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Original Article

Vitexin prevents myocardial infarction in rats via inhibiting oxidative stress and myocardial apoptosis

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Abstract: *Background:* Myocardial infarction is a disease which seriously threatens people's health and life. Vitexin is one of the main active components of the plant hawthorn, and it has a wide range of pharmacological effects. This study aimed to investigate the protective effects of vitexin on myocardial infarction in rats. *Methods:* Sixty SD rats were randomly divided into sham-operated, model, low-, middle- and high-dose vitexin and glyceryl trinitrate groups. The later 4 groups were intraperitoneally injected with 10, 20 and 40 mg/kg vitexin and 10 ml/kg glyceryl trinitrate, respectively. The treatment was performed for 7 days. After 1 h from the last administration, the rats in the model group, low-, middle- and high-dose vitexin groups and glyceryl trinitrate group received the coronary artery ligation. After 24 h, the hemodynamic indexes, serum biochemical indexes and the myocardial B-cell lymphoma-2 (Bcl-2) and Bcl-2 associated X (Bax) protein expressions were determined. *Results:* Compared with model group, in the high-dose vitexin group the ST segment and T wave elevations were significantly decreased ($P < 0.05$), the heart rate and left ventricular end diastolic pressure were significantly decreased ($P < 0.05$), the left ventricular systolic pressure, $+dp/dt_{max}$ and $-dp/dt_{max}$ were significantly increased ($P < 0.05$), the serum aspartate aminotransferase, creatine phosphokinase and lactate dehydrogenase levels were significantly decreased ($P < 0.05$), the serum superoxide dismutase, catalase and glutathione peroxidase levels were significantly increased ($P < 0.05$), the serum malondialdehyde level was significantly decreased ($P < 0.05$), the myocardial Bcl-2 protein level was significantly increased ($P < 0.05$), and the Bax protein level was significantly decreased ($P < 0.05$). *Conclusion:* Vitexin has protective effects on myocardial infarction in rats. The mechanism may be related to its resistance of oxidative stress, and regulation of Bcl-2 and Bax protein expression in myocardial tissue.

Keywords: Vitexin, myocardial infarction, oxidative stress, Bcl-2, Bax

Introduction

Myocardial infarction is a myocardial ischemic injury and myocardial cell necrosis caused by insufficient supply of coronary blood flow. The formation of myocardial infarction is a complex biochemical, hemodynamic and histopathological process, accompanied by changes in arterial pressure parameters, preload, heart rate, as well as the release of myocardial injury marker enzymes and lipid peroxidation. These changes can cause the increase of reactive oxygen species, such as superoxide anion and hydroxyl radical, which leads to oxidative stress damage, thus damaging the lipid, protein and DNA of myocardial cell membranes [1, 2]. It is found that, the oxidative stress induced by increased reactive oxygen species plays an important role in the process of permanent myocardial ischemic injury and apoptosis [3]. Therefore, treatment with the purpose of anti-oxidation can solve the problem of myocardial injury during myocardial infarction. However, some synthetic antioxidants have various limitations such as toxicity and mutagenicity [4]. Therefore, using natural antioxidants to protect myocardial cells has a broad prospect. Hawthorn is a commonly used Chinese medicinal herb in Asia region, and has a long history of clinical application. Vitexin belongs to flavonoids, and is one of the main active components of hawthorn fruits and leaves [5]. Vitexin has a wide range of pharmacological effects, which are mainly presented in the anti-tumor, anti-oxidation, anti-virus, anti-inflammatory, anti-bacterial and antispasmodic aspects. In addition, vitexin has the function of dilating blood vessels, improving coronary blood supply, protecting the myocardium, inhibiting platelet aggregation and lowering blood lipids [6-9].

This study investigated the protective effects of vitexin on myocardial infarction in rats and explored the related mechanisms. The objective was to provide a basis for further development of vitexin related drugs for prevention of myocardial infarction.

