Saudi Pharmaceutical Journal 26 (2018) 528–534

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Self-emulsifying drug delivery system improves preventive effect of curcuminoids on chronic heart failure in rats

Yunbin Jiang [a], Junzhi Wang [b], Yunhong Wang [c], Xiumei Ke [d], Chuanhui Zhang [c], Rongping Yang [a,*]

[a] College of Pharmaceutical Sciences and Chinese Medicine, Southwest University, Chongqing 400715, China
[b] Hubei Key Laboratory of Natural Products Research and Development, College of Biological and Pharmaceutical Sciences, China Three Gorges University, Yichang 443002, China
[c] Institute of Chinese Medicine Preparation, Chongqing Academy of Chinese Materia Medica, Chongqing 400065, China
[d] Jiujiang Key Laboratory of Translational Medicine, Basic Medical College, Jiujiang University, Jiujiang 33200, China

ARTICLE INFO

Article history:
Received 17 September 2017
Accepted 3 February 2018
Available online 5 February 2018

Keywords:
Curcuminoids
Self-emulsifying drug delivery system
Chronic heart failure
Ventricular pump function
Lipid peroxidation damage

ABSTRACT

Several studies have reported the preventive or therapeutic effect of curcuminoids on chronic heart failure (CHF), but their application was limited due to low solubility and bioavailability. Our previous study indicates that self-emulsifying drug delivery system (SEDDS) improves the solubility and bioavailability of curcuminoids. Thus, the aim of this work was to investigate whether SEDDS could improve preventive effect of curcuminoids on CHF in rats. CHF model was were established by coronary artery ligation. Ninety rats were randomly and averagely divided into sham, model, low- or high-dose suspension or SEDDS of curcuminoids (66.68 or 266.68 mg/kg) groups. Hemodynamic indices were recorded by multi-purpose polygraph. Serum oxidative indices, B-type natriuretic peptide (BNP) and heart weight index were determined by kits and electronic balance. Myocardial infarct area, ventricular dilatation degree and collagen volume fraction of myocardial interstitium were analyzed by Masson staining, picric acid and sirius red staining, light microscopy and image analysis system. Myocardial histopathology was observed by hematoxylin and eosin staining, Masson staining and light microscopy. Reduction of ventricular pump function, increase of BNP level and heart weight index, myocardial lipid peroxidation damage, myocardial infarction, myocardial fibrosis, and cardiac enlargement were detected or observed in model group relative to those in sham group. After treatment with suspension or SEDDS of curcuminoids, the above-mentioned pathological changes were obviously reversed relative to those in model group. Meanwhile, the ameliorative effect of SEDDS of curcuminoids was markedly better than that of suspension of curcuminoids. This work provides a valuable reference from pharmacodynamics for development of curcuminoids pharmaceutics.

1. Introduction

Heart failure (HF) is characterized by the obvious reduce of cardiac output leading to the perfusion deficiency of blood in systemic organ. Generally, pulmonary or systemic circulation venous congestion are simultaneously diagnosed in HF patients, so HF can also be known as congestive HF (Stewart and Givertz, 2012). HF is a major public health problem, with a prevalence of more than 23 million worldwide (Roger, 2013). With the evolution of epidemiology and development of social economy in China, the Chinese epidemiological character of HF is more close to that of developed country. For example, coronary heart disease-induced HF in China becomes more and more prominent (Jiang and Ge, 2009). Gratifyingly, with the deeper cognition to pathophysiological mechanism and development of biomedical engineering technology, the clinical therapy of HF has entered into the era of multi-therapy, such as drugs, cardiac resynchronization, stem cell and heart transplantation. The survival quality and prognosis of patients with HF are significantly improved after treatment with multi-therapy (Li and Wang, 2005). However, the patients with end-stage HF still face high mortality risk. Meanwhile, a large number of clinical reports indicate that traditional Chinese medicines (TCMs) show good

* Corresponding author at: College of Pharmaceutical Sciences and Chinese Medicine, Southwest University, No. 2 Tiansheng Road, Beibei District, Chongqing 400715, China.
E-mail address: rongpingyang@swu.edu.cn (R. Yang).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2018.02.003
1319-0164/

clinical effect on HF, so it is vital to develop TCMs for treating HF and offsetting the deficiency of Western medicine in treating HF (Li et al., 2013; Liu et al., 2011).

TCMs from *Curcuma*, such as Curcumae Longae Rhizoma, Curcumae Rhizoma and Curcumae Radix, show therapeutic and preventive effect on cardiovascular diseases, such as chronic heart failure (CHF) and platelet aggregation (Gao, 2017; Wang and Wang, 2001). Curcuminoids, mainly including curcumin, demethoxycurcumin and bisdemethoxycurcumin, is the main therapeutic material basis of TCMs from *Curcuma* and show protective effect on heart function (Morimoto et al., 2008; Nabavi et al., 2011). However, the application of curcuminoids was limited due to low solubility and bioavailability (Kakkar et al., 2011). The early study in our team indicates that self-emulsifying drug delivery system (SEDDS) improves the solubility and bioavailability of curcuminoids (Ke et al., 2014). Based on the results of the early study, this work was designed to investigate whether SEDDS could improve preventive effect of curcuminoids on CHF in rats.

