



## ANTI-INFLAMMATORY AND WOUND HEALING ACTIVITY OF LEAF EXTRACTS OF *COCCULUS PENDULUS* (J.R. & G. FORST.) DIELS.

H. RABARI<sup>\*1</sup>, S. PANDYA<sup>2</sup>, G. VIDYASAGAR<sup>1</sup> AND B. GAJRA<sup>1</sup>

<sup>1</sup>Veerayatan Institute of Pharmacy, Jakhania, Mandvi, Kachchh, Gujarat, India.

<sup>2</sup>Pharmacy College, Rampura-Kakanpur, Panchmahal (District), Gujarat, India.

\*Corresponding Author      harirabari@yahoo.co.in

### ABSTRACT

The chloroform and ethyl acetate extracts of leaves of *Cocculus pendulus*, were tested for anti-inflammatory and wound healing activity at the doses of 200 and 400 mg/kg body weight. Both the extracts at the dose of 400 mg/kg body weight, produced dose dependent and significant inhibition of carrageenan induced paw edema. The exhibited anti-inflammatory activity was comparable with the standard drug aspirin. The wound healing activity was evaluated by using excision wound model of rat. The percentage of wound contraction was found to be significant in animals treated with chloroform extract and ethyl acetate extract when compared to controls. The results were comparable with that of the standard drug povidone iodine ointment. The chloroform and ethyl acetate extract treated wounds were found to epithelize faster as compared to controls.

### KEYWORDS

*Cocculus pendulus*, Chloroform extract, Ethyl acetate extract, Anti-inflammatory activity, wound healing activity.

### INTRODUCTION

The genus *Cocculus* belongs to the family Menispermaceae. It comprises about 35 species, distributed throughout the tropical and subtropical countries of the world. The plants of this genus are shrubs or woody climbers. The members of this genus are used in the traditional system of medicine. The chemical investigation revealed that alkaloids are the main constituents of these plants. Only two species of *Cocculus* are found in Kachchh region of Gujarat, i.e. *Cocculus pendulus* and *Cocculus hirsutus*. The plant *Cocculus pendulus* (synonym: *Cocculus leaeba*) is a

scandent shrub, growing particularly in cultivated areas, along rocks and in the dry mountainous areas of Nakhatrana, Mandvi and Bhachau taluqas of Kachchh district. The roots of the plant are used in the indigenous system of medicine for the treatment of intermittent fevers and as a tonic. Hypotensive and anticancer activity has been attributed to the alkaloid fractions from the leaves and stems<sup>1</sup>. The juice of the leaves contains mucilage which when mixed with water forms a jelly. This is taken as a cooling medicine for gonorrhoea. The roots and leaves are used in rheumatic pains<sup>2</sup>. In view of the available literature, it is clear that though different species of *Cocculus* have been investigated with respect to their chemical



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constituents, yet extensive studies have not been carried out on the plant *Cocculus pendulus* with respect to their pharmacological activities so far.

### MATERIALS AND METHODS

#### *Collection and authentication of the plant material*

Fresh leaves of *Cocculus pendulus* were collected from the outfield area of Jakhaniya village of Kachchh region of Gujarat (India) in the month of June-2007. The plant material was identified and authenticated from the Botanical Survey of India, Pune. The voucher specimen **CPHAR-1** was also kept in the institute for future reference. The collected leaves were shade dried for 15 days and size reduced by laboratory grinder in to coarse powder. It was stored in a well closed container free from environmental climatic changes till usage.

#### *Method of extraction*

Dried leaves of *Cocculus pendulus* (1 kg) were soaked in alcohol (4 liters) and kept covered for 4-5 days and filtered. The filtrate (alcohol extract) was concentrated under vacuum. The concentrate was acidified with 5% hydrochloric acid (200 ml) solution and the fatty material was removed by extraction with petroleum ether. The aqueous layer was extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulfate and concentrated (CECp-1). The remaining solution (aqueous layer) was basified with ammonium hydroxide (up to pH 10) and extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulfate, filtered and evaporated to dryness in vacuum (CECp-2). The remaining solution (aqueous layer) was extracted with ethyl acetate. The ethyl acetate extract was dried with sodium sulfate and evaporated to dryness in vacuum

(EAECp). All the extracts were concentrated in vacuum and were preserved.

#### **Preliminary phytochemical screening of various extracts**

The extracts obtained during the extraction process were subjected to preliminary phytochemical screening to determine the presence of various phytoconstituents by using reported methods<sup>3-6</sup>.

#### **Preparation of test extract**

After concentration and drying of each extract, methanolic and aqueous extracts were selected for the study.

