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Anti-inflammatory Mechanism of Yao Medicine Laggerae Alatae Herba

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Abstract [**Objectives**] To study the anti-inflammatory effect of Laggerae Alatae Herba extract and its mechanism. [**Methods**] Inflammation models of xylene-induced ear edema in mice, acetic acid-induced increased permeability of abdominal capillaries in mice, and carrageenan-induced paw edema in mice were established; xylene-induced ear swelling model in bilateral adrenalectomized mice was established. The levels of MDA, NO and SOD in inflammatory tissues of paw were measured. [**Results**] Compared with the model group, the high and medium dose groups of Laggerae Alatae Herba extract had significant inhibitory effect on xylene-induced ear edema in mice, except for the low dose group ($P>0.05$); Laggerae Alatae Herba extract inhibited the increase of celiac capillary permeability induced by acetic acid and paw edema induced by carrageenan in mice. Compared with the model group, in the mice model with bilateral adrenal glands removed, the high and medium dose groups of Laggerae Alatae Herba extract could significantly inhibit the xylene induced ear swelling of the mice. The high and medium dose groups of Laggerae Alatae Herba extract could significantly decrease the levels of MDA and NO, and significantly increase the level of SOD in the paw tissue. [**Conclusions**] The Laggerae Alatae Herba extracts have anti-inflammatory activity, and the anti-inflammatory effect of the extracts does not depend on the hypothalamic-pituitary-adrenal axis (HPAA) system. In addition, the anti-inflammatory mechanism of Laggerae Alatae Herba extract is related to the decrease of MDA and NO and the increase of SOD.

Key words Laggerae Alatae Herba, Anti-inflammation, Action mechanism

1 Introduction

Ethnic medicine Laggerae Alatae Herba is a kind of plant belonging to *Laggera* genus in Asteraceae family. The whole plant is used as medicine. It is bitter, pungent and slightly warm in nature. It has the effects of dispelling wind, removing dampness and detoxifying. It is used as a good medicine for anti-bacterial, anti-inflammatory, heat-clearing and detoxifying in the folk[1]. It is often used for traumatic injury, rheumatic arthritis, venomous snake bite, abdominal pain, diarrhea, *etc.* Laggerae Alatae Herba mainly contains sesquiterpenes, flavonoids[2], phenolic acids and other chemical components[3-6]. Pharmacological experiments have shown that Laggerae Alatae Herba has the effects of treating acute and chronic inflammation, anti-tumor, antiviral and antimicrobial activity[3,7-8].

Through the preliminary experiment of Laggerae Alatae Herba, our research team found that it has good anti-inflammatory activity. Considering that there are few reports on the anti-inflammatory effect and mechanism of this plant, we investigated the anti-inflammatory activity of Laggerae Alatae Herba extract and discussed its mechanism of action, to provide a basis for the further development and application of this medicinal plant.

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2 Materials and methods

2.1 Materials

2.1.1 Instruments. Full-wavelength microplate reader (Tecan (Shanghai) Trading Co., Ltd.); GL124-1SCN electronic balance (Sartorius Scientific Instruments (Beijing) Co., Ltd.); UV-1780 ultraviolet-visible spectrophotometer (Shimadzu Instruments (Suzhou) Co., Ltd.); TGL-16GB centrifuge (Shanghai Anting Scientific Instruments Factory); BXM-30R Vertical Pressure Steam Sterilizer (Shanghai Boxun Medical Biological Instrument Co., Ltd.).

2.1.2 Drugs and reagents. Enzyme linked immunosorbent assay (ELISA) kits for superoxide dismutase (SOD), malondialdehyde (MDA) and nitric oxide (NO) were purchased from Nanjing Jiancheng Bioengineering Institute (batch numbers were 20190306, 20190304, and 20190312, respectively); Dexamethasone Acetate Tablets (Zhejiang Xianju Pharmaceutical Co., Ltd., batch No.: 190121); Cefixime Dispersible Tablets (Zhejiang SPAS Pharmaceutical Co., Ltd., batch No.: 190160E); xylene and acetic Acid (Sinopharm Chemical Reagent Co., Ltd., batch No.: F20190616 and T20190910); carrageenan (Shanghai Yuanye Biotechnology Co., Ltd., batch No.: YY19702); chloral hydrate (Chengdu Chron Chemical Reagent Factory, batch No.: 2019020102).