2. Material and methods

2.1. Chemicals and regents

Curcuminoids, mainly including 82.22% curcumin, 12.43% demethoxycurcumin and 2.44% bisdemethoxycurcumin, was purchased from Nanjing Zelang Biological Technology Co., Ltd (Nanjing, China). The suspension and SEDDS of curcuminoids were prepared with 0.5% sodium carboxyl methyl cellulose (CMC-Na) solution and the reported method (Ke et al., 2014). Ethyl carbamate and benzylpenicillin sodium were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China) and North China Pharmaceutical Co., Ltd (Shijiazhuang, China), respectively. B-type natriuretic peptide (BNP), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) and malonaldehyde (MDA) kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

2.2. Animals

Specific pathogen-free male SD rats (180 ± 20 g) were provided by the Experimental Animal Center, China Three Gorges University (Yichang, China) and were housed in a temperature-controlled vivarium (22 ± 2 °C) with relative humidity of 60 ± 5% and 12/12-h light-dark cycle. All rats have free access to water and food. All animal treatments were conducted in strict compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (The National Research Council of The National Academy of Sciencies, 2010). All experiments involved animals in this work were performed with the approval of the Ethics Committee of China Three Gorges University.

2.3. Replication of CHF model in rats

Before operation, the electrocardiography of each rat was monitored by Biopac MP150 multipurpose polygraph (Goleta, CA, USA). Rats with normal electrocardiography were used to establish CHF model by coronary artery ligation according to previous procedure (Li et al., 2011). Briefly, after rats were anesthetized by intraperitoneal injection of 20% ethyl carbamate (1.5 g/kg), coronary artery ligation was achieved with a gab occluder fixed onto the left anterior descending coronary artery. A 6-0 silk suture was passed underneath the left anterior descending (1–2 mm inferior to the left auricle) and tied. The electrocardiography of rat was instantly monitored. If the electrocardiography ST segment elevation was observed, the coronary artery ligation was successfully performed. Then, the chest was closed in layers, and the respirator weaned when the rat recovered spontaneous breathing. Subsequently, rats were subcutaneously injected with normal saline (30 mL/kg) to replenishing fluid loss and were locally treated with povidone-iodine and benzylpenicillin sodium to disinfection and anti-infection. Sham-operated rats underwent all the above-described surgical procedures, except that the 6-0 silk suture, passing around the left anterior descending, was not tied.

2.4. Animal grouping and treatment

Ninety rats were randomly and averagely divided into sham, model, low- or high-dose suspension of curcuminoids (66.68 or 266.68 mg/kg), and low- or high-dose SEDDS of curcuminoids (66.68 or 266.68 mg/kg) groups. At 0.5 h before coronary artery ligation operation, rats in sham and model groups were administrated orally with distilled water, and rats in other groups were administrated orally with corresponding drugs. After operation, rats were administrated based on the above-described treatment once a day for 8 weeks.

2.5. Hemodynamic assessment

At 24 h after last administration, rats were weighed by Ohaus AR3130 electronic balance (Pinebrook, NJ, USA) and anesthetized by intraperitoneal injection of 20% ethyl carbamate (1.5 g/kg). A venous cannula was inserted into the left ventricular cavity of rat through the right common carotid artery. Then, heart rate (HR), left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximal rate of the increase of left ventricular pressure ($+dp/dt_{max}$), maximal rate of the decrease of left ventricular pressure ($-dp/dt_{max}$) were recorded with the aid of Biopac MP150 multipurpose polygraph (Goleta, CA, USA). The mean of 5 segments recorded value of above-described hemodynamic indices was used for statistical analysis.

2.6. Determination of serum oxidative indices and BNP levels or activities

After determination of hemodynamic indices, the abdominal aortic blood of each rat was collected and centrifuged at 3500 rpm for 15 min at 4 °C to obtain serum, which was stored at −20 °C for further analysis. Serum oxidative indices (SOD, GSH-Px, CAT and MDA) and BNP levels or activities were determined using corresponding kits according to the manufactures' instruction for each. After reactions were completed, absorbance of each index in each sample was determined using Unico UV-2000 UV–VIS spectrophotometer (Shanghai, China) or Awareness Stat Fax-2100 microplate reader (Palm, FLA, USA). The absorbance for each index was used to calculate its level or activity according to corresponding standard curve.

