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The anti-inflammatory and analgesic effects of *Senecio scandens Buch-Ham.* ethanol extracts (SSBHE).

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Abstract

Objective: This research was to study the anti-inflammatory and analgesic effects of Climbing Groundsel Herb ethanol extracts. And observe its mechanism of action preliminarily.
Methods: HAC writhing reaction and hot plate test were used to observe the analgesic effect of senecio. The mouse ear swelling induced by xylene, the rat granulation tissue hyperplasia induced by cotton ball and rat egg white paw edema study of anti-inflammatory effect of senecio. Through the determination of formaldehyde in mice analgesia experiment and rat foot claws inflammatory exudate of PGE2 content to study the anti-inflammatory and analgesic mechanisms.
Results: Groundsel ethanol extract can significantly decrease The Times of the mice body torsion and significantly increase the pain threshold of mice, the mouse ear swelling induced by xylene, induced rat granulation tissue hyperplasia induced by cotton ball and egg qing to rats foot swelling has obvious inhibitory effect; and to reduce the formaldehyde in mice analgesia experiment II pain reaction, can reduce rats foot claws inflammatory exudate content of PGE2.
Conclusion: The alcohol extracts of *Senecio scandens Buch-Ham.* have obvious anti-inflammatory analgesic effect, and has a certain peripheral analgesic activity, its anti-inflammatory effects may be related to its inhibition of PGE2 synthesis or release from inflammatory tissue.

Keywords: Senecio, Anti-inflammatory, Analgesia, Mechanism of action

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Introduction

Senecio scandens Buch-Ham. (SSBH) is one of commonly used traditional Chinese medicine in China [1]. The historical records named Gleaning Herb recorded its properties anti-inflammatory and antiallergenic [2]. It was mainly distributed in Zhejiang, Jiangsu, Anhui and other places. Its pharmacological activities including heat-clearing and detoxifying, improving eyesight, cooling blood, expelling wind and removing damness [3-5]. The extracts could be mainly classified into several categories of flavonoids, phenolic acids, volatile oils, alkaloids, etc [6]. Researchers reported that the decoction has obvious inhibition on many bacteria like *Staphylococcus aureus*, *Diphtheria bacillus, Salmonella typhi, Escherichia coli*, proteus and *Dysentery bacillus* [2-3]. More importantly, it could protect the liver from its lesion by inhibit the levels of ALT and AST in serum [7]. We therefore designed this study to observe the anti-inflammatory and analgesic effects of the *Senecio scandens Buch-Ham*. ethanol extracts.

Materials and Methods

Extracts preparation

SSBH was collected from Henan Province Hao Xin Chinese medicinal materials co., LTD., verified by the College of Traditional Chinese Medicine of university. 4 kg of this medicine was extracted for three times with 95% ethanol, and got 748 g extracts by the method of low vacuum drying. 150 g extracts were used to the studies of the anti-inflammatory and analgesic effects. Ibuprofen Sustained Release Capsules (Tianjin schick pharmaceutical co., LTD of China and the United States) Pethidine hydrochloride injection (Northeast pharmaceutical group shenyang first pharmaceutical co., LTD)

Animal

210 KM mice in CL grade, weight from 18 g to 20 g, half male and half female. 100 SD rats in CL grade, weight from 150 g to 180 g.

Methods

Twisting in Kunming mice caused by acetic acid [8]

Fifty Kunming mice were randomly divided into 5 groups, including blank, ibuprofen group, alcohol extract of SSBH high, medium and low dose group (the equivalent of 3.0, 1.5, 0.75 g/kg). Administered by intragastric administration (ig) consecutively for 7 days, as for blank group, was given the same amount of 0.5% sodium carboxymethyl cellulose solution. Intraperitoneal injection was given at the last administration with 0.01 ml/g (0.7%). Record mice body torsion times within 10 minutes, extend hind legs, concave abdomen, hip elevation, calculate the rate of analgesia.

KunMing mice hot plate test [9]

Fifty female KunMing mice were put on the hot plate (55 ± 0.2), record the required reaction time of licking enough, the pain response latency as the pain threshold of mice, select fifty mice whose pain threshold range from 5 to 30, including blank, ibuprofen group, alcohol extract of SSBH high, medium and low dose group (the equivalent of 3.0, 1.5, 0.75 g/kg). And then every mouse was put on one by one on the hot plate instrument, got the determination of drug delivery of pain threshold twice, take the average value as the medicine before the pain threshold. Administered by intragastric administration (ig) consecutively for 7 days, as for blank group, was given the same amount of 0.5% sodium carboxymethyl cellulose solution. Record the pain threshold of mice 30 mins after the last administration, and calculate the pain threshold percentage increase.

