Relief Effects of Laoshan Cherry extracts as a Dietary Supplement against the Symptoms of Acute Gouty Arthritis in Rats induced by Urate Crystals

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Research Article

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Abstract

We evaluated the effects of Laoshan cherry as a food or dietary supplement on relieving the symptoms of acute gouty arthritis in rats induced by urate crystals. Rats in groups of 10 were given Laoshan cherry functional extracts by oral gavage for 21 days and then injected with a sodium nitrate suspension in the rear leg ankle area as an induced acute gouty arthritis model. The ankle swelling for the model (no treatment) group increased significantly (P□0.05) compared with blank group and experimental groups receiving 3 different doses of cherry extract; the latter displayed significantly less swelling (P□0.05). Additionally, inflammation of rat ankles were also significantly less for the rats receiving the cherry extracts. Serum uric acid and xanthine oxidase activity also elevated in the model group and these parameters were significantly less in the rats receiving the cherry extracts. The serum levels of the inflammatory cytokine IL-1β were significantly (P<0.05) increased for the model group and was decreased significantly (P<0.05) according to cherry extract dose. These results demonstrated that the cherries possess a functional substance that possessed a significant alleviating effect on the symptoms of gouty arthritis in rats induced by sodium urate injection.

Introduction

Gout is an inflammatory disease caused by increased blood uric acid in the human body and deposition of urate crystals in the joints that causes joint swelling and pain. The primary clinical manifestation is recurrent acute gouty arthritis and the patient will experience severe pain during the attack and this seriously affects the quality of life. Previous studies had shown a clear positive correlation between gout and high-purine eating habits [1] especially in coastal areas and has led to significantly higher levels of gout patients in coastal relative to inland areas. Therefore, gout has typical regional characteristics.

The current preventive and therapeutic drugs for acute gouty arthritis are primarily uric acid-lowering drugs and anti-inflammatory and analgesic drugs represented by non-steroidal anti-inflammatories, colchicine and steroid hormones. These drugs have clear targets and therapeutic effects. However, long-term use of these compounds in humans results in drug resistance, endogenous hormone suppression, gastrointestinal irritation, liver and kidney damage and other adverse reactions [2–5].

With the improvement of living standards and the emphasis on healthy life, there is an increasing tendency to find healthy and effective ways to prevent and treat gout by altering the diet. For example, cherry consumption is linked to lower rates of gout attacks or fewer gout symptoms than those who did not supplement with a cherry product diet [6]. The active ingredients in cherries are primarily anthocyanins, melatonin, quercetin and isoquercetin. Anthocyanins are present in the highest quantities and possess significant antioxidant and anti-inflammatory activities and can effectively alleviate gout symptoms [7–9]. Additionally, the pigment substance extracted from cherries displayed a stronger antioxidant activity than vitamin E and possesses a more effective anti-inflammatory activity than aspirin [10]. Therefore, cherries are rich in anthocyanins and have a higher potential for anti-gouty arthritis treatment when used as a

dietary supplement. However, there are few studies that have addressed the application of cherry anthocyanins to gout treatment.

The Laoshan cherry is a special local product of the Laoshan mountain area in Qingdao, China. Cherry trees are highly adaptable, easy to cultivate and manage and have a short fruit development period and are widely distributed in the Laoshan mountains. These plants are also an important component of the greening and ecological balance of the Laoshan mountains. The mountainous regions thereby receive long hours of solar insolation and experience large temperature fluxuations between day and night and this combination gives Laoshan cherries a unique sweet and sour flavor. These cherries mature earlier than other varieties and are known as the "first branch of spring fruit". At the turn of spring and summer when there are fewer fruit varieties, the market value of cherries is higher and this is an incentive for increased production by farmers and is therefore an important economic fruit tree.

In the current study we utilized the Laoshan cherry as the natural material to conduct a preliminary study on the efficacy of Laoshan cherry as in preventing gouty arthritis using a rat model of the disease.

Materials And Methods

1.1.1 Animals

Sprague Dawley rats (male, specific pathogen-free, body weight 180 ± 20 g) were purchased from Daren Fucheng Animal Husbandry (Qingdao, China). All animals were housed in a standard laboratory at a temperature of 25 ± 2°C, a relative humidity of 50–55% and a light/dark cycle of 12 h. All rats were fed standard chow and purified water. Animal experiments and corresponding protocols (QDU-AEC-2022001) had been approved by the Ethics Committee of the Medical Department of Qingdao University. All procedures strictly followed the laws of the People's Republic of China on the use and care of laboratory animals.