2.7. Determination of heart weight index

After collecting abdominal aortic blood, rat was sacrificed by decapitation, and its heart was removed and washed with 4 °C normal saline, blotted with a piece of filter paper and weighed by Mettler-Toledo AL204 electronic balance (Shanghai, China). Heart weight index was calculated as heart weight (mg)/body weight (g).

2.8. Determination of myocardial infarct area and ventricular dilatation degree

Left ventricle of rat was cut into five equal parts along the long axis from cardiac apex to base, and the myocardial fragment of maximum ventricular perimeter was fixed in 10% formalin. The

fixed myocardial fragment was washed six times with PBS, dehydrated in ethanol, and embedded in paraffin. The embedded myocardial fragment was sliced at 4 μm, and the slices were used for Masson staining. After being photographed under light microscopy, photograph was analyzed by Leica Q500 MC image analysis system (Solms, Germany). Under light microscopy, myocardial scar tissue is blue, and myocardial tissue is red or brown. The myocardial infarct size (MIS), infarct length of left ventricle (LVIL), circumference of left ventricle (LVC), inner diameter of left ventricle (LVID) were calculated according to the results of image analysis system and the previous calculation method (Wei et al., 2013).

2.9. Determination of collagen volume fraction (CVF) of myocardial interstitium

Slices of myocardial fragment were prepared according to the above-described method. The slices were used for picric acid and sirius red staining. After being photographed under light microscopy, photograph was analyzed by above-described image analysis system. Under light microscopy, myocardial cells of CHF rats are yellow, and collagen of CHF rats is red. Collagen and non-collagen parts can be distinguished by adjusting gray level with the aid of image analysis system. CVF of myocardial interstitium was calculated as myocardial collagen area/horizon area. The mean of 6 horizons of each slice was used for statistical analysis.

2.10. Observation of myocardial histopathology

Slices of myocardial fragment were prepared according to the above-described method. The slices were used for hematoxylin and eosin staining, Masson staining. The stained slices were observed under light microscopy.

2.11. Statistical analysis

Statistical analysis was carried out using the SPSS 13.0 software for windows. All data are reported as mean ± standard deviation (SD) and were analyzed by one-way analysis of variance (ANOVA) or Dunnett-*t* test. Differences were considered to be statistically significant at $p < .05$.

3. Results

3.1. Effect and difference of suspension and SEDDS of curcuminoids on hemodynamic indices in CHF rats

As shown in Table 1, the LVSP, $+dp/dt_{max}$ and $-dp/dt_{max}$ in model group were significantly ($p < .01$) lower than those in sham group, and the LVEDP in model group were significantly ($p < .01$) higher than that in sham group, indicating that the CHF model in rats was successfully replicated. After treatment with suspension or SEDDS of curcuminoids, the above-mentioned hemodynamic indices were reversed relative to those in model group with significant ($p < .05$ or .01) difference for some doses of curcuminoids. There was no significant difference for HR among all groups. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on LVSP was significantly ($p < .05$ or .01) better than that of low- or high-dose suspension of curcuminoids and low-dose SEDDS of curcuminoids.

3.2. Effect and difference of suspension and SEDDS of curcuminoids on serum oxidative indices and BNP levels or activities in CHF rats

Compare with those in sham group, the serum SOD, GSH-Px and CAT activities in model group were significantly ($p < .01$) decreased, and the serum MDA and BNP levels in model group were significantly ($p < .01$) increased. After treatment with suspension or SEDDS of curcuminoids, the serum oxidative indices and BNP levels or activities were significantly ($p < .05$ or .01) reversed relative to those in model group, except CAT activity in low-dose suspension of curcuminoids group and GSH-Px activity in low- or high-dose suspension of curcuminoids groups. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on serum SOD, GSH-Px and CAT activities were significantly ($p < .05$ or .01) better than those of low-dose suspension and SEDDS of curcuminoids. The ameliorative effect of high-dose SEDDS of curcuminoids on serum MDA and BNP levels were significantly ($p < .01$) better than those of low- or high-dose suspension of curcuminoids and low-dose SEDDS of curcuminoids. The results are listed in Table 2.

3.3. Effect and difference of suspension and SEDDS of curcuminoids on heart weight index in CHF rats

The heart weight index in model group (3.61 ± 0.31 mg/g) was significantly ($p < .01$) increased relative to that in sham group (1.66 ± 0.39 mg/g). After treatment with low- or high-dose suspension or SEDDS of curcuminoids, the heart weight index (2.44 ± 0.35, 2.37 ± 0.24, 2.35 ± 0.39 and 2.14 ± 0.14 mg/g) was significantly ($p < .01$) lower than that in model group. There was no significant difference for heart weight index among low- or high-dose suspension or SEDDS of curcuminoids groups.