#### *Test extract for anti-inflammatory activity*

A suspension of required quantity of chloroform and ethyl acetate extracts were prepared in 2% gum acacia and used for the oral administration to the animals.

#### *Test extract for wound healing activity*

Both the chloroform and ethyl acetate extracts were suspended in simple ointment base and used for the topical application to the animals.

#### **Experimental animals**

Albino rats (Wistar strain) of either sex weighing between 150-200 g were used for experimental purpose. The animals were kept in polypropylene cages at room temperature and under 12:12 hours light/ dark cycle. The animals had free access to standard rat pellet and water under strict hygienic conditions. Animals were habituated to laboratory



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conditions for 48 hours prior to experimental protocol to minimize, if any non-specific stress. The animals were divided into groups of six animals each and fasted for 12 hours before the experiment. The study was approved by Institutional Animal Ethical Committee of Babaria Institute of Pharmacy, Varnama-Vadodara, Gujarat (India), registered under CPCSEA with Reg. No. 1029/a/07/CPCSEA.

### Acute toxicity studies

An acute toxicity study was conducted for all the extract by the stair-case method <sup>7</sup>. The healthy Wistar rats of either sex were fed with plant extracts in increasing doses of 250, 500, 1000, 2000 and 4000 mg/kg body weight respectively. The toxicity was

assessed by mortality and behavior changes of the animals.

### Selection of dose

Safety of the medicinal plants is equally important when they are used clinically. The doses up to 4000 mg/kg body weight did not produce any signs of toxicity and mortality. The animals were physically active and were consuming food and water in a regular way. A 5% and 10% of the maximum tolerated dose i.e. 200 and 400 mg/kg body weight was selected for the study. A substance is considered safe if it produces no adverse effect in 10 times of the therapeutic dose <sup>8</sup>. These findings support the observation of safety of the plant extracts.

**Table 1.**  
*Experimental design for anti-inflammatory studies in rat*

Group	Treatment	Dose
I-Control	2 % w/v gum acacia prepared in normal saline	10 ml/kg; <i>p.o.</i>
II-Standard	Aspirin (suspended in 2 % w/v gum acacia)	100 mg/kg; <i>p.o.</i>
III-Test Extract CECp-200	Methanol extract of <i>Cocculus pendulus</i> (suspended in 2 % w/v gum acacia)	200 mg/kg; <i>p.o.</i>
IV-Test Extract CECp-400	Methanol extract of <i>Cocculus pendulus</i> (suspended in 2 % w/v gum acacia)	400 mg/kg; <i>p.o.</i>
V-Test Extract EAECp-200	Aqueous extract of <i>Cocculus pendulus</i> (suspended in 2 % w/v gum acacia)	200 mg/kg; <i>p.o.</i>
VI-Test Extract EAECp-400	Aqueous extract of <i>Cocculus pendulus</i> (suspended in 2 % w/v gum acacia)	400 mg/kg; <i>p.o.</i>

The activity of plant extracts were evaluated by using carrageenan induced hind paw edema model <sup>9-14</sup>. The wistar albino rats of either sex were divided into six groups comprising six animals in each group (n=6) as shown in Table 1. The animals were starved overnight and deprived of water only during the experiment. Inflammation of the hind paw was induced by injecting 0.1 ml of 1% w/v carrageenan suspension prepared with 2% gum acacia in normal saline into the sub-plantar surface of the right hind paw. The negative control group was treated with 2% gum acacia at a dose of 10 ml/kg body weight. The positive control group was treated with aspirin (100 mg/kg body weight). The remaining four groups received the chloroform and ethyl



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acetate extracts of *Cocculus pendulus* at the doses of 200 and 400 mg/kg body weight. All the treatments were given one hour before the carrageenan injection. The measurement of paw volume was accomplished immediately by displacement technique using plethysmometer before the carrageenan injection and at 1, 2, 4 and 6 hours after the carrageenan injection. Percentage inhibition of paw edema volume was calculated using the formula: Percentage Inhibition =  $[1 - V_t/V_c] \times 100$

Where,  $V_t$  = difference in paw edema volume of drug treated animals

$V_c$  = difference in paw edema volume of control treated animals

**Table 2.**  
*Experimental design for wound healing studies in rat*

Group	Treatment	Dose
I-Control	Ointment base	100 mg/kg; topically
II-Standard	5 % w/w Povidone iodine ointment	100 mg/kg; topically
III-Test Extract CECp-200	Methanol Extract of <i>Cocculus pendulus</i> (prepared with simple ointment base)	200 mg/kg; topically
IV-Test Extract CECp-400	Methanol Extract of <i>Cocculus pendulus</i> (prepared with simple ointment base)	400 mg/kg; topically
V-Test Extract EAECp-200	Aqueous Extract of <i>Cocculus pendulus</i> (prepared with simple ointment base)	200 mg/kg; topically
VI-Test Extract EAECp-400	Aqueous Extract of <i>Cocculus pendulus</i> (prepared with simple ointment base)	400 mg/kg; topically