1.1.2 Primary reagents

Citric acid, absolute ethanol, sodium urate crystals, physiological saline were obtained from Qingdao Heshun Scientific Instrument Co., Ltd. Commercial kits for the determination of uric acid (UA), xanthine oxidase (XOD), adenosine deaminase (ADA), creatinine (CRE), urea nitrogen (BUN), malondialdehyde (MDA), superoxide dismutase (SOD), ELISA kits for the determination of IL-1β, TNF-α and IL-6 from serum samples were obtained from Nanjing Jiancheng Biotechnology Research Institute.

1.1.3 Primary instruments

JYL-C16V high-speed homogenizer (Mxbaoheng, Ji’nan, China), UV-8000 UV-visible spectrophotometer (EYL Technology, Shanghai, China), SHZ-D (Ⅲ) circulating water multipurpose suction filter (Henan Zhuoxian, Qingdao, China), Xinyi-10 vacuum freeze dryer (Ningbo Xinyi Ultrasonic Equipment Co., Ltd., Ningbo, China), R-1001VN rotary evaporator (Hinotek, Zhengzhou, China)

1.2 Experimental methods

1.2.1 Preparation of cherry anthocyanin extracts

Laoshan cherries were washed, cored and ground into pulp using a homogenizer and 0.5% citric acid: ethanol was added at 1:3 and incubated at 60°C in a water bath for 90 min. The supernatant extract was obtained by filtration and centrifugation to obtain a crude pigment solution. The precipitate was treated in the same way. After filtration, the supernatants were combined and concentrated by rotary evaporation to obtain a cherry anthocyanin extract that was scanned from 380–800 nm intervals of 2 nm to determine the maximum absorption wavelength. The anthocyanin sample solution was obtained by diluting the anthocyanin extract with the citric acid ethanol (see above). The absorbance value was measured at the maximum absorption wavelength and the anthocyanin content was calculated as follows:

$$\mathrm{X} = \frac{A \times MW \times DF \times V \times 100}{\epsilon \times \mathrm{m}}$$

Where X = cherry anthocyanin content (mg/100 g); MW = molecular weight of centaurea 3-glucoside (449.2); DF = dilution ratio; V = total volume of extract (mL);

ε = molar extinction coefficient of cornflow-3-glucoside (26900); M = Mass of raw material (g).

1.2.2 Preparation of sodium urate solution [11]

Under aseptic conditions, 1250 mg of sodium urate crystals were added to 45 mL of physiological saline containing 5 mL Tween 80. The mixture was added and warmed with stirring as appropriate to dissolve the sodium urate crystals.

1.2.3 Experimental grouping and modeling

The SD rats after one week of adaptive feeding were randomly divided into 5 groups of 10 each as follows: blank group, model group, low-dose (2.5 mg/kg) cherry anthocyanin, medium-dose 5 mg/kg) cherry anthocyanin and high-dose (10 mg/kg) cherry anthocyanin experimental groups. The rats received anthocyanin extracts by gavage and the blank and model groups were given the same dose of normal saline. Dosing by gavage was carried out daily for 21 days.

On the 22nd day of the experiment, the rats in the model and 3 experimental groups were treated as previously described [12, 13]. In brief, the outside of right hind ankle joints were used as puncture points and the oblique surface of the needle port facing forward and upward was used to pierce the ankle joint at an angle of 30–40° to the tibia. Then 100 μL of 2.5% sodium urate was injected into the ankle joint with a 6-gauge needle and the bulge on the opposite side of the ankle joint capsule was used as the success criterion to induce the rat model of acute gouty arthritis. The blank group was injected with the same dose of normal saline (Table 1).

Table 1
Rat groupings and treatments

Grouping	Quantity	Processing method	
		Gavage treatment	Modeling treatment
Blank	10	Normal saline	Sterile saline
Model	10	Normal saline	2.5% sodium urate suspension
High dose	10	10mg/kg cherry extract	2.5% sodium urate suspension
Medium dose	10	5mg/kg cherry extract	2.5% sodium urate suspension
Low dose	10	2.5mg/kg cherry extract	2.5% sodium urate suspension

1.2.4 Measurement of ankle swelling

The circumference of the ankle joint of the right hind limb was measured at 1, 2, 4, 6, 8, 10, 12 and 24 h before and after the injection of sodium urate or normal saline for each rat. The increase in the circumference of the ankle joint of the rat and the joint swelling index at each time point was calculated with the following formula: Joint swelling degree= (perimeter diameter after modeling - perimeter diameter before modeling) / perimeter diameter before modeling ×100%.