2.1.3 Medicinal material. The medicinal material was collected from Hezhou City, Guangxi, and was identified as *Laggera alata* (D. Don) Sch. Bip. ex Oliv by Tang Chunli, director of the Department of Pharmacy of the First Affiliated Hospital of the Guangxi University of Chinese Medicine. The medicinal part is the whole herb.

2.1.4 Animals. Kunming mice of clean grade, male, with a body mass of 18 – 22 g, were provided by the Laboratory Animal Center of Guangxi Medical University, with the animal production license number of SCXK Gui 2014-0002. Before the experiment, the mice were adaptively fed in a clean animal room for 5 d, with an ambient temperature of (25 ± 2) ℃, a humidity of about 65%, and an artificial photoperiod of 12 h. Mice were fed ad libitum with standard rodent feed and purified water.

2.2 Methods

2.2.1 Preparation of Laggerae Alatae Herba extract and dosage setting and preparation. 30 kg of Yao medicine Laggerae Alatae Herba was crushed into coarse powder, heated and extracted with 8 times of ethanol under reflux for 3 times, 1 h each time. The three extracting solutions were mixed, and the solvent was recovered under reduced pressure to obtain an ethanol extract. The obtained extract was sequentially extracted with petroleum ether (60 – 90 ℃) and ethyl acetate to obtain petroleum ether, ethyl acetate and ethanol extraction parts.

2.2.2 Establishment of mouse ear swelling model induced by xylene. 110 mice were randomly divided into model group, positive control group (dexamethasone, 0.005 g/kg) and Laggerae Alatae Herba petroleum ether extract high, medium and low dose groups (30, 20, 10 g/kg), Laggerae Alatae Herba ethyl acetate extract high, medium and low dose groups (30, 20, 10 g/kg), Laggerae Alatae Herba ethanol extract high, medium and low dose groups (30, 20, 10 g/kg), 10 mice in each group. The mice in each administration group were given intragastric administration with the volume of 20 mL/kg, qd, for 7 consecutive days; the mice in the model group were given intragastric administration with the same volume of purified water. One hour after the last administration, 10 μL of xylene was smeared on both sides of the right ear of the mice to induce inflammation. Then, 16 min later, the mice were killed by taking off the cervical vertebra, and two ears were cut off along the root of the ear, and the round ears with the same area were made on the same part with a 6 mm punch, and the mass was weighed, and the degree of ear swelling and the swelling inhibition rate were calculated. Ear swelling degree (mg) = Mass of right auricle (mg) – Mass of left auricle (mg); Inhibition rate of ear swelling (%) = [Mean value of ear swelling degree in the model group (mg) – Mean value of ear swelling degree in the administration group (mg)]/Mean value of ear swelling degree in the model group (mg) × 100%.

2.2.3 Establishment of a mouse model of increased capillary permeability in abdominal cavity induced by acetic acid. 110 mice were divided into groups and administered using the method in Section **2.2.2**. One hour after the last administration, 10 mL/kg of 0.3% Evans blue solution and 10 mL/kg of 0.6% acetic acid solution were injected intraperitoneally into mice in each group; 15 min later, the mice were killed by cervical vertebra detachment, 6 mL of normal saline was injected into the abdominal cavity to wash the abdominal cavity, and the abdominal cavity was gently rubbed for 1 min, and then the abdominal cavity was cut open to collect peritoneal fluid. The peritoneal fluid was centrifuged at 3 000 r/min for 12 min, and the absorbance of the supernatant was measured at 590 nm with an ultraviolet-visible spectrophotometer. The capillary permeability was expressed by absorbance value, and the higher the absorbance, the greater the capillary permeability.

2.2.4 Establishment of mouse paw edema model induced by carrageenan. 110 mice were divided into groups and administered using to the method in Section **2.2.2**. One hour after the last administration, 0.02 mL of 1% carrageenan solution was injected intracutaneously into the right hindpaw of mice in each group to induce inflammation[9]; after 15 min, the mice were killed by cervical vertebra detachment, and the equal parts of the hind feet were cut and weighed, and the swelling degree and swelling inhibition rate of the mice feet were calculated. Paw swelling degree (mg) = Mass of right hind paw of mouse (mg) – Mass of left hind paw of mouse (mg); Inhibition rate of paw swelling (%) = [Mean value of paw swelling degree of model group (mg) – Paw swelling degree of administration group (mg)]/Paw swelling degree of model group (mg) × 100%.

