

ANALGESIC EFFECT OF ETHANOLIC EXTRACT OF SEEDS AND LEAVES OF *CORIANDRUM SATIVUM* ON SWISS ALBINO MICE

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ABSTRACT

INTRODUCTION

Pain has been described by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Although NSAIDs and OPIOIDS are available for the treatment, still pain (chronic) is major problem. The present study was designed to study the analgesic effect of ethanolic extract of *Coriandrum sativum* using hot plate method and acetic acid induced writhing method in experimental animals (*Swiss Albino* mice).

MATERIAL AND METHODS

The analgesic effect of leaves and seeds of *Coriandrum sativum* was assessed using Eddy's hot plate method and acetic acid induced writhing method in *Swiss Albino* mice. The animals were treated with the ethanolic extract of leaves and seeds of *Coriandrum sativum* administered orally at two doses of 100, 500 mg/kg body weight after electric heat and acetic acid induced pain in mice.

RESULTS

The study showed that ethanolic extract of leaves and seeds of *Coriandrum sativum* presented significant ($p < 0.05$) and ($p < 0.05$) analgesic activity in mice simultaneously. The data were analyzed by one-way ANOVA followed by Dunette's multiple comparison test. The results demonstrate that ethanolic extract of leaves and seeds of *Coriandrum sativum* has got analgesic potential.

CONCLUSION

The results demonstrate that ethanolic extract of leaves and seeds of *Coriandrum sativum* has got significant analgesic effect.

KEYWORDS

Analgesic effect, *Coriandrum sativum*, Ethanolic extract, Pain.

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DOI: <https://doi.org/10.3126/jucms.v9i02.42008>

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INTRODUCTION

Pain has been described by the International Association for the Study of Pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.¹ Chronic pain and the inflammatory diseases are one of the major health problems in the world.² Several factors including sociocultural, psychological and biological conditions have important roles in pain perception. Although pain is a reaction of the body to harmful stimuli, it is a protective early warning system. In medical diagnosis, pain is regarded as a symptom of an underlying condition.¹ Pain is a vital function of the human body, involving nociceptors and the central nervous system (CNS) to transmit messages from noxious stimuli to the brain.

Types of pain: Simply, pain can be divided into two types- acute pain and chronic pain.

a. Acute pain: Acute pain is pain of sudden onset; lasting for hours to days and disappears once the underlying cause is treated. Acute pain has a clear cause. It could result from any illness, trauma, surgery or any painful medical procedures. Acute pain is beneficial for us as it signals that something is wrong in our body and motivates us to get help soon. Example of acute pain includes- headache, heartache, muscle sprain, bone fracture, cuts in skin etc.

b. Chronic pain: Chronic pain is the pain that starts as an acute pain and continues beyond the normal time expected for resolution of the problem or persists or recurs for various other reasons. It is not the reapeutically beneficial to the patient.³

Analgesic drugs are used in single or in combination to affect peripheral or central nervous system (CNS) to decrease pain sensation. Analgesics are drugs that relieve pain without significantly altering consciousness. They relieve pain without affecting its cause. There are two groups of analgesics:

Opioid (Narcotic analgesics)

Non-opioid (Non-steroidal anti-inflammatory drugs)

Opioids are substances that, when reaching opioid receptors, have effects similar to those of morphine. Medically they are primarily used for pain relief, including anesthesia. Other medical uses include suppression of diarrhea, replacement therapy for opioid use disorder, reversing opioid overdose as well as suppressing cough. Morphine is the most important alkaloid of opium - the dried juice obtained from the capsules of *Papaver somniferous*. Opium contains many other alkaloids, such as codeine, thebaine, papaverine etc. Mechanism of action of opioids: Morphine and other opioids produce their actions by interacting with various opioid receptors - mu (μ), kappa (κ) and delta (δ). They inhibit the

release of neurotransmitters from the primary afferent terminals in the spinal cord as well as activate the descending inhibitory controls in the brain. This results in the sensation of pain relief as well as a relaxing and sedative effect.⁴