1.2.5 Inflammation grade

Twenty-four hours after the rat gouty arthritis was modeled by sodium urate injections, ankle joint inflammation was observed and graded as previously described [14]. In brief; (0) normal, 0 points; (I) erythema on the skin of the joints, mild swelling of the joints but visible bony landmarks, 1 point; (II) significant redness and swelling of the joint, disappearance of bony landmarks but swelling limited to the joint, 2 points; (III) swelling of limbs other than joints, 3 points.

1.2.6 Spleen and kidney index

After the rats were sacrificed, the spleens and kidneys were stripped and weighed. Spleen/kidney index = spleen/kidney mass (g)/body mass×100%.

1.2.7 Serum related indicators

Commercial kits for UA, XOD, ADA, CRE, BUN, MDA, SOD and commercial ELISA kits for detection of serum levels of IL-1β, TNF-α and IL-6 were used following the directions of the manufacturers.

1.2.8 Statistical processing

The experimental data was processed by SPSS 18.0 statistical software (IBM, Chicago, Ill, USA) and the experimental data was expressed as mean ± standard deviation (SD). For the comparison of means

between groups, the F test was first used to investigate the homogeneity of variance. If the variances were uniform, ANOVA analysis of variance was used to compare the means between groups.

Results And Analysis

2.1 Modeling procedure

The right ankle joint of blank group rats that received control injections displayed slender limbs and clearly visible bones (Fig. 1a). In contrast, the gout model rats injection with the sodium urate suspensions presented with redness and swelling of the ankle joint and limb (Fig. 1b). These results indicated that this method of modeling acute gouty arthritis was successful. The body weights of the rats for all 5 groups were not significantly altered by these treatments (Table 2).

Table 2
Rat body weight alterations (n = 10)

Group	7d	14d	21d
Blank	295.6 ± 23.7†	304.2 ± 28.3	313.4 ± 31.1
Model	299.2 ± 15.0	313.4 ± 20.2	325.4 ± 32.5
High dose	288.0 ± 22.8	306.0 ± 29.5	321.6 ± 38.4
Medium dose	296.8 ± 12.4	316.6 ± 13.8	329.2 ± 17.4
Low dose	290.6 ± 20.1	304.6 ± 23.2	320.8 ± 27.7
† Mean ± SD (g)			

2.2 Ankle swelling model

Following 24 h of modeling, ankle joints for the rats significantly ($P < 0.05$) differed between the experimental and blank groups (Fig. 2). The ankle swelling for the model and experimental groups peaked at 4–6 h and the degrees of swelling differed significantly from blank group. By hour 24 swelling for experimental group members was reduced compared with the model group. The order of severity of ankle swelling could be ranked as model > low-dose > middle-dose > high-dose group. At

24 h the high and medium dose groups had similar levels of relief from ankle swelling (Table 3). These results indicated that the cherry anthocyanin extracts could relieve the swelling of gouty arthritis in rats and this effect was positively correlated with the dose.

Table 3
Rat ankle swelling (n = 10)

Group	Swelling degree (%)						
	1h	2h	4h	6h	8h	12h	24h
Blank	0†	0	0	0	0	0	0
Model	19.85 ± 6.21$^{\#\#}$	22.73 ± 3.63$^{\#\#}$	31.97 ± 11.26$^{\#\#}$	35.45 ± 10.8$^{\#\#}$	33.64 ± 5.19$^{\#\#}$	38.22 ± 11.34$^{\#\#}$	35.05 ± 8.99$^{\#\#}$
High dose	14.04 ± 4.61	15.04 ± 3.73**	19.38 ± 4.06*	24.77 ± 4.53*	19.38 ± 8.32**	19.43 ± 7.18**	20.11 ± 7.34**
Medium dose	16.64 ± 7.72	18.31 ± 9.66**	26.51 ± 7.12*	26.51 ± 7.03*	24.28 ± 6.19**	22.66 ± 6.71**	20.48 ± 8.53**
Low dose	22.21 ± 10.33	22.04 ± 6.30	25.52 ± 13.91	30.69 ± 7.89	21.34 ± 9.96*	29.60 ± 6.21	25.43 ± 6.29

† Mean ± SD (%) Compared with the blank group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; compared with the model group, $^{*}P < 0.05$, $^{**}P < 0.01$.

