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Salidroside improves skeletal muscle dysfunction in COPD rats by down regulating SIRT1 signaling pathway

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Abstract

Objective: To investigate the effect of salidroside at different doses on skeletal muscle function and SIRT1\ MuRF-1 \ Atrogin-1 expression in COPD rats .

Methods: Forty adult SD rats were divided into 5 groups with 8 rats in each group: blank group (C), COPD model + placebo group (CS), COPD model + low-dose salidroside group (CS + L), COPD model + medium-dose salidroside group (CS + M), COPD model + high-dose salidroside group (CS + H). Each group was taken to be a simple passive smoking hair model smoking rats, the blank group was established to take pseudo-exposed control group model. Group C and CS were given a placebo (normal saline) for 1 month. The CS + L group , CS + M group , and CS + H group were given low dose (5mg / 100g), medium dose (25mg / 100g), High-dose (125mg / 100g) salidroside was administered by gavage for 1 month. Record changes in body weight, use the exhaustive swimming test to evaluate exercise capacity, collect serum, lung tissue, quadriceps, weigh skeletal muscle, and determine the type I fiber ratio of skeletal muscle samples, SIRT1, P-SIRT1, MuRF-1, Atrogin-1 expression level.

Results: (1) Weight comparison: The weight of rats in the C group was higher than that in the CS group, and the statistical difference was considered significant at p<0.05. The weights of the CS + L group, CS + M group, and CS + H group were compared with the CS group and there was an increase in body weight. The statistical differences between the values in each group were considered significant at P <0.05.

(2) Comparison of exhaustive swimming time: Rats in the exhaustive swimming group were longer in the C group than in the CS group, and the statistical difference was considered significant at P <0.05; compared with the CS group in the CS + L group, CS + M group, and CS + H group, Exhaustive swimming time was prolonged, and the statistical differences between the values in each group were considered significant (P <0.05) .(3) Comparison of quadriceps femoris weights: Rat quadriceps femoris weights in the CS group were reduced compared to the C group, and the statistical difference was considered significant at p<0.05; the CS + L group , CS + M group, CS + H group and Compared with the CS group, the quadriceps muscle weight increased, and the statistical differences between the values in each group were considered significant at P <0.05. (4) Type I muscle fiber ratio comparison: Rat type I muscle fiber ratio CS group compared with C group decreased statistically significant (P <0.05); CS + L group, CS + M group, CS + H group and CS group By comparison, the proportion of type I muscle fibers increased, and the statistical differences between the values in each group were considered significant at P <0.05. (5) rats SIRTl , P-SIRTl , MuRF-. 1 , of Atrogin. 1- protein comparison : the CS group and C compare SIRTl, increased P-SIRT, MuRF-1 expression levels, statisical differences were considered to be significant at p < 0.05; compared with the CS group, the expression levels of SIRT1, P-SIRT, MuRF-1, and Atrogin-1 in the CS + L group, CS + M

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group, and CS + H group decreased, and the effect level was positively correlated with the intervention dose The statistical differences were considered to be significant at $p < 0.05$).
Conclusion: Salidroside can improve the skeletal muscle function of COPD model rats by reducing the expression of SIRT1 \ MuRF-1 \ Atrogin-1 .
Key words: COPD; skeletal muscle dysfunction; SIRT 1 ; salidroside

Introduction

COPD is a multifactorial participation, multi-link interaction chronic systemic diseases, the pathogenesis involves multiple mechanisms , including pulmonary parenchyma and pulmonary vascular inflammatory cell infiltration in lung tissue and protease antiprotease imbalance , increased oxidative stress, and Wait. Wherein the oxidative stress is of COPD, the core of the development mechanisms, oxidative stress (Oxidative St RESS , the OS) through to the interaction with other mechanisms of airway inflammation, and ultimately destruction of the lung architecture and systemic inflammation [1 , 2] .

COPD patients were exposed to repeated infections that raised the level of inflammatory factors throughout the body, increased oxidative stress, damaged DNA and protein, and reduced protein, resulting in skeletal muscle atrophy [3].

Rhodiola is the general name of Rhodiola rosea, a perennial herb or subshrub plant. The main active ingredient of rhodiola is Rhodiolaside. Recent studies have found that rhodiolaside can reduce oxygen free radicals and repair antioxidant levels. effects [4 , 5] .

SIRT (fork head transcription facto r protein - O) is a class of highly conserved transcription factors in various types of cells. SIRT 1, SIRT 3, SIRT 4, and SIRT 6 have been found . They regulate signaling pathways through transcription. It is important in animal growth and development, metabolism and cell cycle [6-8] . In skeletal muscle, on the one hand, oxidative imbalances promote SIRT expression, increase antioxidant enzyme expression, and promote oxygen radical scavenging ; on the other hand , increased expression of SIRT1 and SIRT3 can promote protein degradation , manage skeletal muscle fiber differentiation and affect mitochondrial function Impairs the growth and differentiation of endothelial cells [9, 10] . Elevated expression of SIRT1 can increase the expression of E3 ubiquitin proteasome MurF-1 and Atrogin-1, promote the degradation of skeletal muscle structural proteins and cause skeletal muscle atrophy and dysfunction [11- 14] .

