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Original article

Anti-inflammatory effect and the effect on acute pharyngitis rats model of compound Lobelia oral liquid

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ABSTRACT

Objective: Observe anti-inflammatory effect and the effect on acute pharyngitis rats model induced by ammonia water of compound Lobelia oral liquid, providing experimental basis for its clinical use.
Methods: Use egg white establish foot swelling rats model and use carboxymethyl cellulose establish white blood cell migration rats model. Then observe the anti-inflammatory effect of compound Lobelia oral liquid. Use 15% ammonia spray at pharyngeal establish acute pharyngitis rats model, Visual observation and conduct grading of pharyngeal tissue stimulation in rats, measure the levels of TNF-α and IL-6 in serum. Pharyngeal tissue was taken to observe the morphological changes.
Result: All dose groups of compound Lobelia oral liquid can reduce the rate of foot swelling of rats at all time points ($P < 0.01$ or $P < 0.05$), and significantly reduce the number of white blood cells of rats ($P < 0.01$); And improve the local hyperemia degree, reduce secretion, reduce local swelling of pharyngeal tissue, reduce the serum TNF-α and IL-6 levels of acute pharyngitis rats with different degrees ($P < 0.01$ or $P < 0.05$).
Conclusion: Compound Lobelia oral liquid has a good anti-inflammatory effect on foot swelling and white blood cell migration rats model, as well as significant improvement effect on acute pharyngitis rats model.

1. Introduction

Pharyngitis is a common seasonal disease of the upper respiratory tract. The incidence of pharyngitis is increasing year by year due to environmental factors such as climate change and haze, work pressure and smoking (Faustini et al., 2013; RrincipiI et al., 2013). Many scholars believe that acute pharyngitis is mainly due to viruses, bacteria and other factors that directly stimulate the pharynx, resulting in tissue inflammation (Di et al., 2016). Compound Lobelia oral liquid consists of Lobelia, *Sculellaria barbata*, *Oldenlandia diffusa* and others which has the functions of clearing away heat and toxic materials, relieve swelling and pain. Clinical use for external wind induced sore throat, acute pharyngitis, upper respiratory tract infection, and has remarkable curative effect. Studies have found that Lobelia has significant pharmacological effects on anti-tumor, regulating endothelial cells, relieving pain and reducing inflammation, and *Sculellaria barbata* has significant pharmacological effects on anti-oxidation, anti-tumor, immune regulation (Li et al., 2015; Kou et al., 2011). However, the injection has some adverse reactions in clinical application. The oral dosage form of compound Lobelia oral liquid is the improved dosage form of its injection. Oral dosage form has the advantages that the original injection does not have, such as it is safe to use, easy to carry and store (Tan et al., 2014). In order to verify the anti-inflammatory effect and therapeutic effect on pharyngitis, the anti-inflammatory effect were observed by foot swelling and white blood cell migration rats model and therapeutic effect on acute pharyngitis were observed by acute pharyngitis rats model, so as to provide the experimental basis for the clinical application of compound Lobelia oral liquid.

2. Experimental materials

2.1. Experimental apparatus

Laryngeal spray apparatus, Taizhou huichun medical equipment co. LTD; Type 680 enzyme marker, USA BIO-RAD co. LTD; PV-200

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type rat foot measuring instrument, hengdu taisheng technology co. LTD; Kdc-160 HR high-speed refrigerated centrifuge, Zhong jia branch of keda innovation co. LTD; Fluorescence microscope and imaging system BX61, Olympus of Japan.

2.2. Experiment reagents

Compound Lobelia oral liquid, Henan tongyuan pharmaceutical co., LTD. Batch number: 110701; Yinhuang oral liquid, Shaanxi bailu pharmaceutical co., LTD. Batch number: 160805. Sodium carboxymethyl cellulose, Tianjin hengxing chemical reagent manufacturing co., LTD. Batch no.: 20160728. Ammonia water, Luoyang haohua chemical reagent co., LTD. Batch no.: 151019.