2.4 Ankle inflammation grading

During these experiments we found significant differences in the grades of ankle joint inflammation for each group of rats. We therefore graded the inflammation using a verification index score using the 10 in the blank group as a control (0 points). The model group contained 6 rats with scores of 3 points and 4 with 2 points. This indicated a general elevated degree of inflammation compared with the blank group indicating that the modeling was successful. In the high-dose group there were 7 rats with scores of 2 and 3 with score of 1 point. The middle-dose group included 4 rats with 3 points and 4 with scores of 2 points with the remainder at 1 point. In the low-dose experimental group, there were also 4 rats at 3 points, 4 at 2 points with the remainder at 1 point. Compared with the model group, the inflammatory grading indices for the experimental groups were significantly lower (Table 4). These results were consistent with those of the ankle swelling model and together indicated that the anthocyanin extract of the Laoshan cherry could alleviate the inflammation of gouty arthritis in rats.

Table 4. Comparisons of degree of rat ankle joint inflammation

Group \ Inflammation grade	0 point	1 point	2 points	3 points
Blank	10	0	0	0
Model	0	0	4	6
High dose	0	3	7	0
Medium dose	0	2	4	4
Low dose	0	2	4	4

2.5 Uric acid levels and XOD activity

Serum uric acid and XOD activities have been liked to gout disease severity [15]. Both uric acid levels and XOD activity for the model group were significantly increased compared with blank group. In contrast, both these parameters for the experimental groups were significantly lower than those of the model group. These results could be ranked as low > medium > high dose for both XOD activity and uric acid levels (Table 5). XOD can catalyze hypoxanthine conversion to xanthine to generate uric acid as well as directly converting xanthine to uric acid. Therefore, XOD activity can both directly and indirectly affect uric acid levels. We found that both parameters were significantly positively correlated with the cherry extract dosage indicating a positive effect at reducing disease severity in the rat model. These results were also positively correlated with the ankle swelling results (see Figs. 3 and 4).

Table 5
Rat serum uric acid levels and XOD activity (n = 10)

Group	Uric acid (μmol/L)	XOD activity (U/mL)
Blank	45.07 ± 5.10†	0.12 ± 0.06
Model	66.70 ± 6.13	0.24 ± 0.11
High dose	61.29 ± 2.73	0.16 ± 0.05
Medium dose	64.27 ± 2.14	0.20 ± 0.04
Low dose	64.57 ± 2.10	0.20 ± 0.06
† Mean ± SD (%)		

2.6 Serum inflammatory factors

If our rat model reflected gouty arthritis then the levels of pro-inflammatory cytokines should also differ between the model and blank groups. We found significant ($P < 0.05$) elevations in serum levels of IL-1β

for the model rat group compared with blank group. In contrast, there were no significant (P > 0.05) differences in the levels of IL-6 and TNF-α (Table 6). The presence of urate crystals have been shown to stimulate macrophages to produce and release IL-1β [16] and most likely TNF-α as well. In our experiments, IL-1β levels for the model group were significantly higher than for the blank group and these correlated with the degree of inflammation noted above. Interestingly, IL-1β for the experimental group were reduced to varying degrees according to dose level (Fig. 5). These results indicated that Laoshan cherry extracts could reduce IL-1β levels in the gouty arthritis rat model thereby relieving the inflammatory symptoms.

Table 6
Serum levels of inflammatory factors in rats (n = 10)

Group	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α(pg/mL)
Blank	14.96 ± 1.92†	16.91 ± 1.11	86.56 ± 7.43
Model	17.84 ± 0.94	18.24 ± 0.94	93.31 ± 6.07
High	15.71 ± 3.63	17.69 ± 0.70	86.44 ± 10.29
Medium	17.20 ± 4.74	17.85 ± 0.53	89.13 ± 9.68
Low dose	17.41 ± 2.86	19.06 ± 0.95	97.19 ± 8.25
† Mean ± SD (%)			

2.7 Spleen and kidney indices

We next compared spleen and kidney indices in our test groups to determine whether our model reflected an overall deterioration caused by the local injection of the uric acid. We could find no obvious differences between the model and experimental groups (P > 0.05) indicating no spleen and kidney injury had occurred due to our procedures (Table 7).