Materials and methods

Animal grouping and treatment

Sixty Wistar rats (230 ± 30 g; Medical Laboratory Shandong Laboratory Animal Center, Jinan, China) were randomly divided into 6 groups: sham-operated group, model group, low-, middle- and high-dose vitexin groups and glyceryl trinitrate group, 10 rats in each group. The rats in the low-, middle- and high-dose vitexin groups were intraperitoneally injected with vitexin (HPLC purity ≥ 98%; Chengdu Mansiter Biotechnology Co., Ltd., Chengdu, China) with dose of 10, 20 and 40 mg/kg, respectively. The rats in glyceryl trinitrate group were intraperitoneally injected with glyceryl trinitrate (Shanxi Kangbao Biological Products Co., Ltd., Changzhi, China) with dose of 10 ml/kg. The rats in the sham-operated and model groups were intraperitoneally injected with normal saline. The administration was performed once per day and was continued for 7 days. After 1 h from the last administration, the rats in the model group, low-, middle- and high-dose vitexin groups and glyceryl trinitrate group received coronary artery ligation. The rats were fixed to the operating table under anesthesia. The thoracic cavity between the left third fourth ribs was opened, and the heart was exposed. The left anterior descending branch of coronary artery was exposed. Except in the sham-operated group, the coronary artery in the other groups was immediately ligated using 0# suture. Then, the heart was sent back to the thoracic cavity. The fluid and gas were squeezed out, and the thoracic cavity was quickly closed. The operation time of thoracic cavity opening was less than 30 s. After the model was successful, the rats were routinely cared for. In the sham-operated group, the rats only received the threading, without coronary artery ligation. During the whole experiment, no rats died.

Test of hemodynamic indexes

After 24 h from coronary artery ligation, the rats were anaesthetized by intraperitoneal injection of 10% chloral hydrate, with a dose of 30 mg/kg. The electrocardiograph electrode needle was subcutaneously embedded in the limbs of the rats, and the normal lead II electrocardiogram was recorded. The changes of ST segment and T wave were observed. The right carotid artery was separated. A polyethylene plastic pipe with 1 mm diameter was inserted into the left ventricle through the left carotid artery to perform the cardiac catheterization and was connected with the biological signal acquisition system. The heart rate (HR), left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP) and maximum left ventricular systolic/diastolic rate ($\pm dp/dt_{max}$) were measured.

Determination of serum biochemical indexes

After hemodynamic test, the abdominal cavity of the rats was opened. The blood was taken from the abdominal aorta. After centrifuging at 2000 r/min for 15 min, the serum was obtained. The serum aspartate aminotransferase (AST), creatine phosphokinas (CPK), lactate dehydrogenase (LDH), superoxide dismutase (SOD) catalase (CAT), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels were determined. The procedures were in accordance to the instructions of kits (Shanghai Sangon Biological Engineering Technology and Service Co., Ltd., Shanghai, China).

Determination of myocardial B-cell lymphoma-2 and Bcl-2 associated X protein expressions

The hearts of the rats were taken. After rinsing with normal saline, about 100 mg heart tissue was taken, and homogenized. The protein was extracted. The expressions levels of B-cell lymphoma-2 (Bcl-2) and Bcl-2 associated X (Bax) protein were determined using western blot assays. β-actin was used as the internal reference. The relative expression level of the target protein was presented by the ratio of integral optical density of target protein to β-actin. The procedures were in accordance to the instructions of kits (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China).

Statistical analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The

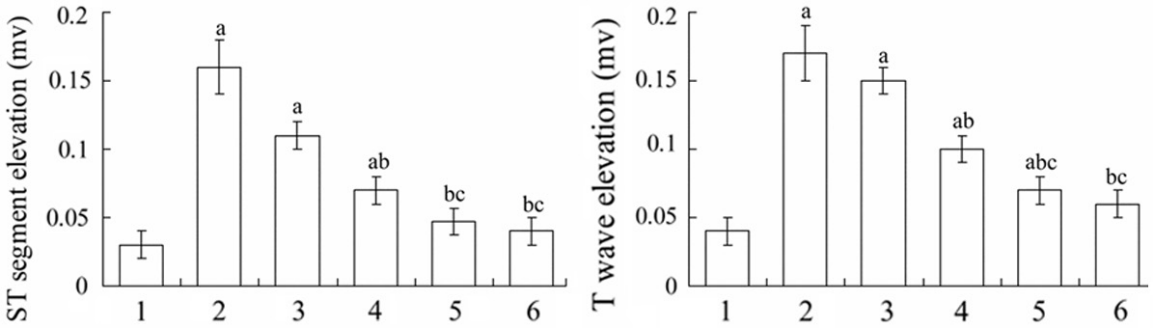

Figure 1. ST segment and T wave elevations in different groups. 1: Sham-operated; 2: Model; 3: Low-dose vitexin; 4: Middle-dose vitexin; 5: High-dose vitexin; 6; Glyceryl trinitrate. [a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group.