The animals were randomly allocated into six groups comprising six animals each (n=6) for the study as described in Table 2. Animals were anesthetized prior to and during creation of the wounds, with light ether anesthesia. The rats were inflicted with excision wounds<sup>15</sup>. The dorsal fur of the animals was shaved with an electric clipper and the anticipated area of the wound to be created was outlined on the back of the animals with methylene blue. A full thickness of the excision wound of 2.5 cm in width was created along the markings using toothed forceps, scalpel and pointed scissors. The negative control group was applied with simple iodine ointment. The positive control group was applied with 5% povidone iodine

ointment. The remaining four groups applied with the chloroform and ethyl acetate extracts of *Cocculus pendulus* at the doses of 200 and 400 mg/kg body weight. All the test extracts at different dose level and standard were administered topically once daily from day 0 to the day of complete healing or the 21<sup>st</sup> postoperative day, whichever occurred earlier. The following parameters were evaluated such as wound area measurement, percentage wound contraction, period of epithelialization and scar area. The rate of wound closure was assessed by tracing the wound on days 0, 4, 8, 12, 16 and 21 post-wounding using transparency papers and a permanent marker. The wound areas recorded were measured using graph



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paper. The day of eschar falling, after wounding, without any residual raw wound was considered as the period of epithelialization. The percentage wound

contraction was calculated by using following formula:

$$\text{Percentage Closure} = \frac{\text{Wound area on corresponding day} - \text{Wound area on zero day}}{\text{Wound area on zero day}} \times 100$$

### Statistical analysis

All data were expressed as standard error of mean ( $\pm$ SEM) and one-way analysis of variance (ANOVA) was applied to determine the significance difference between the rats treated with test extracts, controls and standards. P value  $<0.05$  were considered statistically significant.

## RESULTS AND DISCUSSION

The preliminary phytochemical screening with the various qualitative chemical tests revealed the presence of alkaloids in all the three extracts, and it was the main constituents present in the leaves of *Cocculus pendulus*. Carbohydrates, phytosterols, proteins and mucilage are the other phytoconstituents were present in the leaf extracts<sup>20</sup>.

### Anti-inflammatory studies in rat: Carrageenan induced paw edema model

The chloroform and ethyl acetate extracts of *Cocculus pendulus* leaves shown significant anti-inflammatory activity. The lower dose of chloroform and ethyl acetate extracts (200 mg/kg body weight) did not show significant inhibition of inflammation but the higher dose of chloroform and ethyl acetate extracts (400 mg/kg body weight) shown significant inhibition of inflammation. The inhibition was however, less than that of the standard drug (Aspirin). This anti-inflammatory activity was dose dependent and found to be statistically significant ( $p < 0.05$ ). The results of the animal experiments were shown in shown in Table 4.

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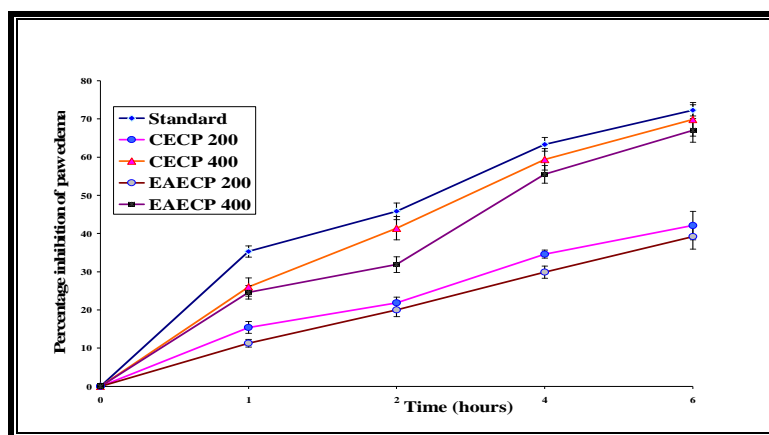
**Table 4.**  
*Effect of various extracts of *Cocculus pendulus* leaves on carrageenan induced paw edema in rat*