Table 7
Rat Spleen and Kidney Index(n = 10)

Group	Spleen index	Kidney index
Blank	0.19 ± 0.03†	0.70 ± 0.04
Model	0.19 ± 0.01	0.68 ± 0.03
High dose	0.21 ± 0.04	0.64 ± 0.01
Medium dose	0.21 ± 0.01	0.66 ± 0.03
Low dose	0.19 ± 0.02	0.62 ± 0.06
† Mean ± SD (%)		

2.8 CRE, BUN, ADA, MDA and SOD levels in rat serum

To augment the overall spleen and kidney indices we also measured common indicators of physiological damage including serum ADA, CRE, BUN, MDA and SOD. The ADA activity is a sensitive index reflecting liver injury and CRE and BUN are indicators of glomerular filtration functions. We found no significant differences for these values between each group indicating the lack of spleen and kidney injury (Table 8). These values also correlated with the spleen and kidney index grading.

MDA levels and SOD activity can indirectly reflect the ability of the body to scavenge free radicals. However, we found no significant differences for MDA and SOD in each group (Table 8). This indicated that our rat model did not impose a general oxidative stress on the rats.

Table 8
Serum CRE, BUN, MDA, ADA levels and SOD activity in rats (n = 10)

Group	ADA (ng/mL)	CRE(μmol/L)	BUN (mg/dL)	MDA (nmol/mL)	SOD (U/mL)
Blank	1.09 ± 0.13†	43.52 ± 22.52	16.10 ± 0.95	5.27 ± 1.44	955.15 ± 31.81
Model	1.10 ± 0.11	46.66 ± 10.64	17.67 ± 2.27	6.49 ± 2.42	991.42 ± 74.94
High dose	1.05 ± 0.08	41.38 ± 6.00	16.26 ± 1.69	7.50 ± 1.04	1020.76 ± 62.15
Medium dose	1.10 ± 0.05	45.77 ± 15.22	21.18 ± 2.47	6.55 ± 0.33	993.87 ± 123.59
Low dose	1.24 ± 0.11	43.02 ± 8.74	17.41 ± 2.10	6.08 ± 0.51	1019.54 ± 71.47
† Mean ± SD (%)					

Discussion

The pathogenesis of acute gouty arthritis is primarily due to the increase of uric acid in the blood and urate crystals are deposited in joints and soft tissues after excessive precipitation. These crystals can then induce chemotactic aggregation of leukocytes. White blood cells are recognized by pattern recognition receptors as endogenous risk signals and activate downstream immune inflammatory signaling pathways. This process then activates inflammation related cells to produce inflammatory factors ultimately leading to the acute inflammatory attacks seen in gout [17, 18]. Gouty arthritis is directly related to hyperuricemia [19] and when the serum uric acid levels increase, the metabolic enzymes related to uric acid production such as serum XOD may become abnormally active. Therefore, we established the gouty arthritis model by directly injecting sodium urate suspension into the rat ankle joints. We then could determine whether Laoshan cherry extracts provided relief from gouty arthritis in rats.

We found that all 3 dose levels of cherry extracts could relieve the symptoms of acute gouty arthritis in SD rats induced by sodium urate and these treatments significantly reduced the levels of serum uric acid, IL-1β and XOD activity. This demonstrated that the functional substances in Laoshan cherry had an anti-

inflammatory effect and could alleviate symptoms of acute gouty arthritis. In contrast, IL-6 and TNF-α in the model group were higher than those in the blank group although these differences were not statistically significant and these results differed from a previous study of Rongmei Yao et al [20]. This may be due to the difference in our method of modeling acute gouty arthritis. Rongmei Yao modeled gout model of hyperuricemia, but this study adopted the method of direct injection of sodium urate. Our model simulated the symptoms of clinical joint gout and better reflected the local joint disease *in vivo*. The Laoshan cherry extracts could effectively inhibit the acute gouty joint inflammation in rats by reducing the level of IL-1β independent of IL-6 and TNF-α.

Previous studies involving the biological activities of cherries were primarily focused on the extraction and analysis of their biologically active ingredients [21–23]. Our study used Laoshan cherry as the natural material to evaluate the functional effects of cherries and in particular anthocyanins. We did not carry our extensive extract purifications for the following reasons: (1) We wanted to study the effects of the fruit itself from the perspective of a nutritional food that differed from traditional anti-gout drugs (2) The specific active anti-gout compunds have not been thoroughly investigated. The high anthocyanin content might act alone or in concert with other components (3) Our model can now be applied to individual cherry components.