We assume Salidroside reduce oxidative stress can reduce the SIRT1 expression, reducing its downstream pathway protein MurF-1, Atrogin-1 expression, decreased bone degradation iliac muscle structural proteins , thereby improving COPD model rat skeletal muscle function Obstacles .

Animal

A total of 40 7-week-old male SPF-grade SD rats were provided by Slaker Jingda Laboratory Animal Company of Hunan Province. The production license number is SCXK (Xiang) 2013-0003, and the license number is SYXK (Xiang) 2011. -0003.

Material

GAPDH antibody , SIRT1 antibody, and p- SIRT1 antibody were purchased from Wuhan Boshide Biological Company. 98% of Rhodiolaside was purchased from Nanjing Jingzhu Pharmaceutical Co., Ltd. Furong cigarettes were purchased from Changsha Cigarette Factory. Protease inhibitors and protein phosphatase inhibitors were purchased from Roche, Switzerland. Acrylamide, bisacrylamide, glycine, and Ponceau were purchased from Sigma, USA. The IX - 71 fluorescence microscope was purchased from Olympus Japan. XD -30 inverted biological microscope was purchased from Ningbo Shunyu Company. The TDL- 5 DB low-speed automatic balance centrifuge was purchased from Hunan Xingke Company. TGL -16 W desktop high-speed refrigerated centrifuge was purchased from Hunan Xianglu Company. The LICARM - 2145 slicer was purchased from Lycra, Germany. The MDF- 382 E ultra-low temperature refrigerator was purchased from Japan's Sanyo Corporation. DTY -5 A super-smart thermostat circulator purchased from Beijing de-day company.

Animal grouping

The number of rats, were randomly divided into 5 groups with 8 rats in each group: control group (C), of COPD model plus placebo group (C S), of COPD model salidroside + low dose group (the CS + L) , COPD model + medium-dose salidroside group (CS + M), COPD model + high-dose salidroside group (CS + H). Record weight changes by number .

COPD model establishment

The smoking group used pure passive smoking to establish a smoking rat model [15] . The rats were smoked in a self-made 72L poisoning box for 4

months. The cigarettes were smoked daily with 14 Hibiscus cigarettes each time, twice a day, with an interval of more than 4 hours. The control group adopted a pseudo-exposure method to establish a model for the blank group. Four months later, 5 rats were anesthetized intraperitoneally with 10% chloral hydrate (3ml / 100g). After disinfection, thoracotomy was performed and blood was drawn from the abdominal aorta to death. Within 15 minutes, the free quadriceps muscle was frozen in tissue tube liquid nitrogen, and the lung tissue was fixed with 4% paraformaldehyde. Evaluate whether the model is established. The smoking components were then divided into four groups, each group with 8 rats was given placebo (normal saline), and low, medium and high doses of Rhodiola rosea were administered by gavage. Once a day for 30 days.

Drug intervention

The passive smoking model rats were divided into 4 groups, of which 3 groups were given 5 mg / ml (COPD model + low dose group), 25 mg / ml (COPD model + middle dose group), 125 mg / ml (COPD model + high dose) Group) Salidroside at a concentration of 1ml / 100g was administered orally twice a day; the group was a control group, and an equal amount of saline 1ml / 100g was administered orally twice a day. The COPD model + placebo group and the blank group were perfused with saline 1ml / 100g twice a day. Lasts 1 month.

Swimming test

Prepare a bucket with a diameter of 80cm and a height of 80cm. Add warm water at a temperature of 25-28 ℃ to a depth greater than 30cm. Put the rats into the water tank to swim, observe and record the time from when the rats enter the water to the time they cannot sink to the surface for 10 seconds (in the exhausted state). This weight-bearing swimming time is regarded as an index for quantitatively and objectively evaluating the degree of fatigue. The longer the weight-bearing swimming time, the better the anti-fatigue effect.

Blood samples specimens

The rats were anesthetized and fixed on a clean operating table. The abdominal hair was cleaned with alcohol, the skin on both sides of the abdomen was lifted with hemostats, the skin was cut with a rough cut, and then the abdominal muscles were cut under the xiphoid with a tissue shear (note to avoid The intestine can avoid contamination of the abdominal cavity, avoid the diaphragm to prevent the formation of pneumothorax, and the death of the rat), and use a blood collection needle and an anticoagulation tube to collect blood through the abdominal aorta. After the blood was collected, it was placed in a refrigerator at 4 ℃ and centrifuged centrally. Use a low temperature centrifuge, temperature: 4 ℃ , speed: 3500r / min, centrifugation for 10 minutes, take the supernatant and store in -80 ℃ refrigerator .

Lung tissue extraction

Open the skin through the neck to expose the trachea. Use tissue forceps to isolate the tissue around the trachea. Take a 15 cm suture around the trachea for backup. Use an ophthalmic scissors to make an inverted T- shaped incision in the second cartilage , insert the prepared tracheal cannula (reconstituted by a mouse gavage needle, the needle tube has a length of about 3 cm , and the needle is flattened), open the chest cavity through the diaphragm, and perform a rough cut Intermittent ribs. Separate and expose the chest cavity, use tissue forceps to fix the chest wall, pay attention to the rib stump, do not intermittently see the lung tissue shrinkage, ligate the right main bronchus with thin lines, cut the right lung lobes and store in the -80 ℃ refrigerator for future use. Tracheal intubation was performed with 4% paraformaldehyde infusion, the perfusion pressure was maintained at 30-40 mmH_2O , and lung tissue was stored at 4% paraformaldehyde at room temperature overnight, paraffin-embedded, and set aside.

