

## Anti-inflammatory and Analgesic Activity of Methanolic Extract of Medicinal Plant *Rhodiola rosea* L. Rhizomes

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### ABSTRACT

*Rhodiola rosea* L. (Crassulaceae) have been used as traditional medicines that can increase someone's physical strength, work productivity, longevity and resistance to high altitude sickness, fatigue, depression, anaemia, gastrointestinal ailments, infections, and nervous system disorders. The objective of this study was to evaluate the anti-inflammatory and analgesic activities from the methanolic extract of the rhizomes of *Rhodiola rosea*. Crude methanolic extract of the herb *Rhodiola rosea* were prepared and analyzed for its pharmacological activity. Swiss albino mice are used for acute toxicity study and also analgesic property of the extract by using Tail flick, Acetic acid induced writhing reflex and tail immersion method. Male Wister rat model are used to detect anti-inflammatory activity of the extract using carrageenan induced rat paw edema. After experiment statistical analysis like one way anova (non-parametric), Dunnet's test was done. Results are plotted in graph and from this the effective activity of the plant is determined. The orally administered methanolic extract of *Rhodiola rosea* demonstrated a significant analgesic and anti-inflammatory in animal model. The findings in the study suggest that the methanolic extract of the herb *Rhodiola rosea* possesses analgesic and anti-inflammatory activities. This results may prove the fact that the herb may be used as analgesic and anti-inflammatory along with its adaptogenic properties.

**Keywords:** Acute toxicity study, analgesic, anti-inflammatory activity, *Rhodiola rosea*

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### INTRODUCTION

*Rhodiola rosea*, also known as "golden root" or "roseroot" belongs to the plant family Crassulaceae. For past few centuries, rhizomes of this plant has been used in the traditional medicine of Russia, Scandinavia, and other countries. In the rhizome it stores the secondary metabolites that have been shown to possess different medical activities and valuable adaptogenic effects.

Traditional folk medicinal system used *R. rosea* to increase physical endurance, work productivity, longevity, and resistance to high altitude sickness, fatigue, depression, anaemia, impotence, gastrointestinal ailments, infections, and nervous system disorders [1].



**Figure 1: *Rhodiola rosea* plant**

Inflammation was described two thousand years ago by Celsus by the four Latin words: Rubor, calor, tumor and dolor. Inflammation has different phases. The first phase is

caused by an increase of vascular permeability resulting in exudation of fluid from the blood into the interstitial space, the second one by infiltration of leukocytes from the blood into the tissues and the third one by granuloma formation. Accordingly, anti-inflammatory tests have to be divided into those measuring acute inflammation, sub-acute inflammation and chronic repair processes. In some cases, the screenings directed to test compounds for local application [2]. Analgesia is an ill-defined, unpleasant sensation, usually evoked by an external and internal noxious stimulus. Analgesics are drugs that selectively relieve pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness. Analgesics relieve pain, without affecting its cause. Analgesics are divided into two groups, opioid analgesic and non-opioid analgesic [3]. The use of herbal medicines worldwide has provided an excellent opportunity to India to look for therapeutic lead compounds from our ancient system of therapy, i.e. Ayurveda, which can be utilized for development of new drug [4]. Epidemiological evidence suggests that dietary factors play an important role in human health and in the treatment of certain chronic diseases including cancer [5]. This study can open a new phase of treatment of pain and inflammation with the extract of this rhizomes.

#### MATERIALS AND METHODS

##### (i) Animals

Male Wistar rats weighing  $218.7 \pm 3.0$  (range 180–250g) were used for this study. They were bred and housed in the animal house, Department of Pharmaceutical technology, Jadavpur University. The animal house was well ventilated; the rats were fed with mouse cubes and had water ad libitum. The animals were randomly divided into groups comprising five rats each. Male Swiss Albino mice (20–25 g) were obtained from animal house Department of Pharmaceutical technology, Jadavpur University. The animals were housed under standard environmental condition (25°C, 12 h light and 12 h dark cycle) and fed with standard diet, water ad libitum [6]. The experiments were performed with subject to minimum pain to the experimenting animals. All the ethical

considerations have been followed. The research was conducted in accordance with the ethical rules on animal experimentation, approved by Ethical committee, Department of Pharmaceutical technology, Jadavpur University Approval No:147/1999/CPCSEA).