2.3. Experimental animals

SD rats, weighing 180–220 g, half male and half female, Shandong experimental animal center. Laboratory animal certificate: no. 37009200003339; Used to establish acute pharyngitis rats model.

SD rats, weighing 180–200 g, male, Hebei experimental animal center, laboratory animal certificate: 1109003. Laboratory qualification certificate: SYXK (Yu) 2015–0005; Used to establish foot swelling and white blood cell migration rats model.

3. Experimental method

3.1. Foot swelling rats model induced by egg white (Shu et al., 2018; Motevalian et al., 2017)

A total of 40 rats weighing 180–200 g were randomly divided into saline group, Yinhuang group (6 ml/kg) and large, middle and small compound Lobelia oral liquid groups (30 g/kg, 15 g/kg, 7.5 g/kg) with 8 rats in each group. In addition to the blank group and model group, the corresponding drugs were given for intervention. The saline group were given the same volume of saline, the remaining groups were given corresponding drugs. Before the administration on the 3rd day, the normal left hind foot volume of the rat was measured with the foot pedal tester, and the linear position of the rat ankle was adjusted to make the normal foot volume of the rat around 1 mL. After 30 min of administration, each rat was subcutaneously injected with 0.1 ml newly prepared 10% fresh egg white solution. The volume of the left hind foot of the rat was measured again with a foot plantar meter at 60 min, 120 min, 240 min and 360 min after given egg white, and the swelling rate of the foot was calculated.

3.2. White blood cell migration rats model induced by carboxymethyl cellulose (Ma et al., 2013; Zeng et al., 2018)

A total of 50 rats weighing 180–200 g were randomly divided into saline group, Yinhuang group (10 ml/kg) and large, middle and small compound Lobelia oral liquid groups (30 g/kg, 15 g/kg, 7.5 g/kg) with 10 rats in each group. Administration is the same as 2.1. After the second day of administration, the backs of rats in each group were depilated by about 2 cm * 2 cm, and 5 ml of air was injected subcutaneously, forming an air bag. At 8 o'clock in the evening, start fasting for 12 h. At 1 h after administration on day 3, 5 ml 1.5% carboxymethyl cellulose was injected into the air bag under the skin of rats. After 3 h and 7.5 h of injection of carboxymethyl cellulose, the intracellular fluid was extracted, diluted 20 times with 0.9% sodium chloride injection, placed on a blood cell counting plate, and observed under light microscope to calculate the number of white blood cells.

3.3. Acute pharyngitis induced by ammonia in rats (Wu et al., 2018)

12 rats were selected from a total of 72 rats as blank group, remaining rats were used to establish acute pharyngitis rats model. Acute pharyngitis model was established by spraying 15% ammonia water on the pharynx of rats in the morning from day 1 to day 3 (Spray 3 thrush with sprayer every time, Causes the pharynx mucosa to be hyperemia swollen due to acute stimulation, forms the acute inflammation). The rats were randomly divided into model group, Yinhuang group (10 ml/kg) and large, middle and small dose compound Lobelia oral liquid groups (30 g/kg, 15 g/kg, 7.5 g/kg) on the 3rd day. Give the corresponding drugs once a day for 5 days. After 1 h of the last administration, the pharynx tissues of rats were integrated (according to the score standard), blood was taken from the eyeball, serum was separated to measure TNF-α and IL-6 levels. The pathological changes of pharyngeal tissue were observed by staining with HE.

Score standard: According to the tissue color, gloss, number of secretions, hyperemia and swelling of pharynx, it can be divided into 4 grades. "−": Pharyngeal tissue was light red, with moist and shiny surface, no secretion, no hyperemia, swelling and other pathological phenomena; "+": Some of the rats had poor glossiness of pharyngeal mucosa, a small amount of secretions and mild acute hyperemia; "++": Pharyngeal tissue color is dark red, glossiness is poor, secretion appears, and accompanied by acute hyperemia, mild swelling and other phenomena; "+++": The pharyngeal tissues of rats were dark red and dull, with increased mucous secretions and obvious acute hyperemia and swelling.