Table 1. Hemodynamic indexes in different groups

Group	HR (beats/min)	LVSP (mmHg)	LVEDP (mmHg)	+dp/dt$_{max}$ (mmHg/s)	-dp/dt$_{max}$ (mmHg/s)
Sham-operated	392.45 ± 54.77	143.28 ± 16.22	8.76 ± 2.57	3501.96 ± 502.78	3446.36 ± 567.67
Model	412.72 ± 56.58[a]	111.47 ± 21.63[a]	18.34 ± 3.27[a]	2988.35 ± 345.27[a]	3117.26 ± 356.83[a]
Low-dose vitexin	412.36 ± 67.56[a]	114.27 ± 16.16[a]	16.17 ± 3.38[a]	3034.26 ± 482.36[a]	3134.63 ± 412.84[a]
Middle-dose vitexin	404.26 ± 73.26[b]	119.73 ± 23.62[a]	14.32 ± 2.41[a]	3205.65 ± 409.49[b]	3204.36 ± 444.52[a]
High-dose vitexin	399.63 ± 45.51[b]	129.26 ± 22.37[b]	12.45 ± 3.42[b]	3232.94 ± 501.63[b]	3302.52 ± 513.67[b]
Glyceryl trinitrate	398.36 ± 67.37[b]	133.58 ± 17.82[b,c]	10.21 ± 2.74[b]	3345.04 ± 412.22[b,c]	3349.27 ± 467.33[b,c]

[a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group. HR, hear rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure.

data were presented as mean ± SD. The difference between the two groups was analyzed using one-way analysis of variance with SNK-q test. P < 0.05 was considered as statistically significant.

Results

Vitexin decreased the ST segment and T wave elevations in electrocardiogram in myocardial infarction rats

After 24 h from myocardial infarction modeling, the ST segment and T wave in the electrocardiogram in each group were elevated. Compared with sham-operated group, the ST segment and T wave elevations in the model group were significantly increased (P < 0.05). Compared with model group, the ST segment and T wave elevations in the middle- and high-dose vitexin groups and glyceryl trinitrate group were significantly decreased (P < 0.05) (**Figure 1**).

Vitexin improved the hemodynamic indexes in myocardial infarction rats

As shown in **Table 1**, compared with sham-operated group, in the model group the HR and LVEDP were significantly increased (P < 0.05), and the LVSP, +d*p*/d*t*$_{max}$ and -d*p*/d*t*$_{max}$ were significantly decreased (P < 0.05). Compared with model group, in the high-dose vitexin group and glyceryl trinitrate group the HR and LVEDP were significantly decreased (P < 0.05), and the LVSP, +d*p*/d*t*$_{max}$ and -d*p*/d*t*$_{max}$ were significantly increased (P < 0.05).

Vitexin decreased the serum AST, CPK and LDH levels in myocardial infarction rats

Table 2 showed that, the serum AST, CPK and LDH levels in the model group were significantly higher than those in sham-operated group (P < 0.05). Compared with the model group, the serum AST, CPK and LDH levels in the high-dose vitexin group and glyceryl trinitrate group were significantly decreased (P < 0.05).

Vitexin increased the serum SOD, CAT and GSH-Px levels and decreased the serum MDA level in myocardial infarction rats

The serum SOD, CAT and GSH-Px levels in the model group were significantly lower than those in sham-operated group (P < 0.05), and the serum MDA level in the model group was significantly higher than that in sham-operated group (P < 0.05). Compared with the model group, the

Table 2. Serum myocardial enzyme levels in different groups

Group	AST (U/L)	CPK (U/L)	LDH (U/L)
Sham-operated	282.02 ± 45.25	235.68 ± 53.37	466.37 ± 75.56
Model	361.33 ± 56.44[a]	505.74 ± 64.56[a]	702.73 ± 91.89[a]
Low-dose vitexin	349.46 ± 61.37[a]	486.58 ± 71.33[a]	678.27 ± 90.70[a]
Middle-dose vitexin	322.12 ± 57.30[a]	367.34 ± 65.94[a,b]	604.78 ± 94.42[a]
High-dose vitexin	303.67 ± 62.29[b]	331.21 ± 63.48[a,b,c]	513.12 ± 98.95[b]
Glyceryl trinitrate	292.27 ± 61.44[b,c]	283.26 ± 64.76[a,b,c,d]	471.78 ± 79.87[b,c,d]

[a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group; [d]P < 0.05 compared with middle-dose vitexin group. AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

serum SOD, CAT and GSH-Px levels in the high-dose vitexin group and glyceryl trinitrate group were significantly increased (P < 0.05), and the serum MDA levels in high-dose vitexin group and glyceryl trinitrate group were significantly decreased (P < 0.05) (**Table 3**).