##### (ii) Plant materials

The rhizomes (*Rhodiola rosea*) used for this study were collected in August 2013 from the Pharmaceutical Technology Department, Jadavpur university. This is to be identified and authenticated by The Botanical Survey of India, Botanical Gardens, Howrah, and West Bengal. Rhizomes were cut on sites 5–10 cm long, splinted and dried in drying case at 40–45°C. The dried rhizomes were reduced to powdery form and 150g of the powdered sample was extracted with 2.5 Litre of methanol (analytical grade) for 72hrs [7]. The macerated mixture was filtered and evaporated in a carefully regulated water bath maintained at 40–45°C to yield a brownish solid extract weighing 8g. The extract was stored in a refrigerator at 4°C. For the pharmacological tests, the extract was dissolved in 0.1% Na-CMC in normal saline solution to prepare 50 mg/kg and 200 mg/kg concentrations.

##### (iii) Drugs and Chemicals

Indomethacin, carrageenan and Diclofenac-Na were purchased from Sigma-Aldrich, Germany. Acetic acid was purchased from Merck, Germany. Morphine Sulfate was purchased from Troikaa Pharmaceutical Ltd, Gujarat, India.



Figure 2: Extracted rhizome powder



Figure 3: Rhizome of *Rhodiola rosea*

### 1. Acute Oral Toxicity Study

Acute oral toxicity study was performed as per OECD (Organization of Economic Cooperation and Development) 423 guideline (Acute toxic class method). Healthy female (should be nulliparous and non-pregnant) albino Wistar rats were randomly divided into 6 groups with 6 animals in each group. The animals were kept fasting overnight providing only water, after which the methanolic extract of *Rhodiola rosea L.* rhizomes was administered orally with increasing doses (50, 100, 500, 1000 and 2000 mg/kg) by intragastric tube to determine the safe doses. The animals were noticed continuously for 1 h, then frequently for 4 h and later at the end of 24 h for general behavioral, neurological and autonomic profile. Further, one group was administered high dose of *Rhodiola rosea L.* rhizomes extract orally once daily for 15 days and observed for any lethality [8].

### 2. Anti-inflammatory activity

#### 2.1. Carrageenan-induced rat hind paw edema

The anti-inflammatory activity of the methanolic extract of *Rhodiola rosea L.* was assessed by the carrageenan-induced right hind paw edema method in Male Wister rats. Acute inflammation was produced by sub-planar injection of 0.1 ml of 1% suspension of carrageenan in normal saline, in the right hind paw of the rats 1 h after the oral administration of test materials. The paw volume was measured by plethysmometer at 0h, 1hr, 1.5hr, 2hr and 3hr after the carrageenan injection. The extract was administered at 50 and 200 mg/kg body weight orally. Diclofenac at a dose of 25 mg/kg body weight was used as standard anti-inflammatory agent. The negative control group received 0.1% Na-CMC in saline solution [9]. The anti-inflammatory effect of the extract was calculated by the following equation:

$$\text{Anti-inflammatory activity (\% inhibition)} = \frac{1 - D}{C} \times 100$$

Where, C= Mean paw volume of control, D= Mean paw volume of test.

### 3. Analgesic activity screening

#### 3.1 Radiant heat tail-flick method

The central analgesic activity of the root extract was studied by measuring drug-induced changes in the sensitivity of the pre-screened (Basal reaction time: 3-5 sec) mice to heat stress applied to their tails by using a Medcraft Analgesiometer. The current intensity passing through the naked nichrome wire was maintained at 5 ampere. The distance between the heat source and the tail skin was 1.5 cm and cut-off reaction time was fixed at 10 sec to avoid any tissue damage. Morphine was used to compare the analgesic effect of the plant extract. The extract was orally administered at 50 and 200 mg/kg body weight. Morphine was administered subcutaneously at a dose of 5mg/kg body weight [10].

#### 3.2 Acetic acid induced writhing reflex

The peripheral analgesic activity of methanolic extract of *Rhodiola rosea L.* rhizomes was measured by the acetic acid induced writhing test in mice. The abdominal writhing was induced by intra-peritoneal injection of acetic acid solution (0.9%) at a dose of 0.1 ml/10 g of body weight to each mouse. Indomethacin at oral dose of 25 mg/kg was used as standard analgesic agent. The extract was administered at 50 and 200 mg/kg body weight. The extract, standard drug and control (normal saline solution, 1 ml/kg) were orally administered 30 min prior to the injection of acetic acid. The number of writhing was calculated for 10 min after the application of acetic acid [11].