4. Experimental results

4.1. Effect of compound Lobelia oral liquid on foot swelling rats model induced by egg white

As we can see from Table 1: Compared with the model group, after 60 min, 120 min, 240 min and 360 min of injected egg white, the large dose of compound Lobelia oral liquid could significantly reduce the foot swelling rate of rats ($P < 0.01$); Yinhuang group and compound Lobelia oral liquid middle and small dose group can obviously reduce the foot swelling rate of rats ($P < 0.01$). The results showed that compound Lobelia oral liquid had a strong anti-inflammatory effect.

4.2. Effect of compound Lobelia oral liquid on white blood cell migration rats model induced by carboxymethyl cellulose

As we can see from Table 2: Compared with the model group, large, middle and small doses of compound Lobelia oral liquid and Yinhuang group can significantly reduce the number of white blood cells of rats at 3 h and 7.5 h ($P < 0.01$), which indicating that compound Lobelia oral liquid had a strong anti-inflammatory effect.

4.3. Effect of compound Lobelia oral liquid on acute pharyngitis rats model induced by mmonia water

4.3.1. General status observation of acute pharyngitis rats model induced by ammonia water

After modeling, rats gradually began to scratch their mouths, and they drank water frequently but in small amounts, oral secretion gradually increased, mental fatigue, food intake and spontaneous activity decreased; There was redness and swelling in pharynx, mucous secretions were accumulated, and superficial ulcer was formed in some rats. The blank group did not show the above situation.

Table 1
Volume comparison of the left hind foot of the rats in each group ($\bar{x} \pm s$, ml, $n = 8$).

Group	Dose	Normal toe volume	left hind foot volume at different times after injected egg white			
			60 min	120 min	240 min	360 min
Saline group		1.00 ± 0.02	1.83 ± 0.03 (0.83 ± 0.05)	1.63 ± 0.02 (0.63 ± 0.04)	1.47 ± 0.02 (0.47 ± 0.06)	1.26 ± 0.04 (0.26 ± 0.06)
Yinhuang group	6 ml/kg	1.00 ± 0.01	1.57 ± 0.04 (0.57 ± 0.06)*	1.46 ± 0.05 (0.46 ± 0.05)*	1.36 ± 0.05 (0.36 ± 0.03)*	1.13 ± 0.05 (0.13 ± 0.05)*
Compound lobelia	30 g/kg	1.00 ± 0.02	1.52 ± 0.04 (0.52 ± 0.06)**	1.38 ± 0.05 (0.38 ± 0.03)**	1.27 ± 0.06 (0.27 ± 0.08)**	1.09 ± 0.07 (0.09 ± 0.03)**
	15 g/kg	1.00 ± 0.03	1.52 ± 0.08 (0.52 ± 0.09)*	1.44 ± 0.06 (0.44 ± 0.08)*	1.38 ± 0.05 (0.38 ± 0.06)*	1.15 ± 0.02 (0.15 ± 0.03)*
	7.5 g/kg	1.00 ± 0.02	1.59 ± 0.03 (0.59 ± 0.04)*	1.49 ± 0.02 (0.49 ± 0.05)*	1.36 ± 0.04 (0.36 ± 0.04)*	1.15 ± 0.07 (0.15 ± 0.06)*

Note: *Represent Compared to the saline group $P < 0.05$, **Represent compared to the saline group $P < 0.01$; The value in brackets is the rate of foot swelling of rats. The rate of foot swelling = (left hind foot volume at different times after administration-Normal left hind foot volume)/Normal left hind foot volume.

Table 2
Comparison of the white blood cell count of each group ($\bar{x} \pm s$, $n = 10$).