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications due to their efficacy for a wide range of pain and inflammatory conditions.⁵ However, the long-term administration of NSAID may induce gastrointestinal ulcers, bleeding, and renal disorders due to their nonselective inhibition of both constitutive (COX-1) and inducible (COX-2) isoforms of the cyclooxygenases enzymes.⁶ Therefore, new anti-inflammatory and analgesic drugs lacking those effects are being searched all over the world as alternatives to NSAIDs and opiates.^{7,8} The research into plants with alleged folkloric use as pain relievers, anti-inflammatory agents, should therefore be viewed as a fruitful and logical research strategy in the search for new analgesic and anti-inflammatory drug. The plant derived natural products such as flavonoids, sterols, polyphenols, alkaloids, tannins and terpenes have gained importance in recent years due to their wide range of pharmacological activities.⁹ *Coriandrum sativum* Linn. (Apiaceae/ Umbelliferae) is a native plant from southern Europe and Southwestern Asia that has been naturalized in North America and acclimatized in many countries with a temperate climate. It is popularly known as coriander, Chinese parsley, or cilantro, and it has been used to add flavor, color and nutritional properties to food in many Asian countries.¹⁰ Parts of *C. sativum* (CS) have been used to treat many diseases and conditions, such as rheumatism/ joint pain, indigestion/ gastrointestinal disorders, anxiety etc. Its antioxidant, anti-diabetic, anticancer properties have previously been reported¹¹.

This study was conducted to explore analgesic effect of leaves and seeds of *Coriandrum sativum* was assessed using hot plate method and acetic acid induced writhing method in Swiss albino mice.

MATERIAL AND METHODS

The analgesic effect of leaves and seeds of *Coriandrum sativum* was assessed using Eddy's hot plate method and acetic acid induced writhing method in Swiss albino mice. The animals were treated with the ethanolic extract of leaves and seeds of *Coriandrum sativum* administered orally at two doses of 100, 500 mg/kg body weight after electric heat and acetic acid induced pain in mice. This study was carried out from October 2020 to May 2021 after the taking approval from Institutional Review Committee of Universal College of Medical Sciences, IRC No. (UCMS/IRC/019/20) at Department of Pharmacology of Universal College of Medical Sciences, Bhairahawa, Rupandehi, Nepal.

Animals

Swiss Albino mice (*Mus musculus*) either sex weighing 23-32 g (four weeks of age) were kept in the animal house in the Department of Pharmacology at Universal College of Medical Sciences for the experimental purpose. All the animals were housed in clean polypropylene cages and were maintained at standard conditions of temperature ($25 \pm 1^\circ\text{C}$) and 12:12 hour light/ dark cycles. They were fed with standard pellet diet and had free access to water ad libitum.

Plant material

The aerial parts of the leaves and seeds of *Coriandrum sativum* were collected from Ranigaun, Bhairahawa, Rupandehi, Nepal. The selected plant was identified and authenticated by Mr. Rukmagat Pathak, Assistant Professor, Department of Soil and Environment Science, TU, IAAS, Paklihawa, Rupandehi on date 4/04/2021. All other chemicals used in the study are of AR grade.

Preparation of extract

The aerial parts of the leaves and seeds of *Coriandrum sativum* collected were washed thoroughly with water and air-dried under shade at room temperature. Then, the dried plant materials were chopped into small pieces and finely ground to give powder form of crude drug. The drug was extracted in the ratio 1:6 using ethanol as solvent by continuous hot percolation with the help of Soxhlet apparatus. The duration of extraction was 48 hours. The extract was reduced to dryness using rotary apparatus. Lastly, the percentage yield of extract was calculated. The seed and leaves were extracted separately using the same method.^{12,13}

$$\text{Yield(Leaves)} = \frac{\text{weight of dried leaves extract}}{\text{weight of dried powder used to be extracted}} \times 100$$

$$\text{Yield(\%)} = \frac{11.56}{100} \times 100 = 11.56$$

$$\text{Yield(Seeds)} = \frac{\text{weight of dried seeds extract}}{\text{weight of dried powder used to be extracted}} \times 100$$

$$\text{Yield(\%)} = \frac{9.36}{100} \times 100 = 9.36$$

Phytochemical screening

Phytochemical screening was carried out for the determination of different secondary metabolites (Carbohydrate, glycosides, saponin, sterols, tannins, terpenoids, flavonoids and alkaloids) present in the leaves and seed extract of *Coriandrum sativum*.¹⁴

Acute oral toxicity studies (oppts 870.1100)

The acute oral toxicity study was performed according to the OPPTS (Office of Prevention, Pesticides, and Toxic Substances) guidelines.

Dose selection

Lethal dose 5000 mg/kg selected and two doses of 100 mg/kg and 500 mg/kg body weight of ethanolic extract of *Coriandrum sativum* leaves and seeds was selected as low dose and high dose as per the acute oral toxicity studies.¹⁵

Experimental design

The mice were randomly divided into four groups each for leaves and seeds extract. So total groups are six including negative control and standard (n=5 mice per group). Thus, 30 mice were used for the evaluation of analgesic effect of *Coriandrum sativum* leaves and seed (Table 1).