Muscle tissue removal

Immediately after the rats were sacrificed, skeletal muscles were taken, stored in liquid nitrogen after weighing, and stored in a -80 ℃ refrigerator.

Frozen section: slice with LICARM 2145 slicer, thickness is 10 um , store in -80 ℃ refrigerator for future use .

HE staining

Take the left lung lobe, the outer third of the subjects, after fixation, embedded in paraffin,. 4 [mu] m slices. Take paraffin sections, thickness of 4 μm, select 3 lung tissue sections from each rat, dewax it with xylene and ethanol to water, dilute with hematoxylin, differentiate with hydrochloric acid and ethanol, counterstain with eosin solution, and then dehydrate the transparent coverslip. Look under the microscope.

Skeletal muscle fiber staining

Before the experiment, put the GENMED

reaction solution (ReagentC) in the kit at -20 ℃ in the ice bath to melt, then remove 200 microliters into a 2 ml centrifuge tube, and add 1.8 ml of GENMED alkaline solution (ReagentA) . Carefully add 200 microliters of GENMED replacement solution (ReagentE), incubate the entire sample surface and incubate for 3 minutes at room temperature. Carefully remove the GENMED replacement solution (ReagentE). At room temperature, carefully place the section into 50 ml of GENMED cleaning solution (ReagentF). During incubation for 2 minutes, gently stir during the removal of the GENMED cleaning solution (ReagentF) carefully . After counterstaining the sample (hematoxylin), place a cover glass or coverslip and observe immediately under a general optical microscope.

Wesron-blotting to detect protein levels

Clipping 0.25 G tissues, ice-cold PBS wash tissue, was added 300 ulRIPA lysate was milled in tissue homogenizer until homogenized state; in lysis on ice, 30 minutes protein;. 4 deg.] C , 12000 RPM centrifuge 15 min .With 10 % separation gel, add TEMED and shake immediately to fill the gel. After pouring, seal with isopropyl alcohol. According to the results of protein quantification, 10 ul of denatured protein was loaded per empty, and electrophoresis was started. The concentration gel electrophoresis voltage is 80V, and the separation gel electrophoresis voltage is 120V. Prepare 6 pieces of filter paper of the same size as the gel and 1 piece of PVDF membrane. The PVDF membrane is first soaked in methanol and then placed in the transfer buffer with the filter paper until it is completely saturated. The protein was transferred to a polyvinylidene fluoride blotting membrane on a 120V trihydrochloride polyacrylamide gel, and a specific polyclonal antibody was used as a probe on the membrane. The same amount of protein was obtained from the protein lysate for electrophoresis analysis. β- actin is used as an internal reference.

statistical methods

Using GraphPad Prism 8 statistical software to analyse data, measurement data are presented as mean ± standard deviation, independent sample t test, using sperman correlation analysis. $p < 0.05$ was considered to demonstrate statistically significant differences.

Result

We have experimental replication to take simple passive smoking room COPD model, visibility coat gloss smoking rats decreased body weight loss, reduce subcutaneous fat; pulmonary function tests show the presence of airway obstruction, airflow limitation exists; HE staining of lung The alveolar septum is reduced, the alveolar wall is thinned, and the formation of alveolar bullae is seen. The inflammatory cells infiltrate the tracheal mucosa, which is consistent with the manifestations of COPD emphysema and chronic bronchitis(**Figure 1**). The model was successfully replicated [16-18] .

Rat weight change

we can see the changes in rat weight. The weight of the rats in the CS group was reduced. The weight of the rats in the C group was reduced. The rats treated with salidroside (CS + L , CS + M , CS + H) Visible weight gain. The statistical differences between the groups were considered significant(**Figure 2**).

Swimming time comparison

we observe that the rats swim. The rats in the CS group have shorter swimming time than the rats in the C group. The statistical difference is considered significant ($P <0.05$). Rats treated with salidroside orally (CS + L , CS + M , CS + H), the swimming time was prolonged, and the prolonged time was related to the dose , and the statistical differences between the groups were considered significant (**Figure 3**).

Changes in quadriceps weight

The weight of the quadriceps of the C group was heavier than that of the group CS , and the statistical difference was considered significant at $P <0.05$. The weight of the quadriceps of the rhodiola intervention group (CS + L , CS + M , CS + H) The weight of the four heads of the CS group increased ($P <0.05$). The quadriceps femoris weight / body weight of CS was lighter than that of group C, and the difference was considered to be statistically significant at $P <0.05$. / Body weight (visceral body ratio) increased, and the statistical differences between groups wereconsidered significant (**Figure 4**).

Effect of Rhodiola on Type I Fiber Ratio (%)

CS Group I muscle fiber type proportion than C group decreased statistically significant (difference $P <0.05$), using Salidroside intervention group (CS + L , CS + M , CS + H) to the CS group I -type muscle fiber ratio There was an increase, and the statistical difference wasconsidered significant at $P <0.05$, but still not restored to the level of the blank group (**Figure 5**).