3.4. Effect and difference of suspension and SEDDS of curcuminoids on myocardial infarct area and ventricular dilatation degree in CHF rats

As shown in Fig. 1, left ventricular free wall infarction region in model group was thinner that in sham group, and obvious scar tis-

Table 1
Effect and difference of suspension and SEDDS of curcuminoids on hemodynamic indices in CHF rats.

Group	HR (beats/min)	LVSP (mmHg)	LVEDP (mmHg)	$+dp/dt_{max}$ (mmHg/s)	$-dp/dt_{max}$ (mmHg/s)
Sham	434.5 ± 18.2	172.5 ± 10.7	7.01 ± 0.91	4193 ± 312	−4014 ± 314
Model	409.2 ± 17.2	107.0 ± 5.4**	17.15 ± 1.71**	2990 ± 339**	−2806 ± 352**
A1	411.8 ± 16.5	119.1 ± 12.1‡	12.17 ± 2.29#	3445 ± 414	−3303 ± 289
A2	422.8 ± 22.1	125.6 ± 14.3#†	11.09 ± 1.87##	3667 ± 459	−3446 ± 346#
B1	421.4 ± 20.2	124.6 ± 12.3#†	11.5 ± 1.48##	3639 ± 450	−3410 ± 430
B2	428.5 ± 19.5	148.0 ± 16.1##	10.90 ± 2.18##	3619 ± 382#	−3490 ± 323#

HR: heart rate, LVSP: left ventricular systolic pressure, LVEDP: left ventricular end-diastolic pressure, $+dp/dt_{max}$: maximal rate of the increase of left ventricular pressure, $-dp/dt_{max}$: maximal rate of the decrease of left ventricular pressure; A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.
** $p < .01$, compared with those in sham group.
# $p < .05$.
$p < .01$, compared with those in model group.
† $p < .05$.
‡ $p < .01$, compared with those in B2.

Table 2
Effect and difference of suspension and SEDDS of curcuminoids on serum oxidative indices and BNP levels or activities in CHF rats.

Group	SOD (U/mL)	GSH-Px (U/mL)	CAT (U/mL)	MDA (nmol/mL)	BNP (μg/L)
Sham	138.2 ± 8.4	383.6 ± 14.5	5.64 ± 0.90	3.22 ± 0.86	10.27 ± 2.01
Model	97.1 ± 6.3**	311.2 ± 12.6**	2.29 ± 0.71**	8.79 ± 0.95**	44.20 ± 5.11**
A1	108.2 ± 7.3$^{\#\ddagger}$	321.9 ± 9.1‡	3.27 ± 0.73†	7.20 ± 0.93$^{\#\ddagger}$	30.21 ± 4.24$^{\#\#\ddagger}$
A2	118.5 ± 8.8$^{\#\#}$	330.5 ± 11.8	3.75 ± 0.86$^{\#}$	6.13 ± 0.78$^{\#\#\ddagger}$	29.27 ± 4.86$^{\#\#\ddagger}$
B1	114.4 ± 8.2$^{\#\#}$	328.9 ± 8.0$^{\#\dagger}$	3.45 ± 0.56$^{\#\dagger}$	7.10 ± 0.58$^{\#\#\ddagger}$	25.79 ± 4.48$^{\#\#\ddagger}$
B2	124.2 ± 7.4$^{\#\#}$	342.6 ± 9.8$^{\#\#}$	4.40 ± 0.62$^{\#\#}$	4.43 ± 0.83$^{\#\#}$	19.21 ± 2.25$^{\#\#}$

SOD: superoxide dismutase, GSH-Px: glutathione peroxidase, CAT: catalase, MDA: malonaldehyde, BNP: B-type natriuretic peptide; A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.
** $p < .01$, compared with those in sham group.
$^{\#}$ $p < .05$.
$^{\#\#}$ $p < .01$, compared with those in model group.
† $p < .05$.
‡ $p < .01$, compared with those in B2.

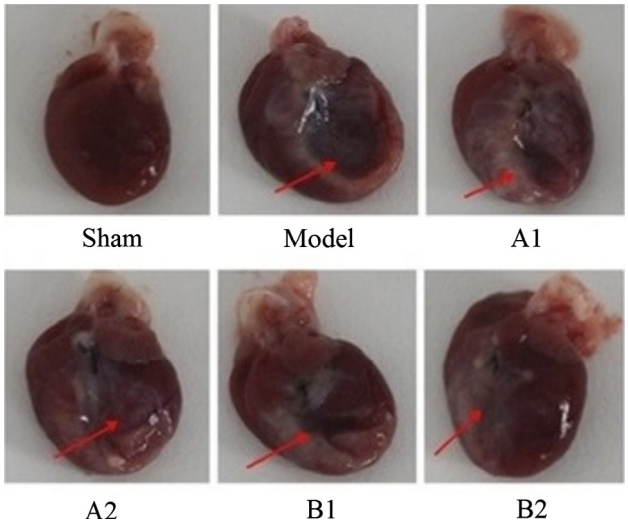

Fig. 1. Effect and difference of suspension and SEDDS of curcuminoids on heart macroscopic morphology in CHF rats (arrows point to infarction region); A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.