2.2.5 Establishment of ear swelling model induced by xylenee in adrenalectomized mice. 110 mice were given cefixime 60 mg/kg by gavage one day before operation to prevent infection. The mice were anesthetized by intraperitoneal injection of 5% chloral hydrate 10 mL/kg. After shaving the back hair and disinfecting the skin with 70% ethanol, an incision about 0.5 cm long was made along the midline of the back and the posterior edge of the dorsal rib at the junction of the thoracolumbar spine. The incision was enlarged with small forceps and the abdominal organs and tissues were gently pushed open. The left and right adrenal glands were gently removed. The incision was slightly stopped by cotton ball, then the muscle and skin were sutured, and then the mice were smeared with iodophor for disinfection. On the second day after operation, the mice were given cefixime 60 mg/kg by gavage, and 5% glucose saline solution was used to replace water for 3 d after operation. The mice were divided into groups and administered using the method in Section **2.2.2**, and the xylene-induced ear swelling test was carried out to calculate the degree of ear swelling and the swelling inhibition rate.

2.2.6 Establishment of carrageenan-induced hind paw swelling model in adrenalectomized mice. 110 mice were taken and bilateral adrenalectomy was performed using the method in Section **2.2.5**. On the third day after operation, the mice were divided into groups and administered using the method in Section **2.2.4**, and the carrageenan-induced paw swelling test was carried out to calculate the inhibition rate of paw swelling. The mice were killed by cervical vertebra detachment, and the right paw was cut into

pieces and soaked in 4 mL of normal saline. After homogenization on ice, the solution was centrifuged at 3 000 r/min for 10 min, and the supernatant was stored at −20 ℃ for measurement. The levels of MDA, NO and SOD in the tissues were determined according to the instructions of the corresponding kits.

2.2.7 Statistical methods. SPSS 23.0 software was used for statistical analysis. The experimental data were expressed as $\bar{x} \pm s$, and one-way analysis of variance was used. If the variance was homogeneous, the *LSD* method was used to compare between groups, and if the variance was uneven, the Dunnett's T3 method was used to compare between groups. $P < 0.05$ indicates a statistically significant difference.

3 Results and analysis

3.1 Effect on xylene induced ear swelling in mice Compared with the model group, the ear swelling degree of mice in the positive control group and the high and medium dose groups of Laggerae Alatae Herba extract was significantly reduced ($P < 0.05$ or $P < 0.01$); compared with the positive control group, the ear swelling of mice in the low dose Laggerae Alatae Herba extract group was significantly increased, and the difference was statistically significant ($P < 0.05$). There was no significant difference in ear swelling degree between high and medium dose groups of Laggerae Alatae Herba extract ($P > 0.05$), indicating that the high and medium dose extracts of Laggerae Alatae Herba had a significant inhibitory effect on xylene-induced ear edema in mice (Table 1).

Table 1 Inhibitory effect of Laggerae Alatae Herba extract on xylene-induced ear swelling in mice ($\bar{x} \pm s$, $n = 10$)

Group	Dose g/kg	Ear swelling degree // mg	Inhibition rate of ear swelling // %
Model		2.56 ± 0.61	–
Positive control	0.005	1.08 ± 0.50 **	57.81 ± 5.51 **
A1	30	1.28 ± 0.46 *	50.39 ± 4.42 *
A2	20	1.42 ± 0.78 *	44.53 ± 4.60 *
A3	10	1.97 ± 0.62 $^{\triangle}$	23.05 ± 3.15 $^{\triangle}$
B1	30	1.26 ± 0.71 *	50.78 ± 4.21 *
B2	20	1.39 ± 0.80 *	45.70 ± 3.82 *
B3	10	1.95 ± 0.59 $^{\triangle}$	23.83 ± 2.48 $^{\triangle}$
C1	30	1.24 ± 0.38 *	51.56 ± 4.21 *
C2	20	1.37 ± 0.41 *	46.48 ± 3.72 *
C3	10	1.92 ± 0.84 $^{\triangle}$	25.39 ± 2.38 $^{\triangle}$

NOTE A1-A3: high, medium and low dose groups of petroleum ether extract; B1-B3: high, medium and low dose groups of ethyl acetate extract; C1-C3: high, medium and low dose groups of ethanol extract. Compared with model group, $^{*}P < 0.05$, $^{**}P < 0.01$; compared with positive control group, $^{\triangle}P < 0.05$, $^{\triangle\triangle}P < 0.01$. The same below.