Effects of salidroside on P-SIRT1 and SIRT1 expression in rats

The expression of SIRT 1 in the CS group was higher than that in the C group, and the statistical difference was considered significant (P <0.05). The level of SIRT 1 expression in the salidroside intervention group (CS + L, CS + M, CS + H) decreased. The statistical difference was considered significant (P <0.05), but still not restored to the level of the blank group (P <0.05). The comparison of active SIRT 1 showed that the expression of CS group was higher than that of group C, and the statistical difference was considered significant (P <0.05). The salidroside intervention group (CS + L, CS + M, CS + H) had the active SIRT 1 level. The statistical difference is considered significant (**Figure 6**).

Effect of salidroside on degradation of quadriceps protein

The expression of MurF -1 in the CS group was higher than that in the C group, and the statistical difference was considered significant at P <0.05. The expression level of MurF-1 in the salidroside intervention group (CS + L , CS + M , CS + H) was The difference was statistically significant (P <0.05). There is no significant difference in Atrogin-1 expression level between the groups (**Figure 7**).

Discussion

Chronic obstructive pulmonary disease (COPD) is a common medical chronic disease. It is characterized by persistent obstructive ventilation dysfunction. The lung pathological changes are emphysema and bronchitis. The main symptoms are repeated cough, sputum and continuous progress. He has difficulty breathing, but in addition to the symptoms of the respiratory system, the patient also develops systemic symptoms such as fatigue, decreased activity tolerance, and so on. Limited mobility is one of the important indicators to assess the severity of patients [19, 20] .

Hypoxemia at rest or during exercise caused by COPD decreased lung function is the main reason for limited exercise capacity, and respiratory muscle dysfunction is also a limiting factor for its exercise capacity [21-24] . However, with the deepening of the research, it was found that during the progression of COPD, not only respiratory muscle dysfunction, but also peripheral skeletal muscle disorder exists. Weight loss is inevitable during the progression of COPD. Among them, weight loss is the mechanism of body adaptation in patients with advanced COPD. At the same time, skeletal muscle consumption (SMW), body composition ratio changes, and skeletal muscle function disorders occur [25-28] .

We adopted a simple passive smoking method to replicate the COPD model. In the COPD model, skeletal muscle oxidative stress is increased, and oxidative stress can increase the expression of SIRT1 [29, 30] . In this experiment, we found that The expression of SIRT1 in the blank group was lower than that in the COPD model group . Meanwhile, we can observe that the expression levels of its downstream factors MurF-1 and Atrogin-1 increased, and this expression level was positively correlated with the expression of SIRT1. The expression of SIRT1 in the salidroside-treated rats decreased, and it was observed that as the dose of salidroside increased, the expression of SIRT1 was lower. This suggests that salidroside may reduce the expression level of SIRT1 by reducing the level of skeletal muscle oxidative stress. The expression levels of MurF-1 and Atrogin-1 decreased with the decrease of SIRT1 expression. The two E3 ubiquitin ligases of MurF-1 and Atrogin-1 ubiquitin proteasome also reduced the degradation of skeletal muscle. Thus, salidroside by decreasing oxidative stress, reduced expression of tissue SIRT1, reducing MurF-1, Atrogin-1 expression, reduction in skeletal muscle protein degradation pathway of ubiquitin , in order to achieve improvement of bone rat COPD model Muscle function, and this protective effect is dose-dependent.

