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Original Article

Anti-inflammatory activity of leaf essential oil from *Cinnamomum longepaniculatum* (Gamble) N. Chao

Yong-Hua Du[1*], Rui-Zhang Feng[1*], Qun Li[3*], Qin Wei[1*], Zhong-Qiong Yin[2*], Li-Jun Zhou[4*], Cui Tao[2], Ren-Yong Jia[2]

[1]*Key Lab of Aromatic Plant Resources Exploitation and Utilization in Sichuan Higher Education, Yibin University, Yibin 644000, Sichuan, China;* [2]*College of Veterinary Medicine Sichuan Agricultural University, Ya'an 625014, Sichuan, China;* [3]*Sichuan Normal University, College of Life Science, Chengdu 610101, Sichuan, China;* [4]*Yibin Vocational and Technical College, Yibin 644003, Sichuan, China.* [*]*Equal contributors.*

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Abstract: The anti-inflammatory activity of the essential oil from *C. longepaniculatum* was evaluated by three experimental models including the dimethyl benzene-induced ear edema in mice, the carrageenan-induced paw edema in rat and the acetic acid-induced vascular permeability in mice. The influence of the essential oil on histological changes and prostaglandin E_2 (PGE_2), histamine and 5-hydroxytryptamine (5-HT) production associated with carrageenan-induced rat paw edema was also investigated. The essential oil (0.5, 0.25, 0.13 ml/kg b.w.) showed significantly inhibition of inflammation along with a dose-dependent manner in the three experimental models. The anti-inflammatory activity of essential oil was occurred both in early and late phase and peaked at 4 h after carrageenan injection. The essential oil resulted in a dose dependent reduction of the paw thickness, connective tissue injury and the infiltration of inflammatory cell. The essential oil also significantly reduced the production of PGE_2, histamine and 5-HT in the exudates of edema paw induced by carrageenan. Both the essential oil and indomethacin resulted relative lower percentage inhibition of histamine and 5-HT than that of PGE_2 at 4 h after carrageenan injection.

Keywords: *Cinnamomum longepaniculatum*, essential oil, anti-inflammatory activity

Introduction

Inflammation is a complex physiological and pathological processes in response to infection and tissue injury. Inflammatory responses play important roles in immune protection and tumorigenesis [1, 2]. The major physiological changes of inflammation are the recruitment of leukocytes, plasma proteins and different mediators such as vasoactive amines (histamine, serotonin, adenosine) and eicosanoids (prostaglandins, thromboxanes, leukotrienes, lipoxins) [3, 4]. The inflammatory process is also associated with the increase of vasodilatation and capillary permeability [4, 5]. Sometimes inflammation may be harm to host when it is inappropriately triggered or not adequately controlled. The traditionally anti-inflammatory such as antihistamines, steroids and other nonsteroidal drugs are available associated with some side effects including immunosuppression, gastrointestinal disturbances [6-8]. It has prompted a search for new, effective, and safe anti-inflammatory agents.

Many plants of the genus *Cinnamomum* such as *Cinnamomum osmophloeum*, *Cinnamomum camphora* and *Cinnamomum insularimontanum* have been proved possess anti-inflammatory activity [9-13]. *Cinnamomum longepaniculatum* (Gamble) N. Chao ex H. W. Li. is an endemic Cinnamomum Schaeffer tree that grows in evergreen broad-leaved forests at an elevation between 600-2000 m in Sichuan province of China [14]. The branchlets and leaves of *C. longepaniculatum* are used as a folk medicine to treat odontalgia, stomatitis and gingivitis in China. *C. longepaniculatum* has been researched with great interest for its abundant essential oil in the branchlets and

leaves. The main chemical constituents of this essential oil are cineole, terpineol, and sabinene [15]. This essential oil has usually been used as the raw material of perfume and medicine to export [16]. Recent researches of *C. longepaniculatum* have focused on increasing the production of oil by tissue culture [17, 18] and endophytic fungi and bacteria [19-21]. To the best of our knowledge, the bioactivity analyses of this essential oil only relate to antibacterial and antifungus activities [22, 23]. In our current study, the effects of leaf essential oil from *C. longepaniculatum* were investigated on the dimethyl benzene induced ear edema model and the carrageenan induced paw edema model. The capillary permeability in peritoneum was observed. The possible anti-inflammatory mechanisms were also evaluated by determining the capillary permeability in peritoneum and prostaglandin E_2 (PGE_2), histamine and 5-hydroxytryptamine (5-HT) production in acute inflammation models.

