the middle-dose cirsimaritin and high-dose cirsimaritin groups and the TNF-α level in low-dose cirsimaritin, middle-dose cirsimaritin and high-dose cirsimaritin groups were significantly decreased, respectively (p<0.05) (Table No. 5).

Table No. 5
Inflammatory response indexes in five groups (n=10)

Group	CRP (mg/L)	TNF-α (ng/L)	IL-6 (ng/L)
Sham-operated	2.97±0.40	21.78±2.97	81.15±7.92
Model	12.87±0.99*	42.57±5.94*	134.64±19.80*
Low-dose cirsimaritin	11.91±2.98*	35.64±4.16$^{*\#}$	122.76±20.16*
Middle-dose cirsimaritin	7.92±1.39$^{*\#\%}$	33.66±4.85$^{*\#}$	109.89±25.74$^{*\#}$
High-dose cirsimaritin	5.94±1.19$^{*\#\%\$}$	29.70±5.07$^{*\%\#}$	85.23±21.88$^{\#\%\$}$

$^{*}p$<0.05 compared with sham-operated group; $^{\#}p$<0.05 compared with model group; $^{\%}p$<0.05 compared with low-dose cirsimaritin group; $^{\$}p$<0.05 compared with middle dose cirsimaritin group. CRP, C-reactive protein; TNF-α, tumor necrosis factor α; IL-6, interleukin 6

DISCUSSION

Heart failure is a common and frequently occurring disease in clinic. With the advancement of medical technology, the incidence of heart failure has been greatly reduced, but its mortality is still high (Lupón & Bayés-Genís, 2019). Wu *et al.* (2016), have found that, cirsimaritin can improve the cardiac function of rats with heart failure. In the present study, the heart failure model of rats was established by coronary artery ligation. Then, the therapeutic effect of cirsimaritin on heart failure was investigated. Results presented that, after one month of treatment, compared with the model group, in the cirsimaritin group the LVEF and LVFS were significantly increased, and the LVIDd and LVIDs were significantly decreased. This indicates that cirsimaritin can improve the cardiac function of rats with heart failure, which is the same as the above study.

Heart failure is often accompanied by the enlargement of the heart. In addition, the CK, LDH and cTnI can directly or indirectly reflect the degree of myocardial injury. When myocardial tissue is damaged, their levels in serum are increased (Zhang *et al.*, 2022). In this study, after treatment, compared with the model group, in the cirsimaritin group the heart index and left ventricular index were significantly decreased, and the serum CK, LDH and cTnI levels were significantly decreased. This suggests that, the cirsimaritin treatment can obviously alleviate the myocardial injury of rats with heart failure.

Excessive production of oxygen free radicals or damage to the intracellular antioxidant defense system can cause oxidative stress. The oxidative stress plays an important role in the occurrence and development of heart failure (Pagan *et al.*, 2022). SOD and GSH-Px are the important antioxidant enzymes in myocardial tissue. MDA is the main end product of lipid peroxidation. When the myocardium is damaged, the SOD and GSH-Px activities decrease, and the MDA level increases (Nie *et al.*, 2024). Previous study finds that cirsimaritin can reduce the severity of liver injury in the experimental mouse model of metabolic dysfunction-associated fatty liver disease by inhibiting oxidative stress (Che *et al.*, 2021). In addition, cirsimaritin can reduced the MDA level and increase the GSH level in diabetic rats (Alqudah *et al.*, 2023). Results of our study showed that, after treatment, compared with the sham-operated group, in the model group the SOD and GSH-Px levels were significantly decreased, and the MDA level was significantly increased. This suggests that oxidative stress is involved in the occurrence of isoproterenol-induced heart failure in rats. Compared with the model group, in the cirsimaritin group the SOD and GSH-Px levels were significantly increased, and the MDA level was significantly decreased. This suggests that the alleviation of heart failure by cirsimaritin may be related to its reduction of oxidative stress, which is similar with its antioxidant activity reported in above

studies.

Inflammatory response is closely related to the heart failure (Hanna & Frangogiannis, 2020). CRP is one of the most important inflammatory factors in body. Under normal conditions, CRP can activate the complement system and remove the pathological substancesy. However, excessive CRP can reduce the endothelial cell function and affect the coagulation and fibrinolysis (Pope & Choy, 2021). TNF-α is an anti-tumor cytokine, which is produced after stimulation by lipopolysaccharide and virus. When heart failure 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 (Jin *et al.*, 2013). IL-6 is mainly produced by monocytes and vascular endothelial cells and participates in the regulation of cardiac dysfunction (Jin *et al.*, 2018). The level of IL-6 increases in the condition of heart failure (Alogna *et al.*, 2023). Results of our study showed that, after treatment, compared with the sham-operated group, in the model group the serum CRP, TNF-α and IL-6 levels were significantly increased. Compared with the model group, each index in the cirsimaritin group was significantly decreased. This suggests that, cirsimaritin can reduce the inflammatory response in rats with heart failure, thus alleviating the myocardial injury and cardiac dysfunction. In study by Wu *et al.* (2016), cirsimaritin can remarkably inhibit the serum levels of TNF-α in rats with heart failure, thus ameliorating the cardiac remodeling and dysfunction. This is similar with the findings of our study.

CONCLUSION

In conclusion, cirsimaritin has obvious therapeutic effect on heart failure in rats. It can effectively improve the cardiac function of rats, alleviate the myocardial injury, reduce the oxidative stress and decrease the inflammatory response. This study has uncovered the action mechanism of cirsimaritin in treating heart failure in in vivo model, and provided a new reference for the clinical application of cirsimaritin. There are still some limitations of this study, and the signaling pathway through which cirsimaritin exerts the therapeutic effect on heart failure should be further explored in future studies.

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