Table 1. Experimental design groups each for leaves and seeds extract

Leaves extract		Seed extract	
Animal Group	Dose	Animal Group	Dose
Negative control	Disease induced and vehicle only	Negative control	Disease induced and vehicle only
Standard (Diclofenac sodium)	10 mg/kg	Standard (Diclofenac sodium)	10 mg/kg
Test-1	100 mg/kg	Test -1	100 mg/kg
Test-2	500 mg/kg	Test-2	500 mg/kg

Eddy's hot plate method

To assess nociceptive responses, hot plate method was used. The mice were placed on the hot plate with temperature setting controlled at $55 \pm 0.2^\circ\text{C}$. Cut-off time will be 30 seconds. Nociceptive or pain response was defined as licking forepaws or moving hind paws. Time duration between placing the animals on hot plate and licking fore paws or moving hind paws was considered as the reaction time. The hot plate test will be performed as a base record 10 min before injection of the drugs and consequently it was repeated five times, every 10 min after injection. Analgesic effects of the extracts (both leaf and seed) or vehicle was calculated as maximal possible effect (MPE).¹⁶

$$\text{MPE \%} = \frac{(\text{Test response time} - \text{Basal response time})}{\text{Cutoff time} - \text{Basal response time}} \times 100$$

Acetic acid induced writhing method

The analgesic effect on the samples was evaluated using acetic acid induced writhing method in mice. In this method, acetic

acid was administered intra-peritoneally to the experimental animals to create pain sensation. As a positive control, diclofenac sodium was used to serve the purpose. The plant extracts were administered orally in two different doses (100 and 500 mg/kg body weight) to the Swiss albino mice after an overnight fast. Test samples and vehicle administered orally 30 minutes prior to intraperitoneal administration of 0.7% v/v acetic acid solution (0.1 ml/10 g) but diclofenac sodium was administered 15 minutes prior to acetic acid injection. Then the animals were placed on an observation table.

Each mouse of all groups was observed individually for counting the number of writhing they made in 15 minutes commencing just five minutes after the intraperitoneal administration of acetic acid solution. The number of writhes in each treated group will be compared to that of a control group where Diclofenac sodium (10 mg/kg) will be used as a reference substance (positive control).¹⁶ Anti-nociception (analgesia) will be expressed as the reduction of the number of abdominal constrictions between control animals and mice pretreated with extracts.

Statistical analysis

$$\text{Inhibition \%} = \frac{(\text{No. of writhes}(\text{control}) - \text{No. of writhes}(\text{Treated}))}{\text{No. of writhes}(\text{control})} \times 100$$

Results of experiment were expressed as mean \pm SEM. Statistical analysis was performed using one-way ANOVA followed by Dunette's multiple comparison test using graph pad prism (version-9). The values of $p < 0.05$ was considered as statistically significant.

RESULTS

Phytochemical screening

Table 2. Preliminary phytochemical screening of the extracts of *C. sativum* revealed the presence of glycosides, sterols, flavonoids, alkaloids, tannins and saponin

S. N	Test	Result
1	Glycoside	+
2	Sterol	+
3	Flavonoids	+
4	Alkaloids	++
5	Tannin	++
6	Saponin	+
7	Carbohydrates	+

(++ high abundance, + less abundance)

Eddy's hot plate method

Table 3. Effect of ethanolic extract of *Coriandrum sativum* on heat induced pain (hot plate) in mice (All values are expressed as Mean \pm SD. The differences are significant at $*p < 0.05$ when analyzed by one-way ANOVA followed by Dunette's multiple comparison test)

Group	Mean Reaction Time			
	30 min	60 min	90 min	120 min
Negative control	3.82 \pm 0.290	4.27 \pm 0.178	3.99 \pm 0.219	3.89 \pm 0.430
Standard (Diclofenac sodium 10 mg/kg)	7.22 \pm 0.355***	10.37 \pm 0.239***	15.74 \pm 0.775***	3.89 \pm 0.430
Leaf extract Test-1 (100 mg/kg)	4.22 \pm 0.186	8.84 \pm 0.400***	12.15 \pm 0.161***	10.23 \pm 0.179***
Leaf extract Test-2 (500 mg/kg)	7.85 \pm 0.137***	12.23 \pm 0.517***	15.08 \pm 0.091***	13.07 \pm 0.148***
Seed extract Test-1 (100 mg/kg)	4.15 \pm 0.172	8.33 \pm 0.548	9.41 \pm 0.136***	8.81 \pm 0.338***
Seed extract Test-2 (500 mg/kg)	7.24 \pm 0.081***	11.96 \pm 0.139***	13.12 \pm 0.235***	11.50 \pm 0.166***