Materials and methods

Plant material

Fresh leaves of *C. longepaniculatum* were collected from a forestry standardization demonstration bases in Yibin city of Sichuan province, China, in July 2009. The plant was identified by the director of Key Lab. of Fermentation Resource and Application of Institutes of Higher Learning in Sichuan (laboratory code D15-BA163). The voucher specimen (Voucher specimen no. 20090701) was deposited in the Key Lab. of Protection and Exploitation of Southwest Special Economic Plant, Yibin University, China.

Chemicals

Carrageenan was purchased from Sigma Aldrich (St. Louis MO, USA). Evans blue was purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Indometacin was purchased from Shanxi Sanji Pharmaceutical Co., Ltd. (China). All other chemicals and solvents were of analytical grade.

Animals

Healthy adult male and female Institute of Cancer Research (ICR) mouse (18-22 g) and Sprague Dawley (SD) rats (180-220 g) obtained from the Institute of Laboratory Animal Research of Academy of Medical Science in Sichuan. All experimental animals were acclimatized for 7 days under the controlled conditions of temperature (25 ± 2°C), a 12 h day/night cycle and fed a standard pellet diet with water ad libitum in the animal holding facility (Laboratory Animal House, Sichuan Agricultural University).

Preparation of essential oil

Fresh leave of *C. longepaniculatum* were ground and the powdered material was extracted by hydrodistillation for 4 h. The essential oil was dehydrated by anhydrous sodium sulfate. The colorless or lightly yellow essential oil with cineole odor was obtained and stored at 4°C until use.

Dimethyl benzene induced ear edema model

The ear edema test was performed according to a previously reports with a slight modification [24, 25]. Fifty mouse were randomly divided into five groups (n=10 per group). Groups I, II and III received essential oil which diluted with 1% Tween 80 (0.5, 0.25, 0.13 ml/kg b.w.); group IV contained indomethacin represented the positive control (2 mg/kg b.w. in 1% Tween 80); group V contained the solvent of 1% Tween 80 as the control group (0.2 ml/10 g b.w). All animals were orally treated with the essential oil, indomethacin and solvent once a day. At the end of the 4th day, inflammation was induced by topical application of dimethyl benzene (20 μl) on the inner and outer surfaces of the left ear of each mouse after 1 h of treatment. The right ear treated nothing as a control. All mouse were sacrificed by cervical dislocation after 1 h of topical application. The ear disks were removed from each ear at the same position with 6 mm diameter punche and weighed in analytical balance immediately. The swelling degree (SD) was estimated as the difference in the weight between the ear disks from left and right ears. The inhibitory rate was calculated as follows:

$$\text{Inhibitory rate (\%)} = \frac{SD_{\text{control}} - SD_{\text{treated}}}{SD_{\text{control}}} \times 100$$

Carrageenan induced paw edema model

The paw edema test was assayed as previously method with a slight modification [25, 26]. Forty rats were randomly divided into five groups (n=8 per group). The groups and the doses of administration were same as the ear

edema test. Animals were orally administrated once a day for 4 days. After 1 h of the last administration, all mouse were injected 0.1 ml of carrageenan suspension (1.0%, w/v) into subplantar area of the right hind paw. The paw volumes were measured immediately before and 1, 2, 4, 5 and 6 h following carrageenan injection by a plethysmometer. The degree of swelling was calculated by the paw volume increase (V_t-V_0) where V_t and V_0 represent the volume of the right hind paw after and before the injection of the phlogistic agent respectively. The swelling degree was calculated as the following formula:

$$\text{Swelling degree (\%)} = \frac{V_t - V_o}{V_o} \times 100$$

The percentage inhibition was calculated as follows:

$$\text{Percentage inhibition} = \frac{(V_t - V_o)_{\text{control}} - (V_t - V_o)_{\text{treated}}}{(V_t - V_o)_{\text{control}}} \times 100$$