Vitexin increased the myocardial Bcl-2 protein level and decreased the myocardial Bax protein level in myocardial infarction rats

Compared with the sham-operated group, the myocardial Bcl-2 protein expression levels in rats in the model group and low- and middle-dose vitexin groups were significantly decreased (P < 0.05), and the myocardial Bax protein expression levels in the model group and low-dose vitexin group were significantly increased (P < 0.05). Compared with the model group, the myocardial Bcl-2 protein levels in the high-dose vitexin group and glyceryl trinitrate group were significantly increased (P < 0.05), and the myocardial Bax protein levels and middle- and high-dose vitexin groups and glyceryl trinitrate group were significantly decreased (P < 0.05) (**Figures 2** and **3**).

Discussion

The flavonoids extracted from hawthorn fruits and leaves have the effect of lowering blood lipid, lowering blood pressure, increasing coronary artery blood flow, protecting myocardial ischemia and antioxidation [10-12]. Vitexin is one of the flavonoids extracted from the hawthorn fruits and leaves. In this study, rats were pre-treated by intraperitoneal injection with vitexin, and then a myocardial infarction model was established by coronary artery ligation. The protective effects of vitexin on myocardial infarction were investigated. Results showed that, after 24 h from myocardial infarction modeling, compared with sham-operated group, in the model group the ST segment and T wave elevations were significantly increased (P < 0.05), the HR and LVEDP were significantly increased (P < 0.05), and the LVSP, +dp/dt$_{max}$ and -dp/dt$_{max}$ were significantly decreased (P < 0.05). This indicates that, the myocardial infarction model has been successfully constructed. Compared with the model group, in the high-dose vitexin group, the ST segment and T wave elevations were significantly decreased (P < 0.05), the HR and LVEDP were significantly decreased (P < 0.05), and the LVSP, +d*p*/dt_{max} and -d*p*/dt_{max} were significantly increased (P < 0.05). This indicates that, vitexin has obvious protection effects on myocardial infarction model.

Studies have shown that, under normal conditions, the production and clearance of oxygen free radicals is balanced in the body. When myocardial ischemia occurs, it causes the depletion of high-energy phosphate compounds, leading to damage of energy-dependent ion pumps. This causes the mitochondrial calcium overload and a large number of toxic oxygen radicals are produced through different signal transduction pathways. Therefore, the integrity of the granular membrane and myocardial cell membrane is destroyed, which increases the permeability of the myocardial cell membrane and leads to the release of myocardial enzymes [13, 14]. The release of CPK is considered to be one of the most sensitive indicators of myocardial injury. The depletion of CPK in the myocardium can reflect the extent of myocardial ischemia, and the amount of CPK in the blood is positively correlated with the degree of myocardial necrosis [15]. AST widely exists in many organs such as heart, liver and skeletal muscle, and its content is high in cardiac myocytes. The increased AST level in the blood is one of the indexes of myocardial injury [16]. It is found that, the activity of serum LHD is increased in the patients with myocardial infarction, and this is the result of the release of LHD from the damaged cardiac myocytes

Table 3. Serum oxidative stress index in different groups

Group	SOD (U/ml)	CAT (U/ml)	GSH-Px (U/ml)	MDA (mmol/ml)
Sham-operated	244.45 ± 45.68	2.34 ± 0.44	316.65 ± 67.45	5.23 ± 1.46
Model	163.23 ± 36.14[a]	1.05 ± 0.26[a]	217.33 ± 45.62[a]	9.45 ± 2.33[a]
Low-dose vitexin	182.11 ± 33.58[a]	1.34 ± 0.35[a]	223.12 ± 46.83[a]	8.13 ± 2.82[a]
Middle-dose vitexin	195.28 ± 31.12[a]	1.62 ± 0.36[a]	276.34 ± 53.56[a]	7.45 ± 3.17[a]
High-dose vitexin	211.05 ± 45.33[a,b]	2.11 ± 0.46[b,c]	298.89 ± 57.12[b,c]	5.92 ± 3.34[b,c]
Glyceryl trinitrate	226.46 ± 52.67[b,c]	2.25 ± 0.51[b,c,d]	302.56 ± 59.36[b,c]	6.02 ± 2.73[b,c]

[a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group; [d]P < 0.05 compared with middle-dose vitexin group. SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

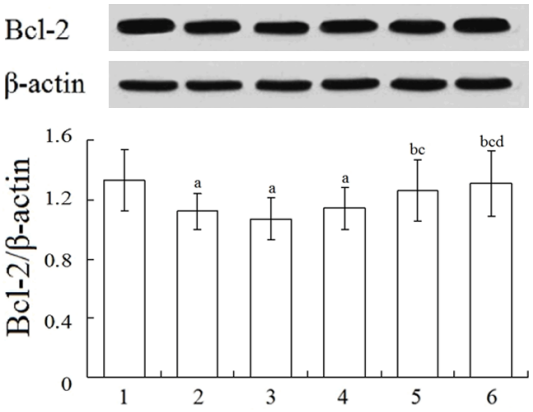

Figure 2. Myocardial Bcl-2 protein expressions in different groups. 1: Sham-operated; 2: Model; 3: Low-dose vitexin; 4: Middle-dose vitexin; 5: High-dose vitexin; 6; Glyceryl trinitrate. [a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group; [d]P < 0.05 compared with middle-dose vitexin group. Bcl-2, B-cell lymphoma-2.

