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Original Article

Protective effects of luteolin on vascular endothelial injury in rats with atherosclerosis

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Abstract: *Objective:* The incidence and mortality of atherosclerotic vascular diseases are increasing year by year. The preferred lipid-regulating drugs are statins, which may have potential risk of diseases such as myositis, diabetes, cataract, etc. This study aimed to investigate the protective effects of luteolin on vascular endothelial injury in rats with atherosclerosis. *Methods:* An atherosclerosis model was established in SD rats. Then, the rats were randomly divided into model group and 20, 40 and 80 mg/kg luteolin groups (12 rats in each group), and were intra-gastrically administrated with normal saline, 20, 40 and 80 mg/kg luteolin, respectively. The rats in the control group (12 rats) were fed with normal saline. After treatment for 6 weeks, the hemodynamic indexes, blood indexes, and aortic tissue adhesion factors of rats were determined. *Results:* After treatment, compared with the model group, the serum total cholesterol, triglyceride and low-density lipoprotein levels in 40 and 80 mg/kg luteolin groups were decreased while the serum high-density lipoprotein level was increased. Furthermore, the maximum rate of left ventricular pressure rise (dp/dt_{max}) was increased, and the time from onset of contraction to dp/dt_{max} was decreased. The serum tumor necrosis factor α, interleukin 6 and C-reactive protein levels were decreased and the serum superoxide dismutase and glutathione peroxidase levels were increased. Serum malondialdehyde level was decreased and the serum endothelin level was decreased. Likewise, the serum nitric oxide level was increased and the aortic tissue intercellular cell adhesion molecule 1 and vascular cell adhesion molecule 1 levels were decreased (all $P < 0.05$). *Conclusions:* Luteolin can mitigate the vascular endothelial injury in atherosclerosis rats. The mechanisms may be related to its resistance of inflammatory response and oxidative stress and regulation of expressions of vasoconstriction and vasodilatation factors and aortic tissue adhesion factors.

Keywords: Atherosclerosis, luteolin, inflammatory response, oxidative stress

Introduction

With improvements of economic level and change of life style, the incidence and mortality of atherosclerotic vascular diseases are increasing year by year. The main reason for the development of atherosclerotic vascular diseases is that, the macrophages bind to and devour the denatured low-density lipoprotein (LDL), resulting in intracellular lipid accumulation in the inner wall of blood vessels, which leads to the persistent inflammatory infiltration of the blood vessel wall [1, 2]. At present, the preferred lipid-regulating drugs are statins. These drugs can alleviate atherosclerosis by inhibiting hydroxymethyl glutaric coenzyme A reductase, reducing LDL, improving endothelial cell function, and inhibiting smooth muscle cell proliferation. However, when treating atherosclerosis, these drugs have potential risk of diseases such as myositis [3], diabetes [4], cataract [5], etc. Luteolin (3',4',5,7-tetrahydroxyflavone), a representative component of flavonoids, is found in many natural medicines, such as *Chrysanthemum* [6], *Elsholtzia blanda* [7] and *Flos Lonicerae* [8], vegetables and fruits. Pharmacological studies show that, luteolin can inhibit proliferation of hepatic stellate cells and collagen synthesis [9], and resist the oxidation [10] and inflammation [11]. Luteolin can reduce the blood pressure [12], alleviate myocardial ischemia-reperfusion injury [13], and increase the coronary flow [14]. However, whether luteolin can alleviate the atherosclerotic vascular endothelial injury has not been reported. This study investigated the protective effects of luteolin on vascular endothelial injury in rats with atherosclerosis and explored the related mechanisms.

Materials and methods

Animal grouping and establishment of atherosclerosis model

Sixty-eight healthy male Sprague-Dawley rats (180-200 g) were fed for one week to adapt to the environment. The rats in the control group (12 rats) were fed with basic diet. The atherosclerosis model was established in remaining rats (56 rats). The rats were administered by intraperitoneal injection of vitamin D_3 with a dose of 700 kU/kg, and then were fed with high-fat diet which contained 3% cholesterol, 0.5% sodium collate, 0.2% propylthiouracil, 5% white sugar, 10% lard, and 81.3% basal feed. After 28 days of feeding, 8 rats were randomly sampled to examine the aorta. The appearance of atherosclerotic plaques indicated successful establishment of the atherosclerosis model. The remaining 48 modeled rats were randomly divided into a model group and 20, 40, and 80 mg/kg luteolin groups, with 12 rats in each group.