Mice ear swelling induced by xylene [10]

Fifty female KunMing mice were grouped and divided randomly, including blank, ibuprofen group, alcohol extract of SSBH high, medium and low dose group (the equivalent of 3.0, 1.5, 0.75 g/kg). Administered by intragastric administration (ig) consecutively for 7 days, as for blank group, was given the same amount of 0.5% sodium carboxymethyl cellulose solution. 30 mins later, Xylene was dropped on the left auricle of mice (20 μl), and 1 hour later, the mice were ultimately killed, cut around the ears to punch 8 mm of diameter respectively in the same place. Each mice was weighed by the analytical balance, the ear swelling degree and the inhibition rate were calculated.

Albumin induced rat paw edema [11]

Fifty male SD rats were grouped and divided randomly, including blank, ibuprofen group, alcohol extract of SSBH high, medium and low dose group (the equivalent of 3.0, 1.5, 0.75 g/kg). All the mice were given the same medicine as mentioned above. Before the last delivery, water displacement of the right rear foot of the researched rats was tested. And after I.g. administration, the right hind paw of every SD rats were hypodermic injected with 0.1 ml 10% egg white. The water displacement was recorded at 1, 2, 3, 5, 6h. The swelling rate differences was swelling volume, calculate the swelling rate, and observes the peak time and fade time, at last the differences were compared between the treatment group and blank group.

Test of cotton induced granuloma in rats [12]

Thirty male SD rats were grouped and divided randomly to five groups as mentioned above. Every rat was light anesthetized, and under the sterile condition, the cotton ball (each weighed 30 mg ± 0.5 mg, high pressure sterilization, and contained 1 mg/0.1 ml, dried at 50) was implanted in the rat groin skin on both sides. Administered at the onset of surgery by intragastric administration (ig) consecutively for 7 days. As for blank group, was given the same amount of 0.5% sodium carboxymethyl cellulose solution. The rats were ultimately killed and the cotton balls were got out and were placed in oven at 60 for 12 hours. The weight of granuloma was calculated out with the difference between the weight of before and after the test.

Effect of SSBHE on the PGE2 in the excretions of rat with paw edema [13]

During this test, after the detection of feet swelling degrees, the rats were killed. Cut out the inflammatory foot ankle and peeled, cut up into 2 ml saline soak for 24 h, centrifuged, 2 ml methanol solution of potassium hydroxide was added to 0.1 ml supernatant liquid. Diluted with methanol to 4 ml, OD value was tested at 278 nm, per gram inflammation tissue equivalent OD value (A/g) showed the content of PGE2.

Effect of SSBHE on the in mice analgesia experiment induced by formaldehyde [14]

Sixty male mice were grouped and divided randomly, including blank, ibuprofen group, alcohol extract of SSBH high, medium and low dose group (the equivalent of 3.0, 1.5, 0.75 g/kg) and pethidine group. The first five groups were all administered as the Twisting test in Kunming mice caused by acetic acid, 6 groups of intraperitoneal injection of pethidine (1.5 mg/kg). The first group were all given pethidine by intraperitoneal injection (1.5 mg/kg). After one hour, 10 μl formalin solution (2.5%) were subcutaneous injected consecutively. Observe the accumulated time of pain reaction in mice after ten minutes and twenty minutes, then were rated. Grading methods: licking, biting or shake foot got 3 points, raise foot got two points, claudication and foot hold with freely about 0. Calculate the cumulative score at phase I and II, cumulative score = (0t1 +1t2 +2t3 +3t4)/(t1 +t2 +t3 +t4) [t1t2t3t4 were the duration at the score of 0,1,2,3]

Results

Twisting in Kunming mice caused by acetic acid

Compared with blank group, ibuprofen group and SSBHE could significantly inhibit the twisting induced by acetic acid. In addition, the inhibition showed a concentration-response

relationship. This result suggested that the SSBHE could obviously inhibit the pain caused by chemical stimulation. The results showed in Table 1.