Groups	Dose	Paw edema volume in ml (% Inhibition of paw edema)				
		0 hr	1 hr	2hr	4 hr	6 hr
<b>Control</b>	10 ml/kg	1.13±0.03	1.30±0.03	1.61±0.01	1.73±0.02	1.78±0.06
<b>Std.</b>	100 mg/kg	1.20±0.03	1.31±0.01 (35.29)	1.46±0.04* (45.83)	1.42±0.01* (63.33)	1.38±0.03** (72.31)
<b>CECp 200</b>	200 mg/kg	1.15±0.05	1.29±0.04 (15.40)	1.52±0.02 (21.90)	1.54±0.01 (34.60)	1.53±0.02 (42.10)
<b>CECp 400</b>	400 mg/kg	1.21±0.01	1.32±0.03* (26.00)	1.43±0.06** (41.40)	1.37±0.02** (59.40)	1.32±0.05*** (69.90)
<b>EAECp 200</b>	200 mg/kg	1.27±0.01	1.42±0.07 (11.30)	1.65±0.05 (20.0)	1.69±0.01 (29.90)	1.67±0.05 (39.20)
<b>EAECp 400</b>	400 mg/kg	1.10±0.06	1.23±0.03 (24.60)	1.43±0.04 (31.90)	1.37±0.05* (55.50)	1.31±0.02** (67.0)

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  as compared to control, as per one way analysis of variance (ANOVA). Values are expressed as mean  $\pm$  SEM of  $n=6$  animals in each group.

The chloroform extract showed 42.10 % and 69.90 % inhibition of paw edema at the dose of 200 and 400 mg/kg body weight respectively, while ethyl acetate extract shown 39.20 %, and 67.00 % inhibition of paw edema at the dose of 200 and 400 mg/kg of body weight respectively, after 6 hours of drug administration as compared to the control group. The standard drug (Aspirin) shows 72.31 % inhibition of paw edema at the dose of 100 mg/kg body weight (Fig 1).

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**Figure 1. Effect of various extracts of *Cocculus pendulus* on carrageenan induced paw edema in rat**

On preliminary phytochemical screening the chloroform and ethyl acetate extract of *Cocculus pendulus*, was found to contain alkaloids, phytosterols, proteins, gums and mucilages, which may be responsible for the anti-inflammatory activity. Alkaloids and phytosterols are known to possess anti-inflammatory activity<sup>16-19</sup>.

**Wound healing studies in rat: Excision wound model**

**Table 5**  
*Effect of various extracts of *Cocculus pendulus* leaves on wound contraction in excision wound model of rat*

Group/ Treatments	Wound area in mm <sup>2</sup> (% Wound contraction)					
	Day 0	Day 4	Day 8	Day 12	Day 16	Day 21
<b>Control (Simple ointment base)</b>	278.12 ±1.4	232.30 ±6.7 (16.47)	199.17 ±2.7 (28.39)	158.54 ±1.2 (43.00)	171.07 ±3.9 (38.49)	134.39 ±5.4 (51.68)
<b>Standard (Povidone Iodine Ointment)</b>	281.37 ±4.8	150.77 ±3.7 (46.42)	97.34 ±1.9* (65.40)	33.09 ±4.1** (88.24)	2.11 ±2.6*** (99.25)	0.00 (100)
<b>CECp (200 mg/kg)</b>	293.17 ±1.2	228.09 ±3.0	174.14 ±5.2	158.90 ±3.1	123.13 ±7.3	112.28 ±1.6



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		(22.20)	(40.60)	(45.80)	(58.00)	(61.70)
<b>CECp</b>	279.93	168.52	101.23	51.16	16.57	0.00
<b>(400 mg/kg)</b>	±5.0	±4.1*	±3.3***	±1.8**	±2.4**	(100)
		(39.80)	(63.84)	(81.72)	(94.08)	
<b>EAECp</b>	292.26	236.31	199.03	173.02	141.75	116.90
<b>(200 mg/kg)</b>	±1.5	±6.3	±4.9	±5.9	±3.0	±3.4
		(19.14)	(31.90)	(40.80)	(51.50)	(60.00)
<b>EAECp</b>	286.53	180.23	125.42	61.89	26.83	3.18
<b>(400 mg/kg)</b>	±2.9	±4.5	±4.0*	±1.1*	±2.6**	±2.0***
		(37.10)	(56.23)	(78.40)	(90.64)	(98.89)

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  as compared to control, as per one way analysis of variance (ANOVA). Values are expressed as mean ± SEM of n=6 animals in each group.