Administration of rats

After establishment of atherosclerosis model, the rats in 20, 40 and 80 mg/kg luteolin groups were intra-gastrically administrated with 20, 40 and 80 mg/kg luteolin (purity, 98%; Shanghai Ronghe Medical Technology Development Co., Ltd., Shanghai, China), respectively. The rats in the control and model groups were fed with equal volume of normal saline. Administration was performed once a day, for 6 weeks. After administration, the rats in each group were fed with normal diet.

Measurement of hemodynamic indexes

After 6 weeks of continuous administration, the rats were anesthetized, and the right common carotid artery was separated. The left ventricular intubation was performed. The hemodynamic parameters, maximum rate of left ventricular pressure rise (lv +dp/dt_{max}) and time from onset of contraction to dp/dt_{max} (t-dp/dt_{max}) were monitored using bio-signal recording system.

Determination of blood indexes

After anesthesia, the blood was taken from abdominal aorta. The serum cholesterol (TC), triglyceride (TG), LDL and high-density lipoprotein (HDL) levels were measured using automatic biochemical analyzer. The serum levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), C-reactive protein (CRP) and endothelin (ET) were determined by ELISA. The serum nitric oxide (NO) level was detected by nitrate reductase method. The serum superoxide dismutase (SOD) level was measured by xanthine oxidase method. The serum glutathione peroxidase (GSH-Px) level was measured by reduced glutathione depletion method. The serum malondialdehyde (MDA) level was determined by thiobarbituric acid colorimetric assay. The procedures were followed according to the instructions of kits.

Determination of aortic tissue adhesion factors

After anesthesia, the rats were killed, the thoracic cavity was opened, and the part of aorta close to the heart was cut off. Perivascular fat was stripped along the artery, and the arterial blood vessels were isolated. Adipose tissue of the inner aorta wall was scraped off. A homogenate of aortic tissue was prepared. The levels of aortic tissue adhesion factors - intercellular cell adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), were detected by ELISA. The procedures were in accordance to the instructions of kits.

Statistical analysis

Statistical analysis was performed using the SPSS 18.0 software (SPSS, Inc., Chicago, USA), and all results are reported as mean ± standard deviation. One-way analysis of variance was performed to compare among different groups. Statistical significance was considered to be $P < 0.05$.

Results

Blood lipid levels in rats after treatment

After 6 weeks of treatment, compared with control group, the levels of serum TC, TG and LDL-C in the model group were significantly increased ($P < 0.05$), and the level of serum HDL-C in the model group was significantly decreased ($P < 0.05$). In 40 mg/kg and 80 mg/kg luteolin groups the levels of serum TC, TG and LDL-C were significantly decreased ($P < 0.05$), and the level of serum HDL-C was significantly increased ($P < 0.05$), when compare with the model group (**Table 1**).

Table 1. Blood lipid levels in rats after treatment (mmol/L)

Group	TC	TG	LDL	HDL
Control	1.31±0.21	0.71±0.12	1.12±0.24	1.29±0.21
Model	3.22±0.59[a]	1.49±0.23[a]	2.23±0.26[a]	0.53±0.09[a]
20 mg/kg luteolin	3.14±0.44[a]	1.12±0.21[a,b]	2.11±0.23[a]	0.76±0.12[a,b]
40 mg/kg luteolin	2.57±0.37[a,b,c]	0.95±0.18[a,b,c]	1.78±0.31[a,b,c]	0.89±0.18[a,b,c]
80 mg/kg luteolin	1.88±0.32[a,b,c,d]	0.79±0.16[b,c,d]	1.51±0.27[a,b,c,d]	1.21±0.16[b,c,d]

[a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with the model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Hemodynamic indexes in rats after treatment

The hemodynamic indexes in rats after treatment are shown in **Figure 1**. After treatment, the lv +dp/dt_{max} in the model group was obviously lower than that in the control group ($P < 0.05$), and the t-dp/dt_{max} was obviously higher than that in the control group ($P < 0.05$). Compared with the model group, the lv +dp/dt_{max} was obviously increased in 40 mg/kg and 80 mg/kg luteolin groups ($P < 0.05$), and the t-dp/dt_{max} was obviously decreased ($P < 0.05$).

Serum inflammatory factor levels in rats after treatment

After treatment, TNF-α, IL-6, and CRP levels in model group were significantly higher than those in control group, respectively ($P < 0.05$), and those in 20 mg/kg, 40 mg/kg and 80 mg/kg luteolin groups were significantly lower than those in control group, respectively ($P < 0.05$) (**Table 2**).