Acetic acid-induced vascular permeability model

Experiments were performed according to previously described [27, 28]. Fifty mouse were randomly divided into five groups (n=10 per group). The groups and the doses of administration were same as the ear edema test. 1 h After the last treatment of drugs, all mouse were injected intravenously 0.5% Evans blue solution dissolve in normal saline (0.1 ml/10 g b.w.), immediately followed by an intraperitoneal injection of 0.6% acetic acid (0.2 ml/mice). Twenty minutes later, all mouse were sacrificed by cervical dislocation. The peritoneal exudates were collected after 5 min of lavage of the peritoneal cavity with 5 ml normal saline, and centrifuged at 3000 r/min for 15 min. The absorbance of the supernatant was determined by a spectrophotometer at 590 nm. The percentage inhibition was calculated as follows:

$$\text{Percentage inhibition} = \frac{OD_{\text{control}} - OD_{\text{treated}}}{OD_{\text{control}}} \times 100$$

Determination of PGE_2, histamine and 5-HT

The experiment groups and the doses of administration were same as the paw edema test. All rats were sacrificed by cervical dislocation at 4 h after carrageenan injection. The edema paws were immediately cut at lateral malleolus and weighed immediately. The skin of the edema paw were taken off and soaked in 7 ml normal saline for 1 h together with the edema paws which were cut into pieces. The extract was centrifuged at 3 000 r/min for 5 min to obtain the supernatant. The determination of PGE_2 was performed according to the method described by Zhou et al. [29] with some modifications. 2 ml of 0.5 mol/L potassium hydroxide solution (dissolved in methanol) were added in the supernatant of 0.25 ml and then incubated at 50°C for 20 min in a water bath. The isomerizate solution was diluted with 5 ml of methanol and determined the absorbance at 278 nm. The concentration of PGE_2 was expressed in terms of weight (μg/g tissue) according to the standard curve of PGE_2.

The determination of histamine was performed as described by Yang et al. [30]. 1.5 ml of above-mentioned supernatant were mixed for 5 min with 0.25 ml of 5 mol/l NaOH, 1 g of NaCl and 5 ml of n-butanol. The mixed liquor were centrifuged at 3 000 r/min for 10 min and 4 ml of n-butanol fraction were added in 4.25 ml of 0.1 mol/L HCl. After 5 min of mixture, the centrifugation was also performed at 3 000 r/min for 10 min. The mixture containing 3 ml of the HCl fraction, 0.9 ml of l mol/L NaOH and 0.15 ml of 0.2% o-phthalaldehyde (methanol solution) were incubated in ice bath for 40 min. The fluorescence value (FV) was determined by a fluorescence spectrophotometer (excitation wave 355 nm) at 440 nm after the last solution was mixed with 0.45 ml of 2 mol/l citric acid.

5-HT levels were analyzed by the method of previously report [31]. The supernatants of edema paws were added 1.5 ml into a mixture which contained 1.5 g NaCl and 3.5 ml of acetous n-butanol and oscillated for 10 min. 2.5 ml of the n-butanol fraction were mixed with 5.0 ml of normal heptane and 1.0 ml of 0.1 mol/l HCl for 10 min. The aqueous phase was incubated in boiling water bath for 10 min with 0.1 ml of 0.5% cysteine and 2.5 ml of 0.008% o-phthalaldehyde (diluted with 10 mol/l HCl). After the solution was cooled, the absorbance (fluorescence value, FV) was determined by a fluorescence spectrophotometer (excitation wave 355 nm) at 475 nm. The percentage inhibition was calculated as follows:

$$\text{Percentage inhibition} = \frac{Value_{\text{control}} - Value_{\text{treated}}}{Value_{\text{control}}} \times 100$$

Histology

After the last measurement of the paw volume in the paw edema test, all animals were anes-

Table 1. Effects of essential oil from *C. longepaniculatum* on the dimethyl benzene induced mice ear edema

Groups	Dose	Swelling degree (mg)	Inhibition rate (%)
Solvent control	0.2 (ml/10 g)	7.08 ± 0.75	-
Indomethacin	2 (mg/kg)	3.73 ± 0.57**	47.32
Group III	0.5 (ml/kg)	5.94 ± 0.74*	16.10
Group II	0.25 (ml/kg)	6.08 ± 0.61*	14.12
Group I	0.13 (ml/kg)	6.74 ± 0.83	4.80

Values are mean ± SEM (n=10). *$p < 0.05$, **$p < 0.01$ significant from solvent control group.

thetized with diethyl ether and the paws were cut at lateral malleolus. The voix pedis of each sample were fixed in 10% formaldehyde solution. A series of 10 μm paw sections were prepared by a paraffin microtome. The sections were stained with haematoxylin and eosin (H&E) for the evaluation of the histological changes.