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Figure legends

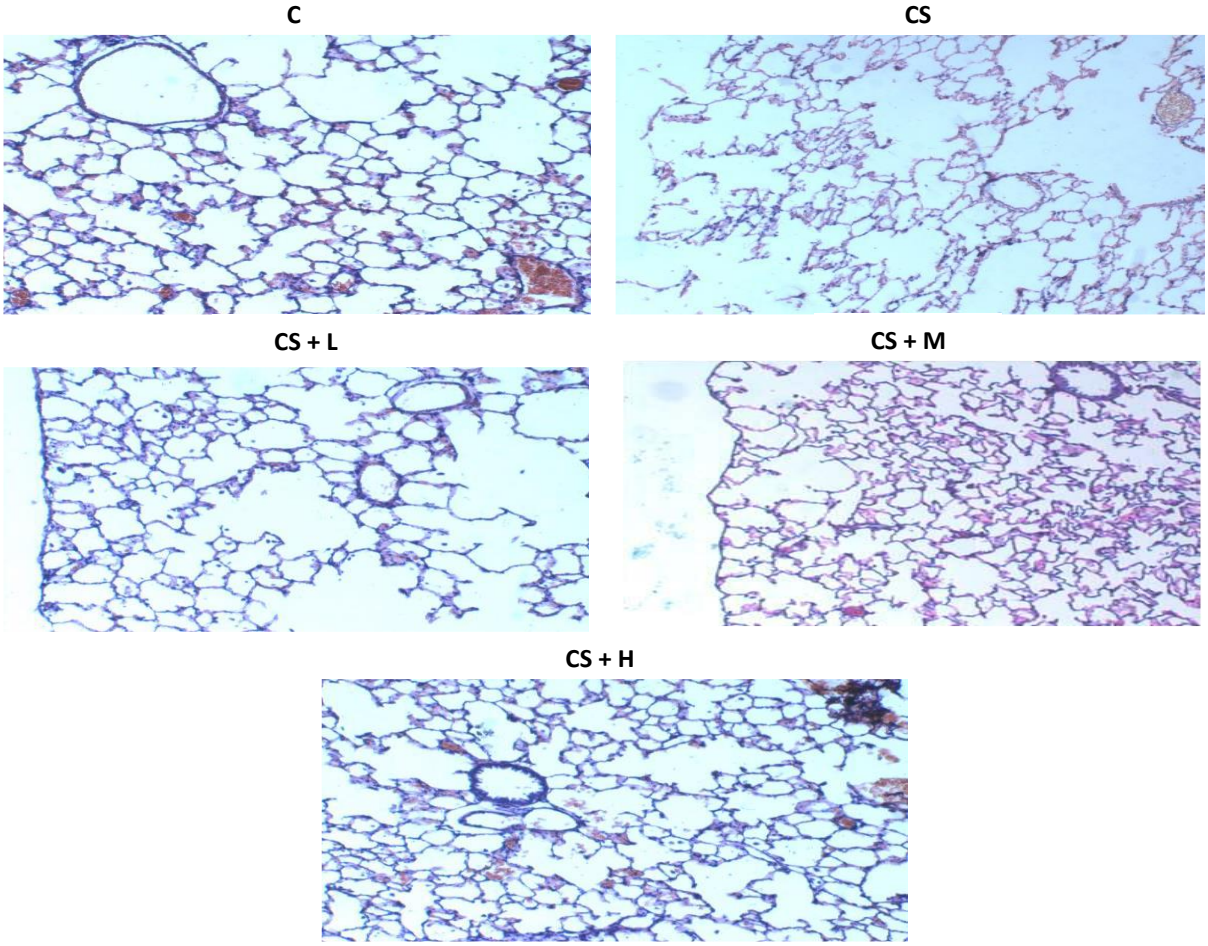


Figure 1. **Pathological changes of lung tissue in COPD rats. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. HE staining showed that the alveolar septum of the smoking group was decreased, the alveolar wall became thinner, and the formation of pulmonary bullae was observed.**

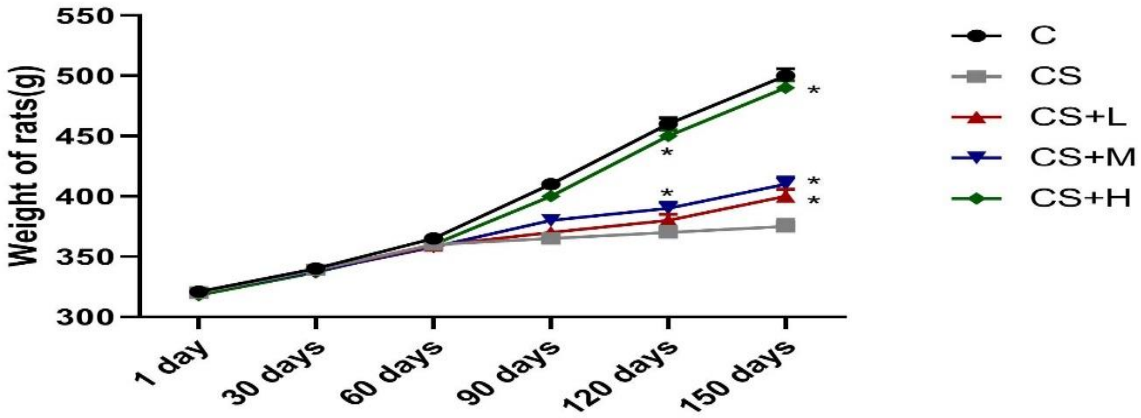


Figure 2. **The weight changes of rats in each group. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Data are means of three separated experiments ± SD, *p <0.05, compared with their control.**