Serum oxidative stress indexes in rats after treatment

After treatment, when comparing with the control group, the serum SOD and GSH-Px levels in the model group were remarkably decreased (all $P < 0.05$), and the serum MDA level was remarkably increased ($P < 0.05$). When comparing with the model group, the SOD and GSH-Px levels in 40 mg/kg and 80 mg/kg luteolin groups were significantly increased (all $P < 0.05$), and the serum MDA level was significantly decreased ($P < 0.05$) (**Table 3**).

Serum ET and NO levels in rats after treatment

In the model group, serum ET level after treatment was significantly increased, and the serum NO level was significantly decreased, compared with the control group ($P < 0.05$). When comparing with the model group, the serum ET level was significantly decreased in 40 mg/kg and 80 mg/kg luteolin groups ($P < 0.05$), and the serum NO level was significantly increased ($P < 0.05$) (**Figure 2**).

Aortic tissue ICAM-1 and VCAM-1 levels in rats after treatment

As shown in **Figure 3**, after treatment, the aortic tissue ICAM-1 and VCAM-1 levels in the model group were significantly higher than those in the control group (all $P < 0.05$), and those in 20 mg/kg, 40 mg/kg and 80 mg/kg luteolin groups were significantly lower than those in the model group (all $P < 0.05$).

Discussion

This study established an atherosclerosis model of rats and investigated protective effects of luteolin on vascular endothelial injury in rats with atherosclerosis. After 6 weeks of treatment, compared with the control group, the levels of serum TC, TG, and LDL-C in the model group were significantly increased, the level of serum HDL-C was significantly decreased, the lv +dp/dt_{max} was significantly decreased, and the t-dp/dt_{max} was significantly increased. This indicates that, there are obvious lipid metabolism disorders and hemodynamic changes in rats with atherosclerosis. Compared with the model group, the levels of serum TC, TG and LDL-C in 40 and 80 mg/kg luteolin groups were significantly decreased, the level of serum HDL-C was significantly increased, the lv +dp/dt_{max} was significantly increased, and the t-dp/dt_{max} was significantly decreased. This indicates that, luteolin can alleviate the lipid metabolism disorder and hemodynamic changes in atherosclerosis rats.

The formation of atherosclerotic vascular endothelial injury is both an immune response and an inflammatory response process. In this process, the vascular endothelial cells and smooth muscle cells secrete a variety of pro-inflammatory cytokines including TNF-α and IL-6 [15]. TNF-α can induce the inflammation, cell necro-

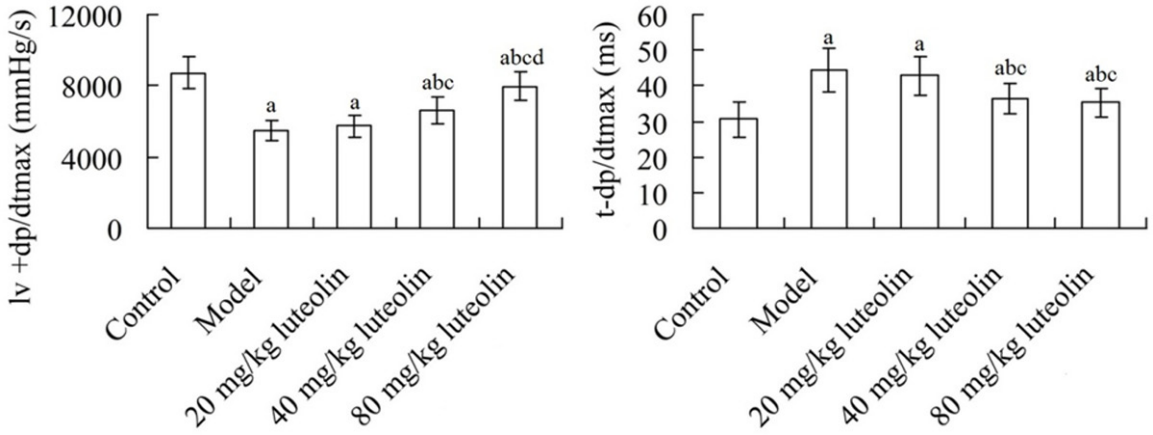

Figure 1. Hemodynamic indexes in rats after treatment. [a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. lv +dp/dt_{max}, maximum rate of left ventricular pressure rise; t-dp/dt_{max}, time from onset of contraction to dp/dt_{max}.