Statistical analysis

Data were expressed as means ± SEM. Statistical analysis of data was performed by using SPSS 13.0 statistical package program for windows. Statistical comparisons of the results were made by using one-way analysis of variance (ANOVA). The significance of difference was calculated by Dunnett's test with $p < 0.05$ considered to be significant.

Results

Effects of the essential oil on dimethyl benzene -induced ear edema in mice

The essential oil of *C. longepaniculatum* caused a dose-dependent decrease of ear edema with topical application of dimethyl benzene (**Table 1**). The essential oil significantly inhibited the ear edemas by 16.10% ($p < 0.05$) and 14.12% ($p < 0.05$) at 0.5 ml/kg and 0.25 ml/kg, respectively. However, the significant effect was not observed at the dose of 0.13 ml/kg ($p < 0.05$). As a positive control, indomethacin (2 mg/kg b.w) exhibited significant anti-inflammatory activity with the inhibition of 47.32% ($p < 0.01$).

Effects of the essential oil on carrageenan-induced paw edema in rat

In the carrageenan-induced rat paw edema test, the paw swelling degree and percentages of inhibition by essential oil are shown in **Table 2**. The essential oil of *C. longepaniculatum* also gave significant dose-dependent inhibitory activity throughout the 6 h experimental period. At the fourth hour after the carrageenan injection, the maximum swelling degree (78.73%) was observed in control rats. The maximum inhibitory effects by 0.5, 0.25 and 0.13 ml/kg of essential oil were 50.34%, 43.74% and 32.53% ($p < 0.01$) at 4 h after carrageenan injection, respectively. The activity appeared to drop slightly over the dose range after 5 h of subplantar injections. A similar inhibitory progression of rat paw edema was observed in the group which treated with indomethacin at a dose of 2 mg/kg and its maximal effect was 50.87% ($p < 0.01$) at 4 h after carrageenan injection.

The histological changes in the paw tissues after the injection of carrageenan are shown in **Figure 1**. The carrageenan provoked the strongest inflammatory response with subcutaneous edema and connective tissue disruption along with heavy infiltration of the inflammatory cells, particularly neutrophils and monocyte in solvent control (**Figure 1A**). The application of essential oil resulted in a dose-dependent reduction of the paw thickness, connective tissue injury and the number of cellular infiltration at all doses (**Figure 1C-E**). At the dose of 0.5 ml/kg, the essential oil ameliorated the inflammatory cells infiltration and it was similar to the positive control indomethacin which did not affect the presence of the connective tissue disruption (**Figure 1B**).

Effect of the essential oil on acetic acid-induced vascular permeability

As shown in **Table 3**, the essential oil of C. longepaniculatum significantly inhibited the peritoneal capillary permeability induced by acetic acid in mice ($p < 0.01$) and exhibited a dose-related inhibitory effect. Indomethacin (2 mg/kg) as a positive drug, also markedly inhibited peritoneal capillary permeability with 76% inhibition ($p < 0.01$) and the same effect was observed at the dose of 0.5 ml/kg of essential oil.