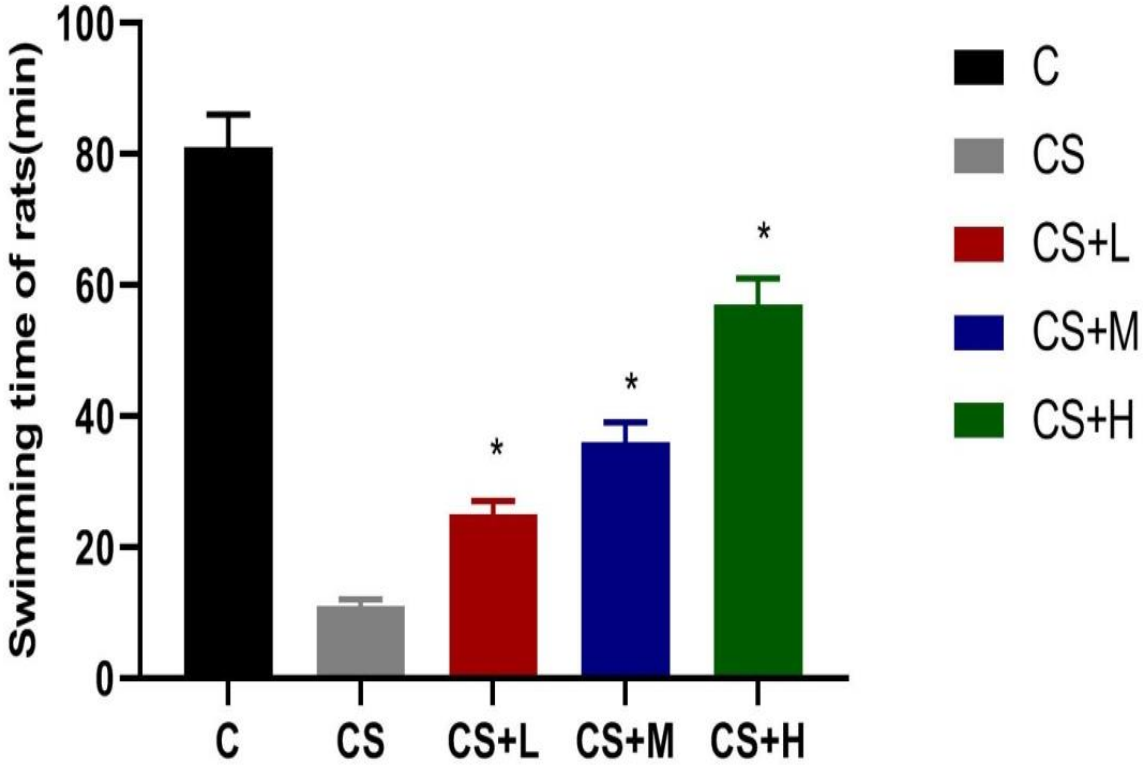


Figure 3. **The swimming time of rats in each group was compared. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Express the data as the mean of three separate experiments ± SD, *p <0.05, compared with their control.**

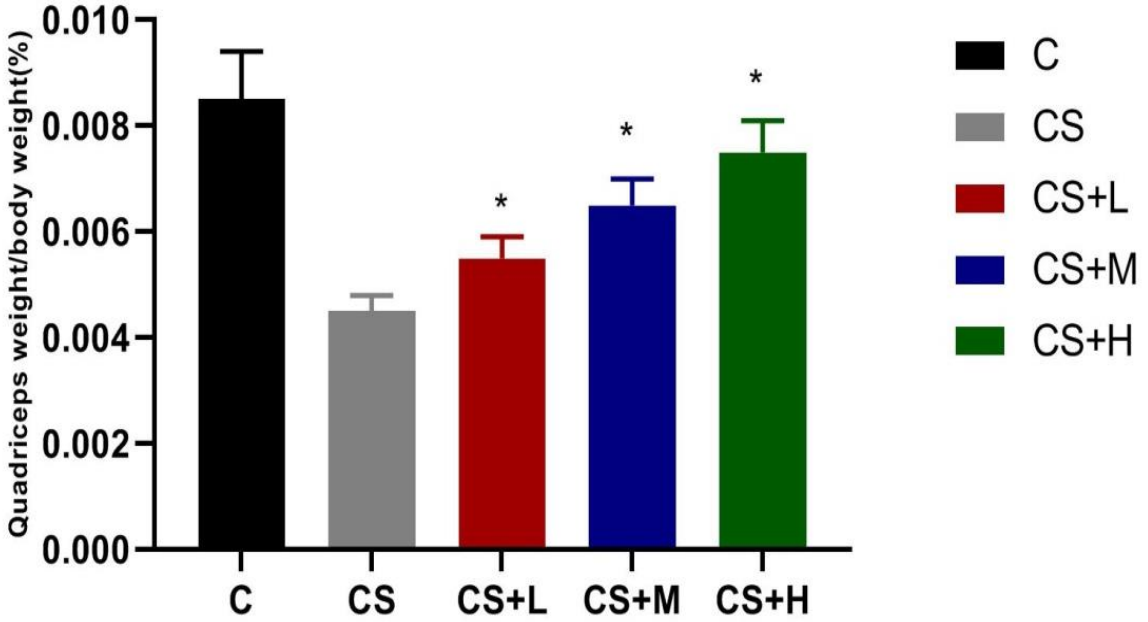
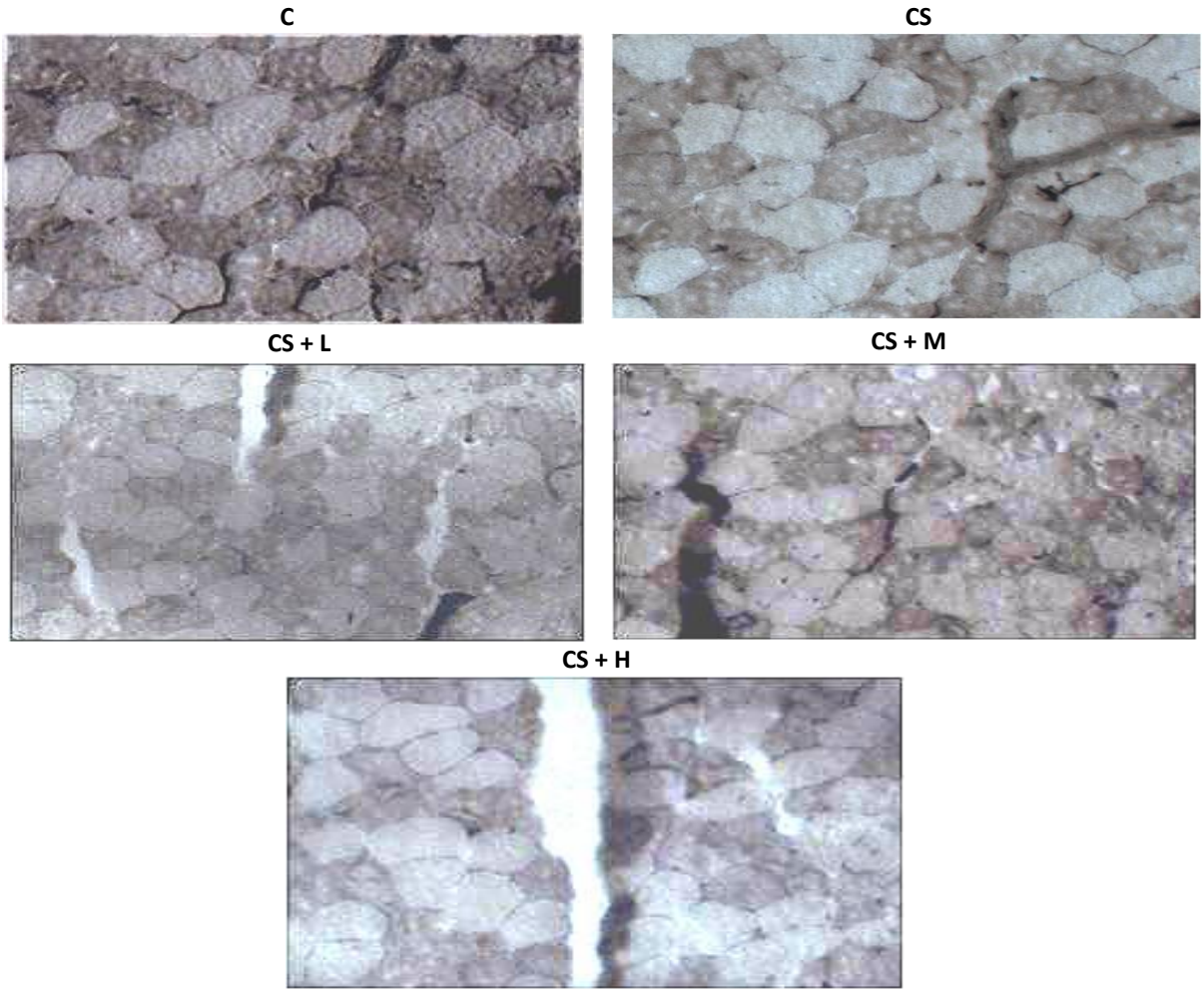