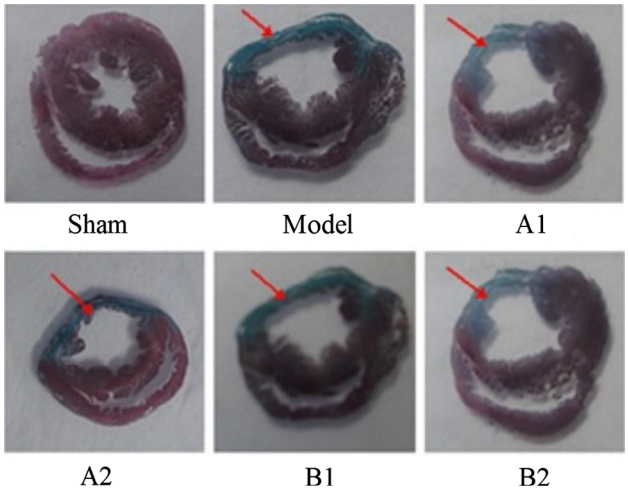

Fig. 2. Effect and difference of suspension and SEDDS of curcuminoids on heart microcosmic morphology in CHF rats (Masson staining, arrows point to infarction region); A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.

sue in model group was observed relative to that in sham group. As shown in Fig. 2, blue collagen fibers (scar tissue) in infarction region of model group was observed relative to that in sham group. After treatment with suspension or SEDDS of curcuminoids, the above-described pathological change was reversed to the condition in sham group. To demonstrate these pathological change more specifically, MIS, LVIL, LVC and LVID were analyzed. As shown in Table 3, the MIS, LVIL, LVC and LVID in model group were significantly ($p < .01$) increased relative to those in sham group. After treatment with suspension or SEDDS of curcuminoids, the MIS, LVIL, LVC and LVID were significantly ($p < .05$ or .01) decreased relative to those in model group. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on MIS was significantly ($p < .05$) better than that of low-dose suspension or SEDDS of curcuminoids. The ameliorative effect of high-dose SEDDS of curcuminoids on LVIL and LVID were significantly ($p < .05$ or .01) better than those of low- or high-dose suspension of curcuminoids and low-dose SEDDS of curcuminoids. The ameliorative effect of high-dose SEDDS of curcuminoids on LVC was significantly ($p < .05$) better than that of low-dose suspension of curcuminoids.

3.5. Effect and difference of suspension and SEDDS of curcuminoids on CVF of myocardial interstitium in CHF rats

As shown in Fig. 3, myocardial cells in model group were yellow and collagen in model group was red relative to those in sham group. After treatment with suspension or SEDDS of curcuminoids, the above-described pathological change was reversed to the condition in sham group. To demonstrate these pathological change more specifically, CVF was analyzed. The CVF in model group (38 .51 ± 1.74%) was significantly ($p < .01$) higher than that in sham group (5.91 ± 0.85%). After treatment with low- or high-dose suspension or SEDDS of curcuminoids, the CVF (29.98 ± 2.29, 27.87 ± 2.15, 27.48 ± 2.26 and 24.34 ± 1.99%) was significantly ($p < .01$) lower than that in model group. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on CVF was significantly ($p < .05$ or .01) better than that of low- or high-dose suspension of curcuminoids and low-dose SEDDS of curcuminoids.

3.6. Effect and difference of suspension and SEDDS of curcuminoids on myocardial histopathology in CHF rats

The myocardial structure was normal in sham group, and no hyperaemia, hemorrhage and inflammatory cell reaction were observed. Meanwhile, the well-arranged myocardial muscle fiber, equilong sarcomere, clear muscle fiber and chromatin in sham group were observed. The myocardial matrix edema, cell volume swelling, thick muscle fibers, and a large number of collagen fibers hyperplasia were observed in myocardial tissue of model group

Table 3
Effect and difference of suspension and SEDDS of curcuminoids on myocardial infarct area and ventricular dilatation degree in CHF rats.

Group	MIS (%)	LVIL (mm)	LVC (mm)	LVID (mm)
Sham	0.00 ± 0.00	0.00 ± 0.00	19.70 ± 2.44	4.92 ± 0.53
Model	37.48 ± 2.43**	10.69 ± 0.78**	31.30 ± 1.90**	9.78 ± 0.81**
A1	31.25 ± 3.03##†	8.27 ± 0.92##‡	27.52 ± 2.15#†	8.49 ± 0.66#‡
A2	28.61 ± 2.02##	7.78 ± 0.49##‡	26.27 ± 2.57##	7.83 ± 0.87##†
B1	29.51 ± 2.08##†	7.62 ± 0.60##†	26.41 ± 1.86##	8.21 ± 0.49##‡
B2	25.58 ± 3.04##	6.75 ± 0.51##	24.11 ± 2.30##	6.69 ± 0.58##

MIS: myocardial infarct size, LVIL: infarct length of left ventricle, LVC: circumference of left ventricle, LVID: inner diameter of left ventricle; A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.
** $p < .01$, compared with those in sham group.
# $p < .05$.
$p < .01$, compared with those in model group.
† $p < .05$.
‡ $p < .01$, compared with those in B2.