Effect of the essential oil on production of PGE_2, histamine and 5-HT

The results of the determination of prostaglandin E2 (PGE_2), histamine and 5-hydroxytrypta-

Table 2. Effects of essential oil from *C. longepaniculatum* on the carrageenan-induced rat paw edema

Groups	Swelling degree % (inhibition %)				
	1 h	2 h	4 h	5 h	6 h
Solvent control	36.56 ± 6.30	55.54 ± 4.23	78.73 ± 4.08	78.21 ± 3.74	72.25 ± 2.76
Indomethacin	24.72 ± 2.55 (32.39)**	27.29 ± 2.82 (50.86)**	38.68 ± 5.60 (50.87)**	39.63 ± 3.78 (49.33)**	57.24 ± 5.68 (20.77)*
Group III	20.68 ± 2.48 (43.44)**	30.39 ± 8.27 (45.28)**	39.10 ± 5.37 (50.34**	48.06 ± 4.42 (38.55)**	52.27 ± 4.70 (27.65)**
Group II	24.85 ± 1.40 (32.03)**	33.34 ± 6.13 (39.97)**	44.29 ± 5.87 (43.74)**	52.94 ± 4.31 (32.31)**	53.52 ± 7.72 (25.92)**
Group I	28.63 ± 3.32 (21.69)*	46.01 ± 7.83 (17.16)*	53.12 ± 6.71 (32.53)**	56.53 ± 4.45 (27.72)**	63.44 ± 3.5 (12.19)*

Values are mean ± SEM (n=8). *$p < 0.05$, **$p < 0.01$ significant from solvent control group.

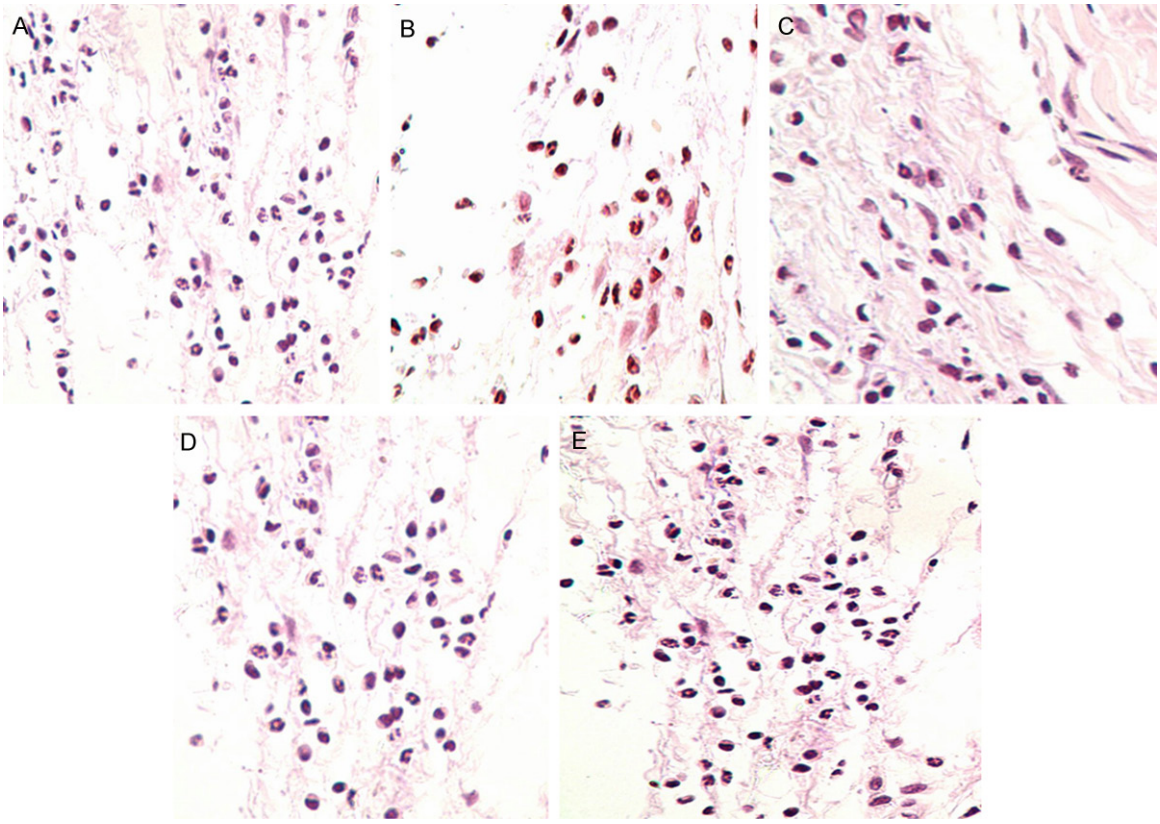

Figure 1. Anti-inflammatory effect of essential oil against carrageenan-induced edema and cellular infiltration as revealed by histological sections. The subcutaneous edema, connective tissue disruption and neutrophils and monocyte cell influx in solvent control (A). The reduction of inflammatory cells and edema in indometacin group (B). The dose-dependent reduction of connective tissue injury and inflammatory cell infiltration in essential oil treatment at 0.5 (C), 0.25 (D) and 0.13 (E) ml/kg. Representative sections in each group are shown (×400).