Table 2. Serum inflammatory factor levels in rats after treatment

Group	TNF-α (ng/ml)	IL-6 (pg/ml)	CRP (μg/ml)
Control	0.55±0.11	36.83±4.59	2.38±0.37
Model	1.44±0.22[a]	62.72±7.27[a]	5.84±0.68[a]
20 mg/kg luteolin	1.07±0.21[a,b]	59.73±5.66[a,b]	4.11±0.55[a,b]
40 mg/kg luteolin	0.88±0.13[a,b,c]	50.15±4.48[a,b,c]	3.62±0.31[a,b,c]
80 mg/kg luteolin	0.69±0.12[a,b,c,d]	46.53±6.12[a,b,c]	2.58±0.22[b,c,d]

[a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with the model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. TNF-α, tumor necrosis factor α; IL-6, interleukin 6; CRP, C-reactive protein.

Table 3. Serum oxidative stress indexes in rats after treatment

Group	SOD (U/ml)	GSH-Px (U/ml)	MDA (mmol/ml)
Control	252.52±31.26	56.34±8.22	6.46±1.58
Model	189.75±24.17[a]	33.16±5.31[a]	11.33±2.12[a]
20 mg/kg luteolin	200.37±28.52[a]	34.72±4.78[a]	9.08±1.32[a,b]
40 mg/kg luteolin	228.48±33.82[a,b,c]	41.26±5.25[a,b,c]	8.81±1.27[a,b]
80 mg/kg luteolin	243.28±36.14[b,c,d]	48.61±6.18[a,b,c,d]	7.75±1.05[a,b,c,d]

[a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with the model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

sis and neovascularization, promote the production of endothelin and cause the vascular wall damage [16]. IL-6 can act on a variety of target cells and regulate and induce cell growth, differentiation and expression of some special genes. IL-6 regulates immune function and metabolic process, participates in endothelial cell injury, sub-membrane migration of monocytes and changes in coagulation-promoting properties [17]. CRP is one of the non-specific sensitive markers after infection, inflammation or tissue injury. It is produced by the liver after the body reacts to TNF-α, IL-6 and other inflammatory factors. The level of CRP is related to the severity and prognosis of atherosclerosis [18]. In the present study, after treatment the TNF-α, IL-6 and CRP levels in 20, 40, and 80 mg/kg luteolin groups were significantly decreased, compared with the model group. This indicates that the mechanism of luteolin alleviating atherosclerosis may be related to its resisting inflammatory response in the body.

Oxidative stress refers to the process of oxidative damage caused by the imbalance between the production and elimination of oxygen free radicals in organisms or cells, resulting in the accumulation of reactive oxygen species (ROS). It is also an important pathological mechanism of atherosclerosis. The antioxidant enzymes (SOD, GSH-Px, etc.) play an important role in maintaining ROS balance. The low activity of antioxidant enzymes will lead to the formation of excess ROS, which will cause the oxidative damage [19].

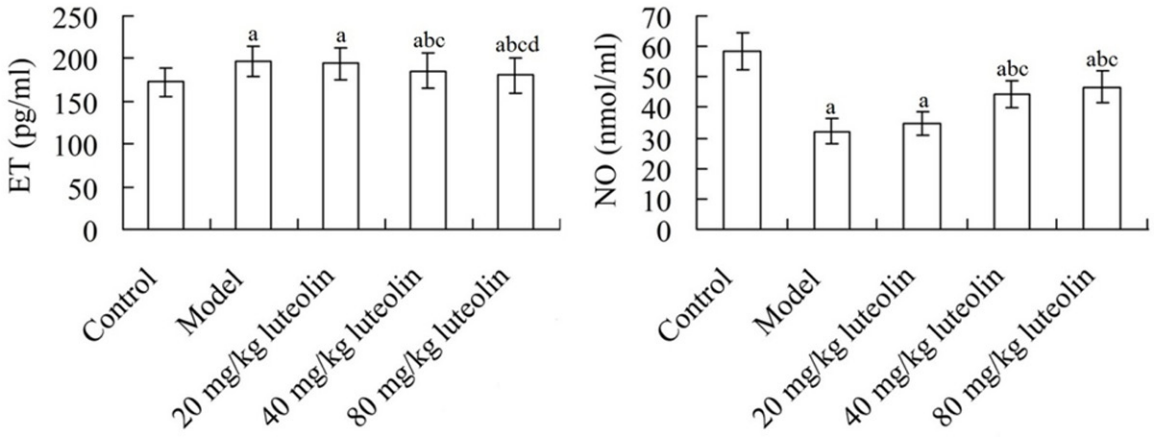

Figure 2. Serum ET and NO levels in rats after treatment. [a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with the model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. ET, endothelin; NO, nitric oxide.