$$\% \text{ inhibition of pain response} = \frac{(C - T)}{C} \times 100$$

[C=control, T=test]

#### 3.3 Tail immersion method

Tail immersion test was used to assess the analgesic activity of *Rhodiola rosea L.* In this method six rats per group were used. Tail immersion method involved immersing the extreme 3cm of the rat's tail in a water bath containing water at a temperature of (55.0±0.5) °C. After immersing within a few minutes, the rat reacted by withdrawing the tail. The reaction time was noted on a stopwatch. Each animal served as its own control and two readings were obtained for the control at 0 and 10min interval. The average of the two values was the initial reaction time. The test groups were given methanolic extract of *Rhodiola rosea L.* (50 mg/kg and 200 mg/kg, p.o.). Morphine (5 mg/kg, S.C.)

were given for standard group, and 1ml/kg saline solution for control group (p.o.). The reaction time of the test groups was taken at 30 min, 1.0 h, 2.0h and 3.0h after a latency period of 30 min following the administration of the tests substances. The cut off time, i.e. time of no response was put at 120 seconds. The reaction time was measured and calculated [12].

#### 4. Statistical analysis

Data were analyzed by one-way ANOVA followed by Dunnett's test and p value of 0.05 was considered statistically significant.

### RESULT

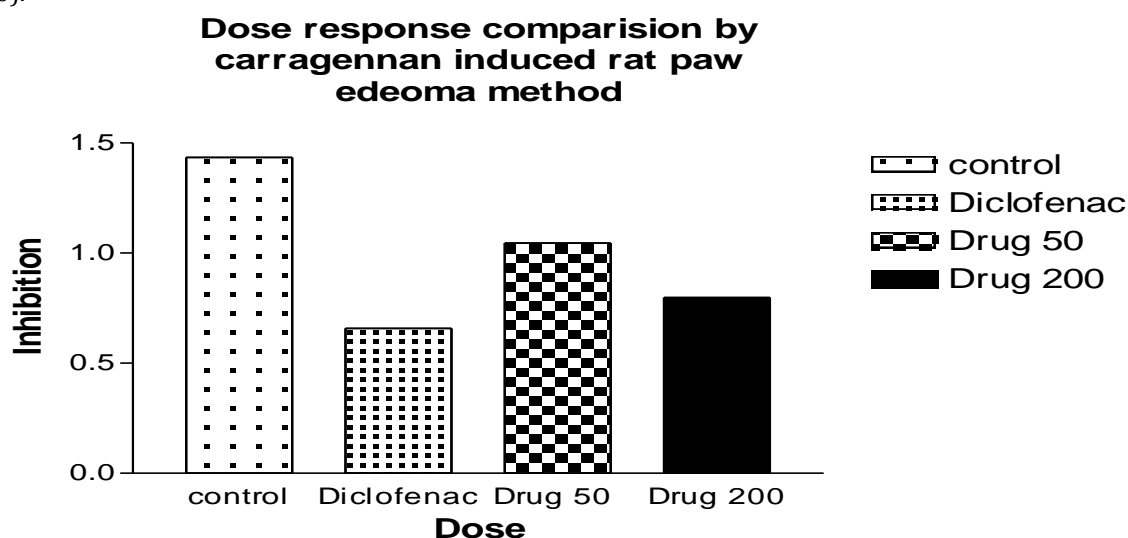
#### 1. Anti-inflammatory activity

The anti-inflammatory activity of the plant extract was measured at a dose of 50 and 200 mg/kg body weight against acute paw edema induced by carrageenan. A strong inhibition of the paw edema was observed with the different doses of the extract and with Diclofenac (standard drug). The two doses tested (50 and 200 mg/kg) produced significant ( $p < 0.05$ ) anti-inflammatory activity and reduced the paw by 50.99% and 64.24% respectively, whereas Diclofenac caused 79.47% reduction when used as a standard drug. Result of anti-inflammatory activity is written on (Table 1) and plotted in (Fig. 1).