From a food safety perspective, the material used in this study such as citric acid are non-toxic and harmless and possess the added advantages of stability and mildness [24]. All our components were suitable for long-term and safe animal and human consumption. Our future studies will optimize cherry extraction processes and examine their anti-gout properties using the rat model. We also will examine suitable formulations to improve the stability of the extract and screen preparations for trial production from the aspects of quality and safety, effective content and shelf life. It is necessary to develop a mature and complete preparation process of a nutritious food using the cherry as the raw material. The expected result would solve the seasonal limits of cherries to meet the long-term needs of gout patients and form an effective complement to gout medications. This work also contributes to the development of an effective and complete experimental method for improving acute gouty arthritis from the aspect of a functional food.

Declarations

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Availability of data and material

All data generated or analysed during this study are included in this published article.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Daqing Sun, Xiaoxiao Xu and Pei Liu. The first draft of the manuscript was written by Jiamin Guo and Haixin Sun. And all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Animal experiments and corresponding protocols (QDU-AEC-2022001) had been approved by the Ethics Committee of the Medical Department of Qingdao University. All procedures strictly followed the laws of the People's Republic of China on the use and care of laboratory animals.

Consent to participate

Not applicable (no human subjects were involved in this study).

Consent to publish

Not applicable (no human subjects were involved in this study).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figures

Figure 1

Comparison of rats before and 12 hours after modeling(a) blank group rats (b) rats receiving sodium urate injections

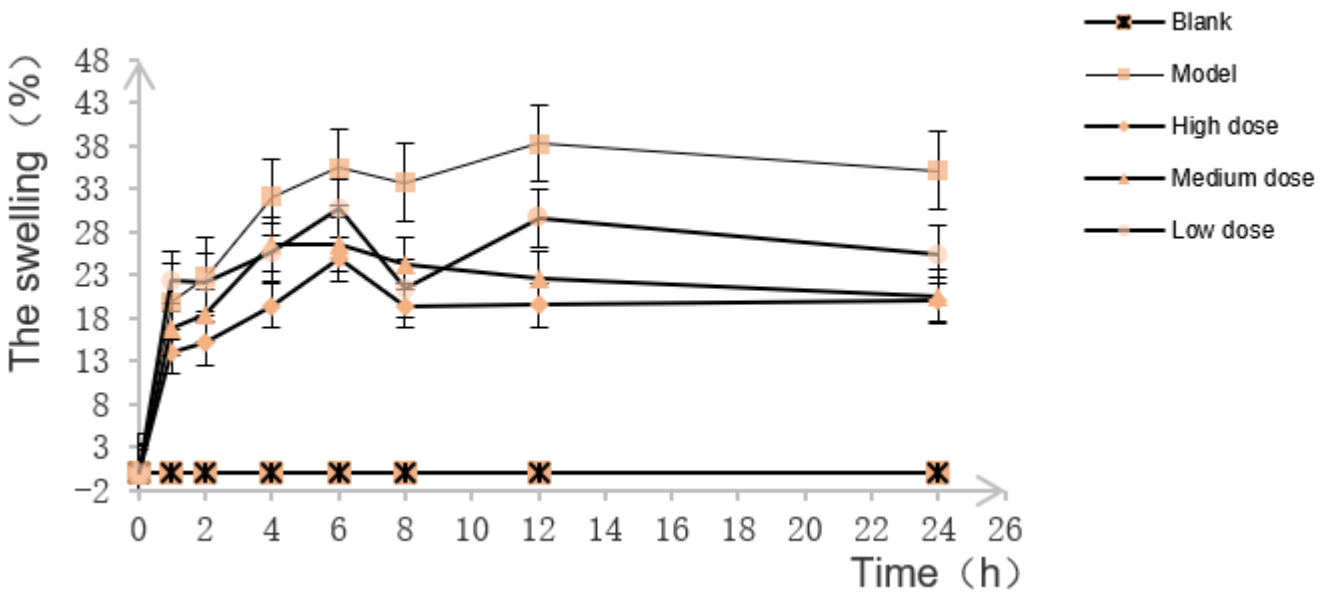

Figure 2

Examples of rat ankle swelling

Figure 3

Comparison of uric acid levels in rats. [a]P□0.05 compared with the blank group, [b]P□0.05 compared with the model group.

Figure 4

Comparison of XOD activity in rats. [a]P□0.05 compared with the blank group, [b]P□0.05 compared with the model group.

Figure 5

Comparison of IL-1β levels in rats. [a]P□0.05 compared with the blank group, [b]P□0.05, compared with the model group.