Table 1. *Twisting in Kunming mice caused by acetic acid ($\bar{x}$ ± s, n=10).*

Group	Number	Dose	Times of body sprain
Blank group	10		32.1 ± 3.23
High dose	10	3	12.5 ± 1.31**
Middle dose	10	1.5	17.2 ± 2.92**
Low dose	10	0.75	26.3 ± 5.12*
Ibuprofen	10	0.1	8.2 ± 1.05**

Note: Compared with blank group, **means significant statistical differencesp<0.01, *means statistical differences, p<0.05.

The KuMing mice hot plate test

Compared with pre-administration and blank group, the incubation period of mice on the hot plate could be slightly extended by high dose of SSBHE, but middle dose and low dose could not exhibit great effect, as showed in Table 2.

Mice ear swelling induced by xylene

The results showed that the high, middle, low dose of SSBHE has inhibit the ear swelling obviously compared with blank group, had significant difference (P<0.01).

Table 2. *The effect of SSBHE on hot plate test ($\bar{x}$ ± s, n=10).*

Group	Number	Dose	Latencies of licking paws (s) Analgesic ratio (%)	
			Pre-administration	1h after treatment
Blank group	10		15.4 ± 3.52	15.4 ± 4.34
High dose	10	3	15.2 ± 2.83	16.5 ± 3.65
Middle dose	10	1.5	15.3 ± 2.75	15.3 ± 2.90
Low dose	10	0.75	14.8 ± 2.58	14.9 ± 2.74
Ibuprofen	10	0.1	15.3 ± 2.61	22.1 ± 3.17

Note: Compared with blank group, **means significant statistical differencesp<0.01, *means statistical differences, p<0.05.

And the effect of high dose group was same as the ibuprofen group, showed in Table 3.

Effect of SSBHE on the albumin induced rat paw edema test

Each dose mentioned in this study could all inhibit the edema induced by egg white, and exhibits a concentration-efficiency relationship, suggested that SSBHE has a good anti-inflammatory effect, showed in Table 4.

Table 3. *The effects of SSBHE on the test of mice ear swelling induced by xylene ($\bar{x}$ ± s, n=10).*

Group	Number	Dose (g/kg)	Ear swelling value (mg)	Swelling ratio (%)
Blank group	10		4.29 ± 1.52	
High dose	10	3	2.82 ± 0.32**	34.27
Middle dose	10	1.5	3.45 ± 0.52**	3.26
Low dose	10	0.75	4.15 ± 1.26*	43.59
Ibuprofen	10	0.1	2.42 ± 0.33**	49.18

Note: Compared with blank group, ** means significant statistical differencesp<0.01, * means statistical differences, p<0.05.

Table 4. *Effect of SSBHE on the albumin induced rat paw edema test.*

Group	Number	Dose	Swelling rate (%)					
		(g/kg)	1h	2h	3h	4h	5h	6h
Blank group	10		43.16 ± 11.05	51.23 ± 12.62	57.34 ± 10.51	53.15 ± 4.79	49.25 ± 13.52	47.56 ± 8.43
High dose	10	3	15.22 ± 2.71**	23.24 ± 2.89**	37.45 ± 3.52**	35.12 ± 3.84**	31.26 ± 2.16**	32.71 ± 3.95**
Middle dose	10	1.5	20.61 ± 2.37**	28.81 ± 3.75**	47.37 ±3 . 98**	45.28 ± 4.52*	40.79 ± 4.01*	37.94 ± 3.88**
Low dose	10	0.75	38.34 ± 3.13*	40.58 ± 4.04*	52.15 ± 4.63*	49.39 ± 4.28	46.41 ± 4.51*	40.28 ± 2.82*
Ibuprofen	10	0.1	12.65 ± 1.28**	15.92 ± 2.01**	33.65 ± 3.25**	37.23 ± 3.44**	37.89 ± 3.75**	35.47 ± 3.94**

Note: Compared with blank group, ** means significant statistical differencesp<0.01, * means statistical differences, p<0.05.

The effects of SSBHE on the test of cotton induced granuloma in rats

The ethanol extracts of SSBH could greatly inhibit the proliferation of granulation tissue of rats induced by cotton ball, and showed a concentration-efficiency relationship, seen in Table 5.

Effect of SSBHE on the PGE2 in the excretions of rat with paw edema

Each dose of SSBHE could obviously decrease the content of PGE2 in the excretions of paw edema, suggested that SSBHE

may could suppress the synthesis or release of PGE2 to show the anti-inflammatory activity, showed in Table 6.