Group	Dose (g/kg)	white blood cell count at 3 h ($\times 10^3$/mm^3)	white blood cell count at 7.5 h ($\times 10^3$/mm^3)
Saline group	–	8.86 ± 0.54	29.02 ± 0.79
Yinhuang group	10 ml/kg	6.26 ± 0.47**	22.62 ± 0.70**
Compound lobelia	30 g/kg	4.94 ± 0.52**	19.46 ± 0.54**
	15 g/kg	5.98 ± 0.44**	22.67 ± 0.61**
	7.5 g/kg	7.13 ± 0.51**	25.89 ± 0.55**

Note: *Represent Compared to the saline group $P < 0.05$, **Represent compared to the saline group $P < 0.01$.

4.3.2. Visual observation of pharyngeal tissue 1 h after the last administration of acute pharyngitis rats model induced by ammonia water

According to the scoring criteria, the pharynx tissues of rats in each group were observed. As we can see from Table 3: The pharyngeal inflammatory reaction of rats in the blank group was all "–" level, without the appearance of inflammatory characteristics. In the model group, the pharyngeal inflammatory reaction was mostly "++" and "+++" level, the pathological changes of the pharyngeal mucosa and tissue were significantly. The inflammatory symptoms of pharyngeal tissue of rats in each drug-given group were improved in different degrees.

4.3.3. Effects of compound Lobelia oral liquid on TNF-α and IL-6 levels in serum of acute pharyngitis rats model

As we can see from Table 4: Compared with the blank group, the levels of TNF-α and IL-6 in model group increased significantly ($P < 0.01$); Compared with the model group, the levels of TNF-α and IL-6 in Yinhuang group and large dose compound Lobelia oral liquid group were decreased significantly ($P < 0.01$); The middle dose compound Lobelia oral liquid group could decrease TNF-α level significantly ($P < 0.01$), and decrease IL-6 obviously ($P < 0.05$); The small dose compound Lobelia oral liquid group could decrease TNF-α level obviously ($P < 0.01$).

Table 3
Comparison of visual observation of pharyngeal tissue of rats in each group ($\bar{x} \pm s$, $n = 12$).

Group	Dose	–	+	++	+++
Blank group	–	12	0	0	0
Model group	–	0	0	5	7
Yinhuang group	10 ml/kg	0	4	8	0
Compound lobelia	30 g/kg	0	6	6	0
	15 g/kg	0	4	7	1
	7.5 g/kg	0	3	6	3

Table 4
Effect on TNF-α and IL-6 levels in serum of rats in each group ($\bar{x} \pm s$, $n = 12$).

Group	Dose	TNF-α	IL-6
Blank group	–	151.23 ± 28.17**	85.76 ± 11.44**
Model group	–	219.44 ± 35.13	125.65 ± 8.78
Yinhuang group	10 ml/kg	157.19 ± 24.9**	97.80 ± 14.61**
Compound lobelia	30 g/kg	156.62 ± 32.62**	97.30 ± 9.35**
	15 g/kg	181.45 ± 29.86**	110.87 ± 16.67*
	7.5 g/kg	192.40 ± 22.07*	135.01 ± 19.89

Note: *Represent Compared to the model group $P < 0.05$, **Represent compared to the model group $P < 0.01$.

4.3.4. Effects of compound Lobelia oral liquid on pathological changes of pharyngeal tissue of acute pharyngitis rats model

As we can see from Fig. 1: In blank group, the mucosal and submucosal mucosal glands of the pharyngeal tissue of rats were normal. In model group, the mucous membranes of the pharyngeal tissue of rats form ulcers of varying degrees. Hyperemia and infiltration of inflammatory cells can be seen under the mucous membranes of ulcers. In Yinhuang group, the scaly epithelium of the pharyngeal tissue of rats became thin, and a small amount of inflammatory cell infiltration was seen in the submucosa. In large dose compound Lobelia oral liquid group, the mucosa of the pharyngeal tissue of rats was basically normal, and the inflammatory cells in the submucosa were significantly reduced, and the mucosal glands were also decreased. In middle dose compound Lobelia oral liquid group, a small number of inflammatory cells were observed in the mucosa and submucosa of the pharyngeal tissue of rats. In small dose compound Lobelia oral liquid group, the mucosa of the pharyngeal tissue of rats became thin, the inflammatory cells decreased significantly, and the mucosal gland in the submucosal layer was basically normal.