Acetic Acid induced pain

Table 4. Effect of Ethanolic extract of *Coriandrum sativum* acetic acid induced pain in mice

Group	No. of writhing					
	5 min	10 min	15 min	20 min	25 min	30 min
Negative control	11.8 \pm 0.955	11.2 \pm 0.593	10.2 \pm 1.585	12.2 \pm 1.308	12.0 \pm 1.265	10.2 \pm 1.585
Standard (Diclofenac sodium 10 mg/kg)	3.2 \pm 0.593	3.4 \pm 0.456	3.6 \pm 0.829	2.6 \pm 0.607	4.0 \pm 0.632	4.2 \pm 0.867
Leaf extract Test-1 (100 mg/kg)	9.4 \pm 0.669	8.8 \pm 0.867	9.0 \pm 1.720	9.2 \pm 1.035	7.4 \pm 1.345*	8.6 \pm 0.456*
Leaf extract Test-2 (500 mg/kg)	5.8 \pm 0.522***	6.0 \pm 0.400***	6.2 \pm 0.769***	7.2 \pm 0.716 ns	7.8 \pm 0.438***	7.8 \pm 0.996 ns
Seed extract Test 1 (100 mg/kg)	10.2 \pm 0.912	10.2 \pm 0.716	7.8 \pm 0.657*	10.8 \pm 0.522	9.2 \pm 0.769	6.6 \pm 1.513*
Seed extract Test-2 (500 mg/kg)	7.2 \pm 0.522**	7.2 \pm 0.593**	6.6 \pm 0.963**	8.0 \pm 0.632**	6.0 \pm 1.166	5.2 \pm 0.769**

(Results are expressed as mean \pm SEM from observation as compared to control group by one-way ANOVA followed by Dunette's multiple comparison test. Significant at $*p < 0.05$)

DISCUSSION

The present study revealed that the seeds and leaves of *C. sativum* possess analgesic effect. The hot plate method is one of the widely used methods for evaluation of analgesic effect and has been validated for use with both rats and mice. Therefore, we chose this test in addition with acetic acid induced writhing test to investigate the analgesic potential of ethanolic extract of *Coriandrum sativum* leaves and seeds. The analgesic effect of ethanolic extract of seeds and leaves was comparable to diclofenac.

In previous study, the analgesic effects of the aqueous extract of the seeds of *Coriandrum sativum* had been reported using hot plate and tail flick tests.¹⁷

The chemical compound responsible for the analgesic effect of the extracts could not be identified in the present study and needs to be studied in future. However, the presence of the

flavonoids such as quercetin has been reported.¹⁸ It has been shown that the flavonoids have considerable analgesic and anticonvulsant effects.¹⁹ Sedative, CNS depressant and analgesic effects of flavonoids such as quercetin has been attributed to the affinity for the central benzodiazepine receptors.^{20,21} The beneficial effect of linalool in pentyletel-razole seizure models as well as its analgesic effects has been suggested.^{22,23}

It can be suggested that the beneficial effects of the extracts which were observed in the present study are at least in part due to linalool which is a main compound in coriander.²⁴ Analgesic effects of polyphenols including rutin, caffeic acid and gallic acid has also been reported which can be isolated from *Coriandrum sativum*.²⁵

Each of these compounds may also have a role in the analgesic effects of the extracts which were seen in present study however it needs to be investigated more.

This study has few limitations analgesic activity of plant parts (seeds and leaves) was studied in acute condition but not in chronic condition due to lack of time and feasible methodology. Active components responsible for the analgesic activity were not isolated and identified due to lack of instruments. Apart from this there is no foreseen limitation of the study. Limitations encountered during the conduct of the study will be addressed accordingly. The main strength of this study is to compare the analgesic effect of plant extract with the standard drug.

CONCLUSION

The qualitative phytochemical study reveals the presence of sterols, carbohydrates, flavonoids, glycosides, tannins, alkaloids and saponins. The present study demonstrated that the ethanolic extract of seeds and leaves of *Coriandrum sativum* possess analgesic activity. The above effects may be due to the presence of flavonoids, linalool, borneol, camphor, tannins and sterols in the extracts.

CONFLICT OF INTEREST

None

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