A significant increase in the wound healing activity was observed in the animals treated with the chloroform and ethyl acetate extracts of *Cocculus pendulus* leaves at a dose of 200 and 400 mg/kg of body weight, when compared with the control treatments. Table 5 and 6 shows the effect of the chloroform and ethyl acetate extract of *Cocculus pendulus* on wound healing activity in rats inflicted with excision wound. In this model, the extract treated animals showed a more rapid decrease in wound size, decreased time to epithelialization and reduction in scar area compared with the control rats which received simple ointment base. Percentage closure of wound area was significantly high in standard drug treated group followed by chloroform extract treated group and then ethyl acetate extract treated group.

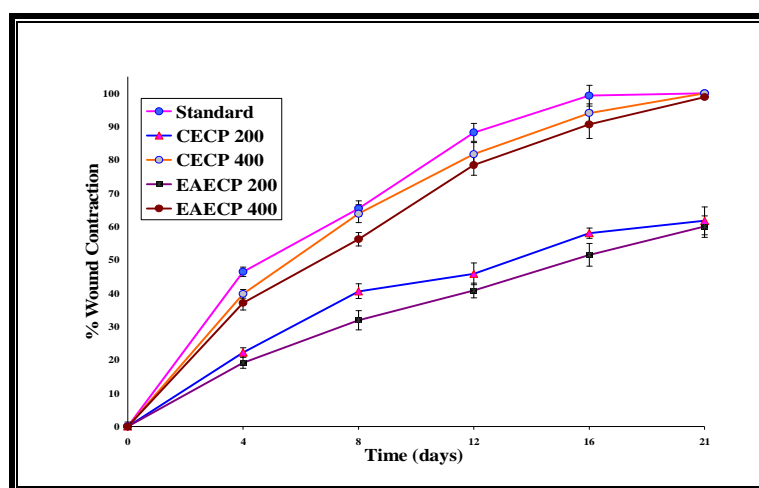
**Table 6.**  
*Period of epithelialization and scar area*

<b>Group/Treatments</b>	<b>Period of epithelialization (in days)</b>	<b>Scar area (in m<sup>2</sup>)</b>
Control (Simple ointment base)	28.48±0.13	21.08±2.6
Standard (Povidone Iodine Ointment)	16.02±0.11	13.66±1.9
CECp (200 mg/kg)	23.37±0.16	17.03±3.2
CECp (400 mg/kg)	17.82±0.15	15.78±2.8
EAECp (200 mg/kg)	22.26±0.10	18.15±1.9
EAECp (400 mg/kg)	21.34±0.18	16.57±3.4



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Control rats showed a time dependent increase in percent wound contraction from 16.47 % to 51.68 % from day 4<sup>th</sup> to day 21<sup>st</sup>, while complete wound closure and epithelialization was observed on 24<sup>th</sup> day of wound induction compared with day 0 which was taken as 0 %. The mean epithelialization period and scar area were 24.48 days and 21.08 mm<sup>2</sup> respectively. Standard drug (Povidone iodine ointment) treated rats showed increase in percent wound contraction from 46.42 % to 99.25 % from day 4<sup>th</sup> to 16<sup>th</sup>. The mean epithelialization period and scar area were found to be 16.02 days and 13.66 mm<sup>2</sup> respectively (Fig 2).



**Figure 2. Effect of various extracts of *Cocculus pendulus* on percentage wound contraction in excision wound model of rat**

The dose of both chloroform and ethyl acetate extract of *Cocculus pendulus* (200 and 400 mg/kg of body weight) shown dose dependent increase in percent wound contraction. The chloroform extract of *Cocculus pendulus* at a dose of 400 mg/kg (CECp 400) shown increase in percent wound contraction from 39.80 % to 94.08 % from day 4<sup>th</sup> to 16<sup>th</sup>, while epithelialization period and scar area were 17.82 days and 15.78 mm<sup>2</sup> respectively. The ethyl acetate extract of *Cocculus pendulus* at a dose of 400 mg/kg (EAECp 400) showed increase in percent wound contraction from 37.10 % to 90.64 % from day 4<sup>th</sup> to 16<sup>th</sup>, while epithelialization period and scar area were

21.34 days and 16.57 mm<sup>2</sup> respectively. Possibly, the constituents like phytosterols and mucilage which may be present in the leaves of *Cocculus pendulus* may play a major role in the process of wound healing. It may be either due to their individual or additive effect, hastening the process of wound healing.

### CONCLUSION

The present results indicate the efficacy of chloroform and ethyl acetate extract of leaves of *Cocculus pendulus* as an efficient therapeutic agent



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in inflammatory conditions and also possess significant wound healing potency. However, it needs further evaluation in clinical settings before consideration for the treatment of inflammations and wounds.

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