As we can see from Table 5: By *Radit* test, compared with the blank group, the mice in the model group had obvious hyperplasia of mucosal squamous epithelium in the pharyngeal tissue and a large number of inflammatory cells infiltrated under the mucosa ($P < 0.01$); Compared with the model group, the increase of mucosal squamous epithelium and infiltration of submucosal inflammatory cells in the pharyngeal tissues of rats in the Yinhuang oral liquid group and the compound Lobelia oral liquid large-, middle-, and small-dose group were significantly reduced ($P < 0.01$).

5. Discuss

Pharyngitis is clinically common multiple respiratory infection disease, incomplete treatment will lead to repeated attacks. According to the theory of traditional Chinese medicine, acute pharyngitis is usually caused by the invasion of exogenous

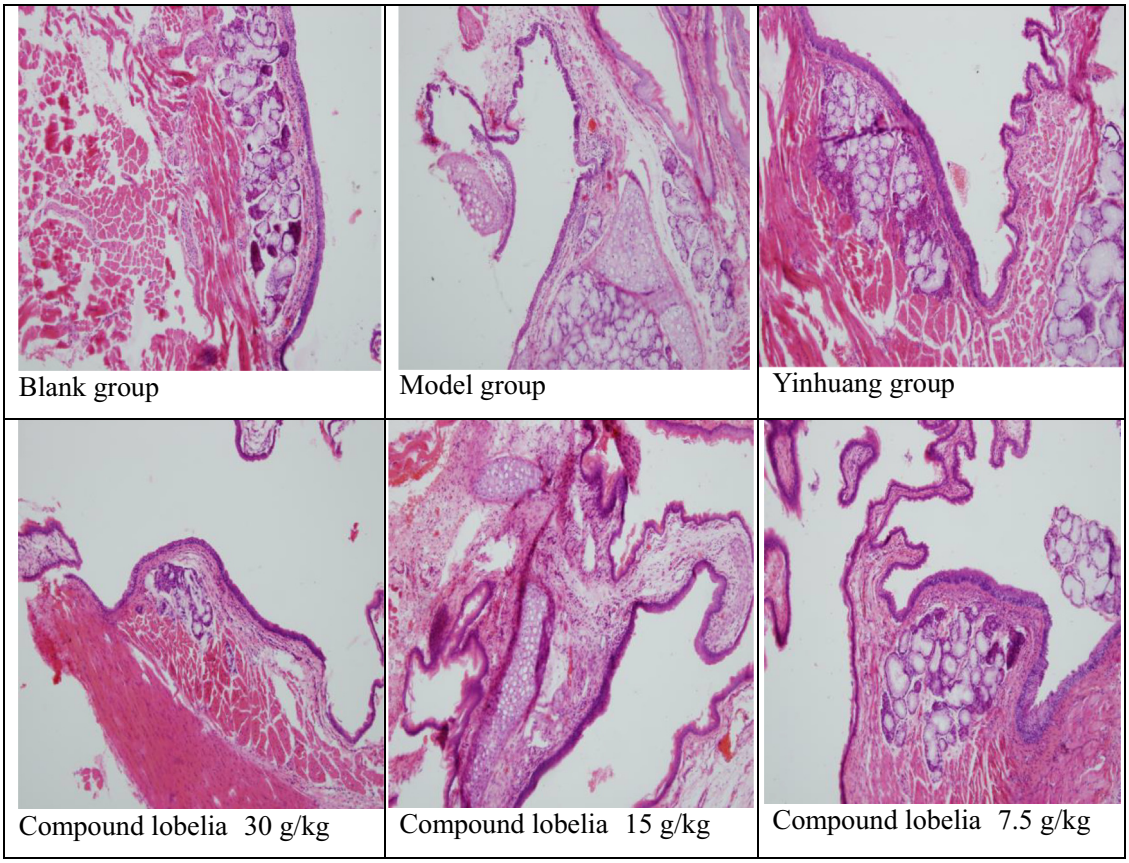

Fig. 1. Pathological changes of pharyngeal tissues in each group (HEx100).