Table 3. Effect of essential oil on acetic acid-induced vascular permeability in mice

Groups	Dose	OD Value	inhibition %
Solvent control	0.2 (ml/10 g)	0.25 ± 0.02	-
Indomethacin	2 (mg/kg)	0.06 ± 0.01	76**
Group III	0.5 (ml/kg)	0.06 ± 0.01	76**
Group II	0.25 (ml/kg)	0.08 ± 0.02	68**
Group I	0.13 (ml/kg)	0.09 ± 0.03	64**

Values are mean ± SEM (n=10). **$p < 0.01$ significant from solvent control group.

mine (5-HT) in the exudates of edema paw induced by carrageenan are shown in **Table 4**. The treatment of essential oil displayed a dose-dependent decrease in the production of PGE_2, histamine and 5-HT in carrageenin-induced inflammatory response. The essential oil exhibited a significantly inhibitory activity on PGE_2 ($p < 0.01$) and histamine ($p < 0.05$) at all doses. The same effects were found in the 5-HT both at the doses of 0. 5 and 0.25 ml/kg ($p < 0.05$), while it could not be founded a significant sup-

Table 4. Effects of essential oil on PGE_2, histamine and 5-HT in the exudates of rat edema paw induced by carrageenan

Groups	Dose	PGE_2 (μg/g) (inhibition %)	Histamine (FV) (inhibition %)	5-HT (FV) (inhibition %)
Solvent control	0.2 (ml/10 g)	435.23 ± 24.94	29.24 ± 3.97	25.31 ± 0.99
Indomethacin	2 (mg/kg)	228.63 ± 15.58 (47.47)**	21.24 ± 2.87 (27.36)**	24.06 ± 0.77 (4.94)*
Group III	0.5 (ml/kg)	251.26 ± 13.41 (42.27)**	22.81 ± 2.01 (21.99)*	23.90 ± 0.31 (5.57)*
Group II	0.25 (ml/kg)	284.94 ± 17.94 (34.53)**	24.34 ± 4.67 (16.76)*	24.96 ± 0.39 (1.38)*
Group I	0.13 (ml/kg)	320.25 ± 16.83 (26.42)**	24.98 ± 3.07 (14.57)*	25.28 ± 0.69 (0.12)

Values are mean ± SEM (n=8). *$p < 0.05$, **$p < 0.01$ significant from solvent control group.

pression activity on 5-HT at the dose of 0.13 ml/kg. The maximum inhibitory effects of essential oil against PGE_2, histamine and 5-HT production, which represented by the percentage inhibition rate of 42.27% ($p < 0.01$), 21.99% ($p < 0.05$) and 5.57 ($p < 0.05$), respectively, were observed at the dose of 0.5 ml/kg. Indomethacin (2 mg/kg) served as positive control also significantly decreased the production of PGE_2 ($p < 0.01$), histamine ($p < 0.01$) and 5-HT ($p < 0.05$). After the topical application of essential oil and indomethacin, the percentage inhibition rate of histamine and 5-HT were relative lower than that of PGE_2.