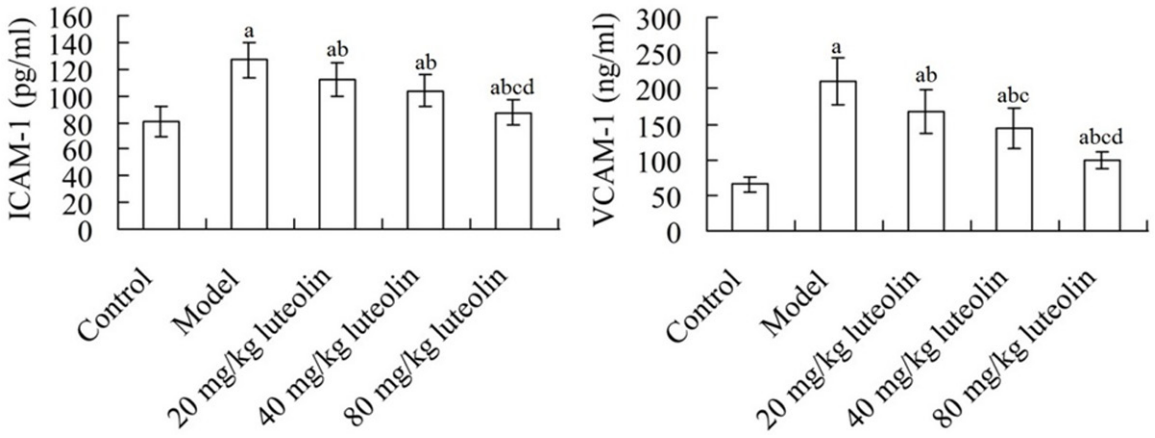

Figure 3. Aortic tissue ICAM-1 and VCAM-1 levels in rats after treatment. [a]$P < 0.05$ compared with the control group; [b]$P < 0.05$ compared with the model group; [c]$P < 0.05$ compared with the 20 mg/kg luteolin group; [d]$P < 0.05$ compared with the 40 mg/kg luteolin group. ICAM-1, intercellular cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1.

MDA is the end product of lipid peroxidation, and its content can indirectly reflect the degree of oxidative stress injury in arteries [20]. In this study, compared the model group, the SOD and GSH-Px levels were significantly increased in 40 and 80 mg/kg luteolin groups, and the serum MDA level was significantly decreased. This suggests that luteolin can inhibit the oxidative stress injury in atherosclerotic rats.

ET and NO are a pair of strong vasoconstriction and vasodilatation factors secreted by vascular endothelial cells. Their abnormal levels or imbalance is related to the damage of vascular endothelial function [21]. In atherosclerosis, the endothelial damage can increase the expression of ET gene, increase its release, and promote the further increase of atherosclerotic plaque [22]. NO has a strong vasodilating effect, and also has the functions of preventing platelet adhesion and aggregation, preventing monocytes chemotaxis to vascular endothelium, and inhibiting smooth muscle cell proliferation. When endothelial cells are damaged, the synthesis of NO is decreased, leading to the vascular diastolic dysfunction and acceleration of atherosclerosis formation [23]. Here, compared the model group, the serum ET level in 40 and 80 mg/kg luteolin groups was significantly decreased, and the serum NO level was significantly increased. This indicates that, the

role of shikonin in protecting vascular endothelium may be related to its down-regulation of ET expression and regulation of NO expression.

ICAM-1 and VCAM-1 are the glycoproteins existing on the cell surface, and belong to the immunoglobulin superfamily. Under normal conditions, ICAM-1 and VCAM-1 are weakly or not expressed on the surface of resting endothelial cells. However, when the cells are activated, ICAM-1 and VCAM-1 participate in T-cell-T cell, T-cell-matrix and killer-target cell interactions through acting with ligands, which is closely related to inflammatory response [24]. It has been found that, ICAM-1 and VCAM-1 are involved in the early pathological changes and plaque progression in atherosclerosis [25]. Results of this study showed that, compared with model group, the aortic tissue ICAM-1 and VCAM-1 levels in 20, 40 and 80 mg/kg luteolin groups were significantly decreased. This indicates that, the protective effects of luteolin on vascular endothelial injury are also related to its down-regulation of ICAM-1 and VCAM-1 expression.

In conclusion, luteolin can mitigate the vascular endothelial injury in atherosclerosis rats. The mechanisms may be related to its resistance of inflammatory response and oxidative stress and regulation of expression of vasoconstriction and vasodilatation factors and aortic tissue adhesion factors.

Acknowledgements

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Disclosure of conflict of interest

None.

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