Table 5
Histopathological grading table of pharyngeal tissue of rats in each group.

Group	Dose	Pharyngeal histopathologic classification			
		–	+	++	+++
Blank group	–	12	0	0	0
Model group	–	0	0	0	12
Yinhuang group	10 ml/kg	2	8	2	0
Compound lobelia	30 g/kg	2	9	1	0
	15 g/kg	1	8	3	0
	7.5 g/kg	0	8	4	0

"–" means that the mucosa of pharynx and submucosa are normal; "+" indicates that the scaly epithelium of pharynx has little hyperplasia and a small amount of inflammatory cells infiltrate under the mucosa. "++" means scaly epithelium hyperplasia of pharynx mucosa, and inflammatory cell infiltration is seen in the lower layer. "+++" means the pharynx mucosa scaly epithelium hyperplasia, a large number of inflammatory cells infiltrated under the mucosa.

pathogens, or the heat of the lungs and stomach, attack of the throat. Therefore, the main clinical manifestations are throat pain, redness and fever (Zhang et al., 2017). And it is advisable to nourish the lung and kidney, clear the heat and detoxify. compound Lobelia oral liquid is composed of Lobelia, *Sculellaria barbata*, *Oldenlandia diffusa*, etc. Lobelia has the functions of clearing heat and detoxify, dispersing blood stasis and reliving pain (Tao and Balunas, 2016); *Sculellaria barbata* and *Oldenlandia diffusa* all can clear heat and detoxify, and have more applications in the treatment of tumor, inflammation, and often in the form of drug pairs (Zheng et al., 2018; Fan et al., 2010; Peng et al., 2018). Combined with the indications and the composition of prescription of compound Lobelia injection, it is suggested that the oral liquid of compound Lobelia oral may have curative effect on acute pharyngitis.

It is reported that acute pharyngitis may appear within one week of chemical stimulation. In this study, the acute pharyngitis model of rats was prepared by spraying ammonia water on the pharynx of rats (Miao et al., 2018). The stimulation of ammonia water can make the blood vessels of pharynx tissue dilate and hyperemia, causing a large number of inflammatory cell infiltration (Ma et al., 2017). TNF-α and other inflammatory factors can increase the permeability of vascular endothelial cells, promote lymphocyte activation, and induce IL-6 self-secretion (Matsumoto et al., 2018; Song et al., 2018). Increased IL-6 secretion can stimulate the activation of mononuclear macrophages, and produce TNF-α and interleukin, etc., thus aggravating the inflammatory reaction (Zhang et al., 2018). It has been reported that egg white and carrageenan gum can cause foot swelling in rats, and sodium carboxymethylcellulose can attract white blood cells to migrate to loose connective tissue and participate in immune response and inflammatory response (Duan et al., 2015; Lee et al., 2018).

In this study, the effects of compound Lobelia oral liquid on acute pharyngitis rats model were investigated by observing the

anti-inflammatory effect, as well as the apparent symptoms, TNF-α and IL-6 levels and pharyngeal histopathological changes of acute pharyngitis rats. Results showed that compound Lobelia oral liquid could improve the infiltration of inflammatory cells in the pharynx and repair the pharynx mucosa of acute pharyngitis rats, so as to improve the symptoms of pharyngitis. It also could reduce the degree of foot swelling and the number of white blood cells in rat model of white blood cells migration. The experimental results show that compound Lobelia oral liquid has a good effect on improving acute pharyngitis model in rats, as well as good anti-inflammatory effect which provides an experimental basis for the clinical medicine of compound Lobelia oral liquid.

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