3.2 Effect of acetic acid on the increase of peritoneal capillary permeability in mice Compared with the model group, the peritoneal capillary permeability of mice in the positive drug group and Laggerae Alatae Herba extract groups was significantly increased, and the difference was statistically significant ($P < 0.05$ or $P < 0.01$). Compared with the positive control group, the peritoneal capillary permeability of mice in the high and medium dose groups of Laggerae Alatae Herba extract was not significantly increased, and the difference was not statistically significant ($P > 0.05$), while the peritoneal capillary permeability of mice in the low dose group of Laggerae Alatae Herba extract was significantly increased, and the difference was statistically significant ($P < 0.05$), indicating that different doses of Laggerae Alatae Herba extract had obvious inhibitory effect on acetic acid induced acute inflammatory reaction in mice (Table 2).

Table 2 Inhibitory effect of Laggerae Alatae Herba extract on acetic acid induced capillary permeability in mice ($\bar{x} \pm s$, $n = 10$)

Group	Dose // g/kg	Peritoneal fluid absorbance A
Model	–	0.303 8 ± 0.058 0
Positive control	0.005	0.126 8 ± 0.045 3 **
A1	30	0.159 3 ± 0.060 5 *
A2	20	0.177 0 ± 0.068 2 *
A3	10	0.236 1 ± 0.082 5 $^{*\triangle}$
B1	30	0.159 0 ± 0.062 1 *
B2	20	0.176 8 ± 0.060 8 *
B3	10	0.235 9 ± 0.082 7 $^{*\triangle}$
C1	30	0.158 2 ± 0.062 0 *
C2	20	0.176 0 ± 0.065 5 *
C3	10	0.235 1 ± 0.080 4 $^{*\triangle}$

3.3 Effects on carrageenan-induced paw edema in mice Compared with the model group, the paw swelling degree of mice in the positive control group and the high and medium dose groups of Laggerae Alatae Herba extract was significantly reduced, and the differences were statistically significant ($P < 0.05$), while the paw swelling degree of mice in the low dose group of Laggerae Alatae Herba extract was not significantly reduced, and the difference was not statistically significant ($P > 0.05$), indicating that high and medium doses of extracts had significant inhibitory effects on carrageenan-induced paw swelling in mice. Compared with the positive control group, the paw swelling degree of mice in the low dose Laggerae Alatae Herba extract group was significantly increased, and the difference was statistically significant ($P < 0.05$), while the paw swelling degree of mice in the high and medium dose Laggerae Alatae Herba extract groups was not significantly increased, and the difference was not statistically significant ($P > 0.05$), indicating that high and medium doses of Laggerae Alatae Herba extract had significant inhibitory effect on carrageenan-induced paw swelling in mice (Table 3).

3.4 Effect of xylene induced ear swelling in adrenalectomized mice Compared with the model group, the ear swelling of the mice with bilateral adrenalectomy in the positive control group and the high and medium doses of Laggerae Alatae Herba extract groups was significantly reduced, and the differences were statistically significant ($P < 0.05$), there was no significant difference in the low dose group of Laggerae Alatae Herba extract ($P > 0.05$). Compared with the positive control group, the xylene induced ear swelling of adrenalectomized mice in the low dose of Laggerae Alatae Herba extract group was significantly increased ($P < 0.05$). There was no significant difference in ear swelling between high

Table 3 Inhibitory effect of Laggerae Alatae Herba extract on carrageenan-induced paw swelling in mice ($\bar{x} \pm s$, $n = 10$)

Group	Dose g/kg	Paw swelling degree//mg	Inhibition rate of paw swelling//%
Model	–	47.25 ± 4.61	–
Positive control	0.005	20.43 ± 3.29**	56.76 ± 4.21**
A1	30	21.85 ± 3.60**	53.76 ± 5.02**
A2	20	26.81 ± 2.72*	43.26 ± 3.75*
A3	10	37.03 ± 4.10△	21.63 ± 3.16△
B1	30	22.01 ± 3.25**	53.42 ± 4.80**
B2	20	25.79 ± 2.62*	45.42 ± 4.68*
B3	10	38.21 ± 4.21△	19.13 ± 2.82△
C1	30	21.98 ± 3.17**	53.48 ± 4.25**
C2	20	27.01 ± 2.61*	42.84 ± 3.69*
C3	10	39.20 ± 4.20△	17.04 ± 2.21△

and medium doses of Laggerae Alatae Herba extract groups ($P > 0.05$), indicating that high and medium doses of Laggerae Alatae Herba extract had a significant inhibitory effect on xylene-induced ear swelling in adrenalectomized mice (Table 4).