Figure 4. **The weight ratio of quadriceps femoris to body weight of rats in each group. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Express the data as the mean of three separate experiments ± SD, *p <0.05, compared with their control.**



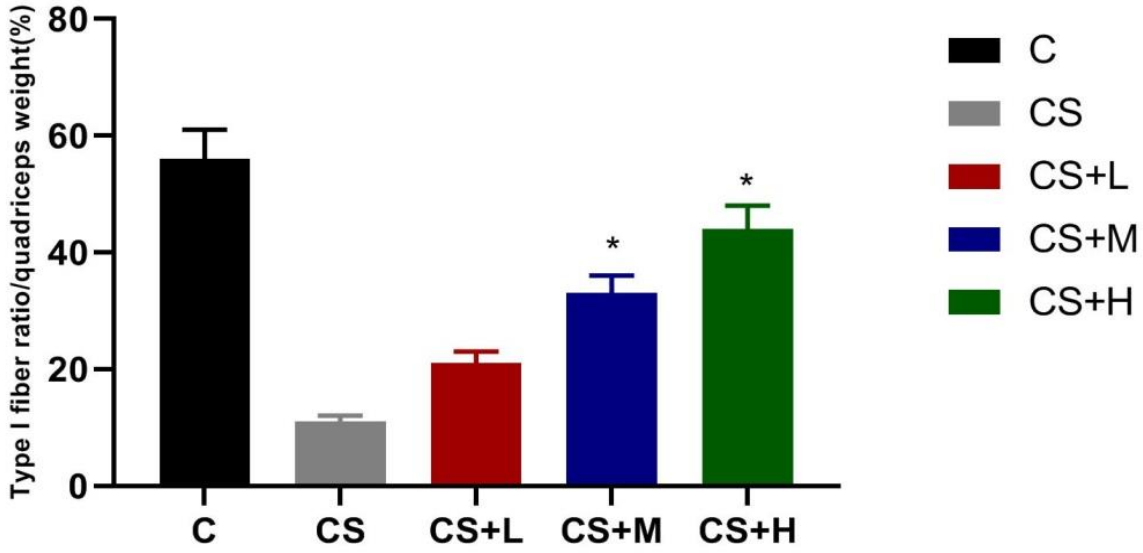


Figure 5. **The weight type I fiber ratio to quadriceps weight of rats in each group. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Express the data as the mean of three separate experiments ± SD, *p <0.05, compared with their control.**