Table 5. The effects of SSBHE on the test of cotton induced granuloma in rats ($\bar{x} \pm s$, n=10).

Group	Number	Dose (g/kg)	Granuloma Weight (g)	Inhibition rate (%)
Blank group	10		24.51 ± 2.46	
High dose	10	3	16.13 ± 1.22**	34.19
Middle dose	10	1.5	20.65 ± 2.13**	15.75
Low dose	10	0.75	23.10 ± 1.58*	5.75
Ibuprofen	10	0.1	16.30 ± 1.52**	33.50

Note: Compared with blank group, ** means significant statistical differencesp<0.01, * means statistical differences, p<0.05.

Table 6. Effect of SSBHE on the PGE2 in the excretions of rat with paw edema ($\bar{x} \pm s$, n=10).

Group	Number	Dose(g/kg)	PGE_2(A/g paw weight)	Inhibition rate(%)
Blank group	10		0.3121 ± 0.0462	
High dose	10	3	0.1589 ± 0.0316**	49.09
Middle dose	10	1.5	0.2147 ± 0.0267**	31.21
Low dose	10	0.75	0.2487 ± 0.0321*	20.31
Ibuprofen	10	0.1	0.1673 ± 0.0158**	46.40

Note: Compared with blank group, **means significant statistical differencesp<0.01, *means statistical differences, p<0.05.

Table 7. Effect of SSBHE on the in mice analgesia experiment induced by formaldehyde ($\bar{x} \pm s$, n=10).

Group	Number	Dose (g/kg)	Pain Score	
			Phase	Phase
Blank group	10		1.61 ± 0.12	1.64 ± 0.15
High dose	10	3	1.56 ± 0.08	1.52 ± 0.09**
Middle dose	10	1.5	1.57 ± 0.11	1.48 ± 0.12*
Low dose	10	0.75	1.59 ± 0.15	1.56 ± 0.10
Ibuprofen	10	0.1	1.45 ± 0.14**	1.28 ± 0.12**
Pethidine	10	0.015	1.27 ± 0.08**	1.15 ± 0.07**

Note: Compared with blank group, **means significant statistical differencesp<0.01, *means statistical differences, p<0.05.

Effect of SSBHE on the in mice analgesia experiment induced by formaldehyde

The effect of SSBHE on first phase was not obvious, but could significantly inhibit the second phase, suggested that it has a good analgesic effect on the pain induced by peripheral sensitization (Table 7).

Discussion

This research had proved that the ethanol extracts of *Senecio scandens Buch-Ham*. (SSBHE) has obvious anti-inflammatory and analgesic pharmacological effects, actually this two activity were also related with its excellent antibacterial activity closely. SSBHE contains many flavonoids, including Hyperoside, linarin and other same kinds [15]. Meanwhile, it could exhibit a great inhibition on the *Staphylococcus aureus*, *Salmonella enteritidis*, *Bacillus anthracis* [2-3].

Both of hot plate test and acetic acid body torsion experiment were used to study the analgesic effect of SSBHE. However, there are differences between the above two methods. The hot plate method is suitable for evaluation of the effect of high pericranium participated in, but acetic acid body torsion experiment was suitable for peripheral analgesic mechanism research. Results showed that SSBHE had peripheral analgesic activity, but central analgesic activity was not obvious. The formalin test in mice was internationally recognized for screening of weak analgesic drugs. As for this model, the pain response was classified into two phases, which represent different types of pain, the first phase was a direct pain effect on nerve endings, and however the second phase was generated by peripheral nerve stimulation. Results show that the SSBHE could significantly weaken the pain at the second phase, but SSBHE showed few effect on the pain reaction, suggested that the it has certain peripheral analgesic activity. This was in line with the results of the hot plate test and the acetic acid twisting test, all the results got in this study clarify commendably analgesic mechanism of SSBHE.

PEG2 is one of a very important inflammatory mediator, exists in inflammatory tissue, synergy was played after its interaction with bradykinin and leukotrienes. Then, vasodilation and vascular permeability were all increased, at last the synthesis of PEG2 was inhibited, therefore the inflammatory reaction was remitted. The results of this study showed that the anti-inflammatory effects may be related to the two reduction of the PEG2 content in the inflammatory tissue, the analgesic effect also might be related to the synthesis and release of PEG2 content in the inflammatory tissue. In addition, PEG2 also was a kind of important medium pain and peripheral pain could be caused by PEG2 was already clear to us.

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