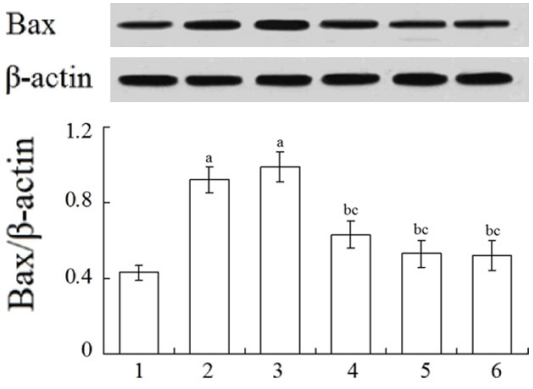

Figure 3. Myocardial Bcl-2 protein expressions in different groups. 1: Sham-operated; 2: Model; 3: Low-dose vitexin; 4: Middle-dose vitexin; 5: High-dose vitexin; 6; Glyceryl trinitrate. [a]P < 0.05 compared with sham-operated group; [b]P < 0.05 compared with model group; [c]P < 0.05 compared with low-dose vitexin group. Bax, B-cell lymphoma-2 associated X.

into the blood [17]. Results of this study showed that, compared with sham-operated group, the serum AST, CPK and LDH levels in the model group were significantly increased (P < 0.05). Compared with the model group, the serum AST, CPK and LDH levels in the high-dose vitexin group were significantly decreased (P < 0.05). This suggests that, the pretreatment with vitexin can prevent the leakage of intracellular AST, CPK and LDH into blood, thus exerting myocardial protection function.

In the process of myocardial infarction, with the production of a large number of free radicals, the activities of endogenous antioxidant enzymes are reduced. This oxidation-anti-oxidation imbalance causes the oxidative stress, leading to the damage of myocardial cells [18]. SOD, CAT and GSH-Px are the common antioxidant enzymes, which are the first line of defense against reactive oxygen species [19]. MDA is the product of lipid peroxidation. Excessive MDA indicates oxidative damage of cell membrane structure. Studies have shown that, there is a significant increase in MDA level during myocardial infarction, suggesting that oxidative damage occurs during the myocardial infarction [20]. In the present study, the serum SOD, CAT and GSH-Px levels in the model group were significantly lower than those in sham-operated group (P < 0.05), and the serum MDA level in model group was significantly higher than that in sham-operated group (P < 0.05). Compared with model group, in high-dose vitexin group the serum SOD, CAT and GSH-Px levels were significantly increased (P < 0.05), and the serum MDA level was significantly decreased (P < 0.05). This indicates that, vitexin can prevent oxidative stress, thus protecting the myocardial injury.

Apoptosis is regulated by many related genes and proteins, among which Bcl-2 and Bax are the most concerned apoptosis-related genes. Bc1-2 can regulate the permeability of mitochondrial membrane and inhibit cell apoptosis by preventing cytochrome C from releasing into the cytoplasm [21]. Bax can directly bind to the mitochondrial membrane, change the permeability of the membrane, cause cytochrome C to release into the cytoplasm, activate the Caspases family, and eventually cause the apoptosis [22]. Results of this study showed that, compared with the sham-operated group, the myocardial Bcl-2 protein expression level in the model group was significantly decreased ($P < 0.05$), and the Bax protein expression level was significantly increased ($P < 0.05$). Compared with the model group, in the high-dose vitexin group the myocardial Bcl-2 protein level was significantly increased ($P < 0.05$), and the Bax protein level was significantly decreased ($P < 0.05$). It is suggested that, vitexin can up-regulate the expression of Bax protein and down-regulate the expression of Bcl-2 protein in myocardial tissue, thus preventing myocardial infarction.

In conclusion, vitexin has protective effects on myocardial infarction in rats. The mechanism may be related to its resistance to oxidative stress, and regulation of Bcl-2 and Bax protein expression in myocardial tissue. This study has provided a theoretical basis for the clinical application of vitexin to prevention of myocardial infarction.

Disclosure of conflict of interest

None.

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