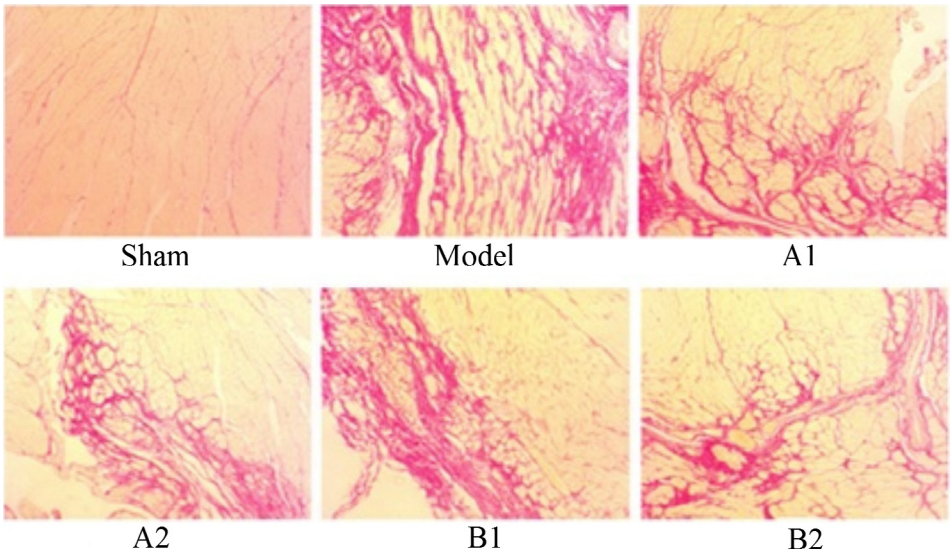

Fig. 3. Effect and difference of suspension and SEDDS of curcuminoids on CVF of myocardial interstitium in CHF rats (picric acid and sirius red staining, magnification ×200); A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.

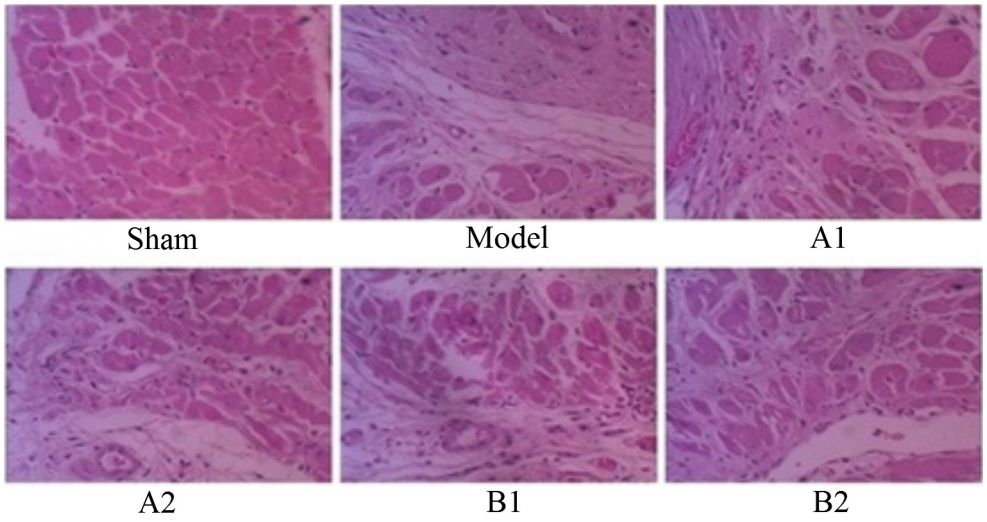

Fig. 4. Effect and difference of suspension and SEDDS of curcuminoids on myocardial histopathology in CHF rats (hematoxylin and eosin staining, magnification ×400); A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.

relative to those in sham group. After treatment with suspension or SEDDS of curcuminoids, the above-mentioned pathological changes were obviously reversed relative to those in model group. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on myocardial histopathology was significantly ($p < .05$ or .01) better than that of low- or high-dose suspension of curcumi-