Table 4 Inhibitory effect of Laggerae Alatae Herba extract on xylene-induced ear swelling in adrenalectomized mice ($\bar{x} \pm s$, $n = 10$)

Group	Dose //g/kg	Ear swelling degree//mg	Inhibition rate of ear swelling//%
Model	–	7.85 ± 2.60	–
Positive control	0.005	3.25 ± 0.68**	58.60 ± 6.58**
A1	30	4.29 ± 2.25**	45.35 ± 6.32**
A2	20	5.42 ± 2.31*	30.96 ± 4.69*
A3	10	7.31 ± 2.40△	6.88 ± 3.62△
B1	30	4.42 ± 2.05**	43.69 ± 4.48**
B2	20	5.98 ± 2.31*	23.82 ± 5.25*
B3	10	7.34 ± 2.80△	6.50 ± 3.82△
C1	30	4.32 ± 1.02**	44.97 ± 4.21**
C2	20	5.26 ± 1.04*	32.99 ± 3.02*
C3	10	7.22 ± 1.21△	8.03 ± 2.26△

3.5 Levels of MDA, SOD and NO in inflammatory parts of paw Compared with the model group, the levels of MDA and NO in the positive control group and the high and medium doses of Laggerae Alatae Herba extract groups were significantly decreased, while the level of SOD was significantly increased, and the differences were statistically significant ($P < 0.05$). Compared with the positive control group, the levels of MDA and NO in the low dose of Laggerae Alatae Herba extract group were significantly increased, while the level of SOD was significantly decreased ($P < 0.05$). However, there was no significant difference in the levels of MDA, NO and SOD between the high and medium dose groups of Laggerae Alatae Herba extract in the inflammatory sites of adrenalectomized mice ($P > 0.05$), indicating that high and medium doses of Laggerae Alatae Herba extract could inhibit the levels of inflammatory cytokines in the inflammatory sites of carrageenan-induced paw swelling in adrenalectomized mice (Table 5).

Table 5 Regulatory effects of Laggerae Alatae Herba extract on the levels of MDA, SOD and NO in the hind paw of carrageenan induced adrenalectomized mice ($\bar{x} \pm s$, $n = 10$)

Group	Dose g/kg	MDA//nmol/L	SOD//pg/mL	NO//μmol/L
Model	–	2.83 ± 0.24	12.11 ± 1.25	23.48 ± 2.81
Positive control	0.005	1.81 ± 0.31*	24.85 ± 3.32*	13.15 ± 1.53*
A1	30	2.05 ± 0.18*	19.04 ± 2.06*	14.21 ± 2.50*
A2	20	2.29 ± 0.15*	17.12 ± 1.53*	16.90 ± 1.21*
A3	10	2.68 ± 0.27△	13.68 ± 1.54△	21.15 ± 1.37△
B1	30	2.01 ± 0.21*	19.85 ± 2.26*	14.16 ± 2.41*
B2	20	2.20 ± 0.18*	17.72 ± 1.40*	16.72 ± 1.26*
B3	10	2.57 ± 0.25△	14.25 ± 1.93△	21.10 ± 1.32△
C1	30	1.92 ± 0.16*	20.26 ± 2.82*	14.02 ± 1.55*
C2	20	2.10 ± 0.12*	17.98 ± 1.95*	16.31 ± 1.92*
C3	10	2.52 ± 0.21△	14.51 ± 1.14△	20.05 ± 3.30△

4 Conclusions

In this study, our results show that Laggerae Alatae Herba extract exerts its anti-inflammatory effect by reducing MDA and NO levels and increasing SOD levels in mouse paws. The anti-inflammatory effect of Laggerae Alatae Herba extract on normal mice and adrenalectomized mice was investigated using xylene-induced ear swelling and carrageenan-induced paw swelling models. The results show that the extract of Laggerae Alatae Herba had significant anti-inflammatory activity in mice with or without adrenalectomy, suggesting that its anti-inflammatory mechanism may not be related to the function of HPAA system.

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