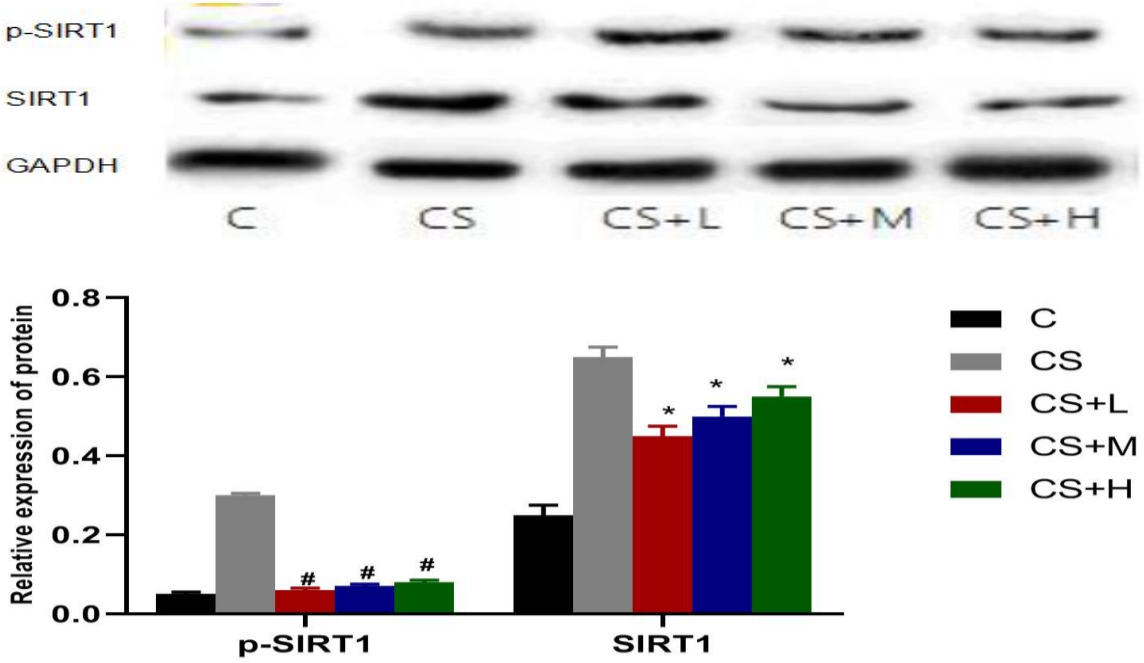


Figure 6. **The protein expression of SIRT1 and p-SIRT1 in each group. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Express the data as the mean of three separate experiments ± SD, *p <0.05, compared with their control group, #p <0.01, compared with CS group.**

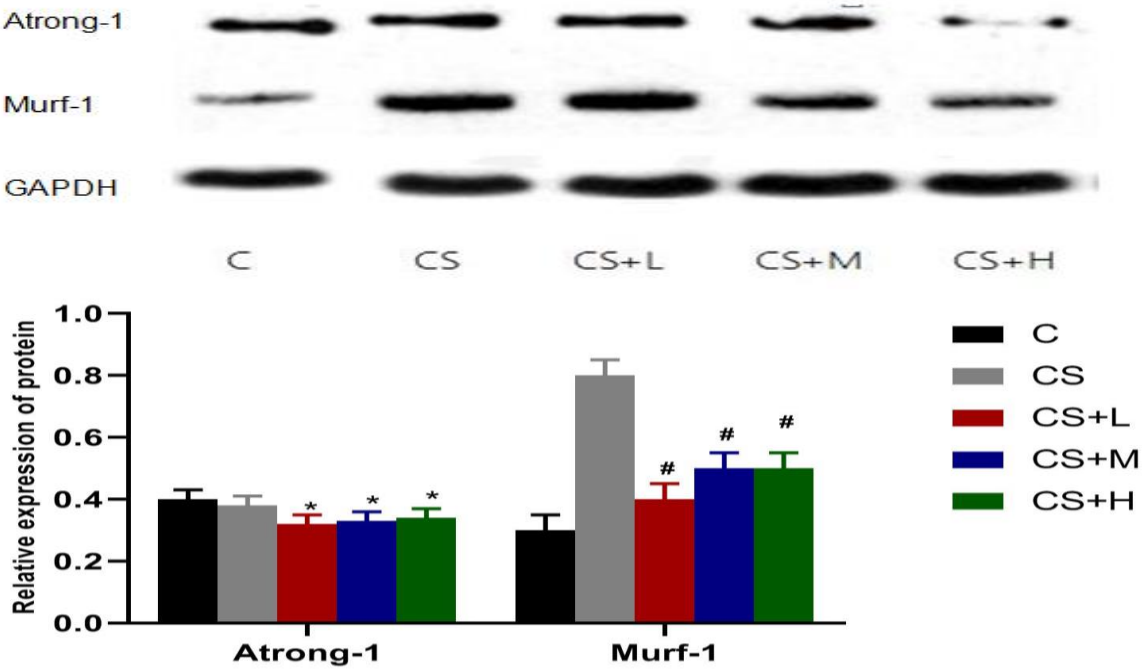


Figure 7. **The protein expression of Atrong-1 and Murf-1 in each group. (C): control group; (CS): COPD model plus placebo group; (CS + L): COPD model + low-dose salidroside group; (CS + M):COPD model + medium-dose salidroside group; (CS + H):COPD model + high-dose salidroside group. Express the data as the mean of three separate experiments ± SD, *p <0.05, compared with their control group, #p <0.01, compared with CS group.**