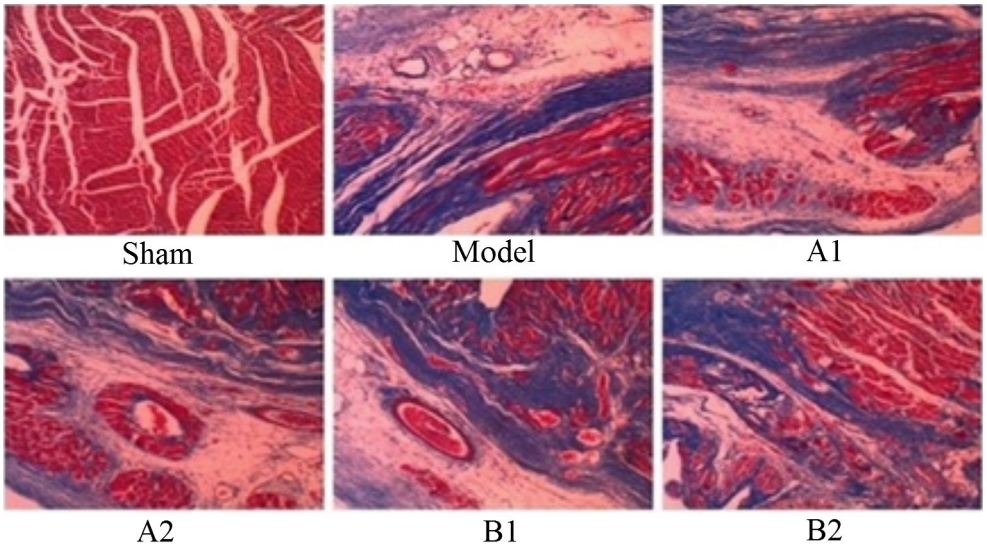

Fig. 5. Effect and difference of suspension and SEDDS of curcuminoids on myocardial histopathology in CHF rats (Masson staining, magnification ×400); A1: low-dose suspension of curcuminoids, A2: high-dose suspension of curcuminoids, B1: low-dose SEDDS of curcuminoids, B2: high-dose SEDDS of curcuminoids.

noids and low-dose SEDDS of curcuminoids. The results are shown in Figs. 4 and 5.

4. Discussion

In this work, the effect and difference of suspension and SEDDS of curcuminoids on CHF in rats were investigated for the first time. The results indicated that the suspension and SEDDS of curcuminoids showed well preventive effect on CHF in rats, and the preventive effect of SEDDS on CHF was better than that of suspension.

Decline of ventricular pump function is the primary cause for occurrence of CHF. Hemodynamic indices, mainly including LVSP, LVEDP, $+dp/dt_{max}$ and $-dp/dt_{max}$, can reflect ventricular pump function (Prinzen and Peschar, 2002). Overmuch reactive oxygen species (ROS) can be found in the heart of patients with CHF and cause myocardial lipid peroxidation (LPO) damage leading to myocardial infarction and reconstruction (Morrissey et al., 2011). MDA, the end product of LPO, can indirectly reflect ROS-induced peroxidation degree of body, and SOD, GSH-Px and CAT can directly reflect antioxidant ability of body. BNP, mainly secreted by left ventricular myocardial cells, shows diuretic, natriuretic and vasodilative effect and inhibits renin-angiotensin-aldosterone system and sympathetic nervous system activities (anti-HF effect) (Dessi Fulgheri and Sarzani, 2003). BNP level is obviously increased in the blood of patients with CHF, and the increased degree is positively related to the severity of CHF (Hans and Mery, 2004). Therefore, BNP level in blood is a sensitive biochemical index used to judge the severity and prognosis of patients with CHF, and therapeutic effect of anti-HF drug.

Coronary artery ligation-induced CHF model belongs to low cardiac output type CHF model, the pathophysiological evolution process of which is close to congestive HF (Zhang et al., 2005). The CHF model can cause myocardial ischemia leading to myocardial infarction, myocardial fibrosis and cardiac enlargement (Ren and Zhang, 2017). Myocardial ischemia can guide heart to provide more power for blood transport, which can lead to myocardial compensatory hypertrophy and myocardial pachynsis (Matsushima et al., 2014).

Reduction of ventricular pump function, increase of BNP level and heart weight index, myocardial LPO damage, myocardial infarction, myocardial fibrosis, and cardiac enlargement were detected or observed in model group relative to those in sham group, indicating that the CHF model in rats was successfully replicated. After treatment with suspension or SEDDS of curcuminoids, the above-mentioned pathological changes were obviously reversed relative to those in model group. Meanwhile, the ameliorative effect of high-dose SEDDS of curcuminoids on the above-mentioned pathological changes were markedly better than those of low- or high-dose suspension of curcuminoids and low-dose SEDDS of curcuminoids.