Discussion

The dimethyl benzene-induced ear edema and carrageenan-induced paw edema are frequently used as an experimental model of acute inflammation to assess the anti-inflammatory effect of natural products [32, 33]. In the present study, the anti-inflammatory activities of leaf essential oil from C. longepaniculatum were evaluated by the two experimental models. The data showed that the essential oil could significantly inhibit dimethyl benzene-induced ear edema in mice and carrageenan-induced paw edema in rats. Both dimethyl benzene and carrageenan used by topical application cause an acute inflammatory response. Acute inflammation is characterized by the exudation of tissue fluid and plasma resulting in edema formation and concurrent the accumulation of mainly neutrophilic granulocytes [34]. The results of this investigation indicated that the essential oil of C. longepaniculatum relieved the subcutaneous edema and connective tissue injury induced by carrageenan and also reduced the presence of neutrophils and monocyte in the inflammatory area. In general, the initial step of the inflammatory process is vascular response including vasodilatation and increased capillary and venular permeability. The excess vascular response provokes the accumulation of fluid in the inflammatory tissue which results in the edema of tissue [35]. The acetic acid-induced vascular permeability model usually imitates the clinical features and pathogenesis of swollen inflammatory zone [36]. Our results showed that the essential oil had remarkable inhibitory activity with a dose-related property in this test model. Manly endocrine factors such as histamine, 5-HT, thrombin, bradykinin and vascular endothelial growth factor induce increased vascular permeability through direct action on the endothelial cells [37-39]. The increase of blood flow induced by prostaglandin E2 (PGE_2) also augment inflammatory edema and the permeability increasing ability of inflammatory mediators such as bradykinin and histamine [40]. It is well known that manly inflammatory mediators are used as the target of action of anti-inflammatory drugs [41]. The data showed that the essential oil significantly reduced the production of PGE_2, histamine and 5-HT in the exudates of edema paw induced by carrageenan. The inhibition of PGE_2 production are also observed in the anti-inflammatory activity of C. camphora and C. osmophloeum which evaluated by lipopolysaccharide (LPS)-activated macrophages model [10, 12]. It has been well established that the carrageenan-induced paw edema is biphasic: the first phase is mediated by release of histamine, serotonin and bradykinin, while the late phase is linked to the release of prostaglandins, proteases and lysozymes [42, 43]. The release of histamine and serotonin peak at 3 h after injection of carrageenan [42]. This is supported by the observation that both the essential oil and indomethacin caused relative lower inhibitory effects on the production of histamine and 5-HT than that of PGE_2 at 4 h after carrageenan injection. Our results also revealed that the essential oil significantly inhibited the formation of the rat paw edema in each phase, in fact

somewhat more effect in the late phase and peaked at 4 h. It indicates that the essential oil of C. longepaniculatum has potential anti-inflammatory activity.

Previous literatures have revealed that the anti-inflammatory activities of several plants of the genus Cinnamomum (C. osmophloeum, C. camphora and C. insularimontanum) are due to the inhibitory activity of cytokine including PGE_2, nitric oxide, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-12 and IL-6 [9-13]. Few active compounds isolated and identified from C. osmophloeumare are flavonol glycosides [9]. Tung et al [12] have reported that the anti-inflammatory activity of the essential oil of C. osmophloeum on PGE_2 is not attributable to the major constituents such as caryophyllene oxide and L-bornyl acetate, the anti-inflammatory activity may be attributable to the effects of minor constituents or synergetic effects among the constituents. The species of C. longepaniculatum is closely related to C. osmophloeum. More than twenty six compounds have been identified from the leaf essential oil of C. longepaniculatum and the major constituents are 1, 8-cineole, 1-α-terpineol and sabinene [15]. It is reported that 1, 8-cineole isolated from other plant displays a 26% inhibition on paw edema induced by carrageenan at the dose of 100 mg/kg [44]. However, whether the 1, 8-cineole is response for the anti-inflammatory activity of leaf essential oil from C. longepaniculatum is unknown.

In conclusion, the leaf essential oil from C. longepaniculatum has favorable anti-inflammatory activity, which is involved in the inhibition of the peritoneal capillary permeability and the production of PGE_2, histamine and 5-HT. It is suggested that this essential oil may be a potential anti-inflammatory agent. However, further studies are necessary to isolate and identify the anti-inflammatory active compound from this essential oil.

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Disclosure of conflict of interest

None.

Address correspondence to: Qin Wei, Key Lab of Aromatic Plant Resources Exploitation and Utilization in Sichuan Higher Education, Yibin University, Yibin 644000, China. Tel: 86-0831-3547707; Fax: 86-0831-3547707; E-mail: weiqin2001-67@163.com; Zhong-Qiong Yin, College of Animal Medicine, Sichuan Agricultural University, Ya'an, 625014, China. Tel: +86 835 2885614; E-mail: yinzhongq@163.com

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