5. Conclusion

The findings of this work indicated that the suspension or SEDDS of curcuminoids showed good preventive effect on CHF in rats by enhancing ventricular pump function and reducing myocardial LPO damage, infarction, fibrosis and pachynsis. The ameliorative effect of SEDDS of curcuminoids was markedly better than that of suspension of curcuminoids. This work provides a valuable reference from pharmacodynamics for development of curcuminoids pharmaceutics.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

References

Dessi Fulgheri, P., Sarzani, R., 2003. Rappelli a role of the natriuretic peptide system in lipogenesis/lipolysis. Nutr. Metab. Cardiovasc. Dis. 13, 2249.
Gao, J.T., 2017. Experience of Professor Ren Jianhua for treating chronic heart failure with the Huoxue Huayu decoction. Clinic. J. Chin. Med. 9, 41–42.
Hans, K., Mery, B., 2004. B-type natriuretic peptide (BNP) and N-termi-nalpro BNP in patients with end-tage heart failure supported by a left ventricular assist device. Clin. Chem. 50, 1670.
Jiang, H., Ge, J., 2009. Epidemiology and clinical management of cardiomyopathies and heart failure in China. Heart 95, 1727–1731.
Kakkar, V., Singh, S., Singla, D., Kaur, I.P., 2011. Exploring solid lipid nanoparticles to enhance the oral bioavailability of curcumin. Mol. Nutr. Food Res. 55, 495–503.
Ke, X.M., Yang, R.P., Guo, X.X., Zhou, W.J., Chen, X.C., Liang, X.M., Wang, Y.H., 2014. Solubilization of self-emulsifying drug delivery system (SEDDS) for curcumin components. Chin. Tradit. Herb. Drugs 45, 935–941.

Li, N., Wang, J.A., 2005. Brain natriuretic peptide and optimal management of heart failure. J. Zhejiang Univ. Sci. B 6, 877–884.
Li, C., Gao, Y., Tian, J., Shen, J., Xing, Y., Liu, Z., 2011. Sophocarpine administration preserves myocardial function from ischemia-reperfusion in rats via NF-κB inactivation. J. Ethnopharmacol. 135, 620–625.
Li, Y.L., Ju, J.Q., Yang, C.H., Jiang, H.Q., Xu, J.W., Zhang, S.J., 2013. Oral Chinese herbal medicine for improvement of quality of life in patients with chronic heart failure: a systematic review and meta-analysis. Qual. Life Res. 23, 1177–1192.
Liu, H.X., Wang, S.R., Lei, Y., Shang, J.J., 2011. Characteristics and advantages of traditional Chinese medicine in the treatment of acute myocardial infarction. J. Tradit. Chin. Med. 31, 269–272.
Matsushima, S., Tsutsui, H., Sadoshima, J., 2014. Physiological and pathological functions of NADPH oxidases during myocardial ischemia-reperfusion. Trends Cardiovasc. Med. 24, 202–205.
Morimoto, T., Sunagawa, Y., Kawamura, T., Takaya, T., Wada, H., Nagasawa, A., Komeda, M., Fujita, M., Shimatsu, A., Kita, T., Hasegawa, K., 2008. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J. Clin. Invest. 118, 868–878.
Morrissey, R.P., Czer, L., Shah, P.K., 2011. Chronic heart failure: current evidence, challenges to therapy, and future directions. Am. J. Cardiovasc. Drugs 11, 153–171.
Nabavi, S.F., Nabavi, S.M., Ebrahimzadeh, M.A., Eslami, S.H., Jafari, N., Hajizadeh Moghaddam, A., 2011. The protective effect of curcumin against sodium fluoride-induced oxidative stress in rat heart. Arch. Biol. Sci. 63, 563–569.
Prinzen, F.W., Peschar, M., 2002. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin. Electrophysiol. 25, 484–498.
Ren, J., Zhang, Y., 2017. Emerging therapeutic potential targeting genetics and epigentics in heart failure. Biochim. Biophys. Acta. 1863, 1867–1869.
Roger, V.L., 2013. Epidemiology of heart failure. Circ. Res. 113, 646–659.
Stewart, G.C., Givertz, M.M., 2012. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. Circulation 125, 1304–1315.
The National Research Council of The National Academy of Sciencies, 2010. Guide for the Care and Use of Laboratory Animals. The National Academies Press, Washington, D.C..
Wang, Y., Wang, M.Z., 2001. Research progress of common traditional Chinese medicines from Curcuma. Chin. Pharm. J. 36, 80–84.
Wei, N., Yuan, D., He, H.B., Xu, Y.Q., Zhang, C.C., Wang, T., He, Y.M., 2013. Cardioprotective effects of saponins from from Panax japonicas on heart failure in rats induced by ligation of left anterior descending branch. Chin. J. Gerontol. 33, 5877–5881.
Zhang, D.Y., Luo, Y.H., Yang, H., Tan, S., Li, F.Q., 2005. Comparison between experimental models of chronic heart failure established by coronary artery ligature and abdominal aorta constriction. J. Chin. Microcirc. 9, 171–174.