**Table 1: Anti-inflammatory activity of *Rhodiola rosea* extracts in Rats**

Treatment group	Dose mg/kg	Paw volume (mm <sup>3</sup> )					% Inhibition
		0 min	30 min	60 min	120 min	240 min	
Control	0.9%	0.79±0.03	1.35±0.15	1.72±0.11	1.80±0.11	1.51±0.03	-
Diclofenac	25mg/kg	0.75±0.09	0.88±0.11	0.77±0.15	0.58±0.16	0.31±0.05*	79.47
<i>R. rosea</i> L. extract	50mg/kg	0.81±0.10	1.44±0.13	1.38±0.17	0.86±0.150	0.74±0.21*	50.99
<i>R. rosea</i> L. extract	200mg/kg	0.76±0.11	0.94±0.11	0.85±0.15	0.70±0.14	0.74±0.21*	64.24

The data represent the Mean±SEM (n=8). \*:  $P < 0.05$ , compared to corresponding control. Control: 0.9% CMC (p.o); Standard drug: Diclofenac (p.o.); Extract: Methanolic extract of *R. rosea* (50 and 200mg/kg) (p.o).



**Figure 4: Dose response comparison graph for *R.rosea* extracts by Carrageenan induced rat paw edema method**

#### 2. Radiant heat tail-flick method

In the radiant heat tail-flick method, the *Rhodiola* extract prolonged the heat stress tolerance capacity of the mice. In radiant heat tail-flick test, the extract produced 29.50% and 62.68% ( $p < 0.05$  significant)

increase in analgesic activity after oral doses of 50 and 200 mg/kg body weight respectively. Morphine caused 74.650 % ( $p < 0.01$ ) increase in analgesic activity when used as a standard drug at 5 mg/kg body weight. Result of radiant heat tail flick

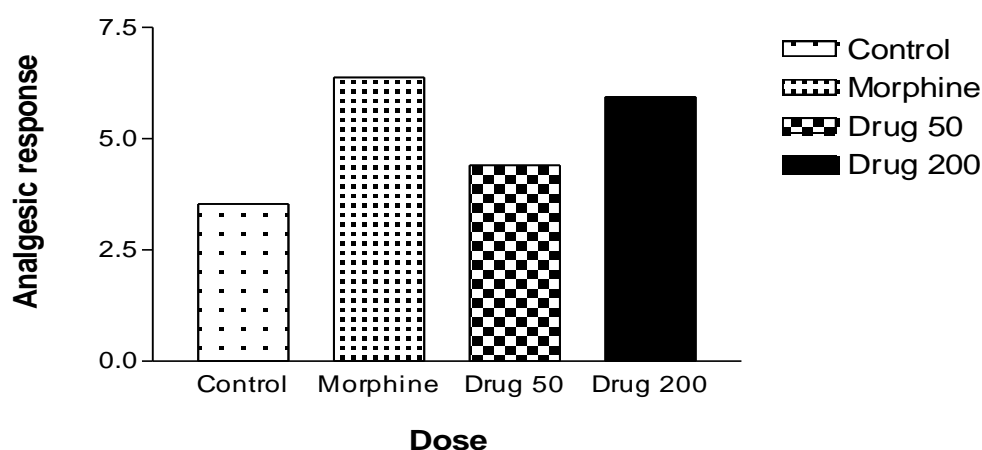
method is written on (Table 2) and plotted in (Fig. 2).

**Table 2: Analgesic Activity of *Rhodiola rosea* extracts by Tail-Flick Method in Mice**

Treatment Group	Flicking response of tail			% Increase in analgesic activity
	Before treatment	After treatment	Difference	
Control	3.500±0.1890	3.531±0.05984	0.031	-
Morphine(5mg/kg)	3.650±0.2053	6.375±0.6847**	2.725	27.25%
<i>R. rosea</i> ext(50mg/kg)	3.400±0.2179	4.403±0.3021	1.003	10.03%
<i>R. rosea</i> ext(200mg/kg)	3.650±0.1309	5.938±0.5984*	2.288	22.88%

Data presented as mean ± SEM, n = 8 for all groups. \*\*P<0.01(Morphine)\*P<0.05.P value <0.05 taken as significant

**Dose response comparison by using Tail flick method**



**Figure 5: Dose response comparison of different dose of *R. rosea* extract by radiant heat tail flick method**

### 3. Acetic acid induced writhing method

The methanolic extract of the plant *Rhodiola rosea* L. rhizomes at the doses of 50 and 200 mg/kg body weight and indomethacin 25 mg/kg body weight induced respectively significant (p<0.01) 22.67%, 49.38% and 62.76% decrease in the number of writhes

when compared to control untreated groups. The two doses tested (50 and 200 mg/kg) produced significant (p<0.01) analgesic activity. Result of acetic acid induced writhing reflex is written on table-3 and plotted in (Fig. 3).

**Table 3: Analgesic Activity of *Rhodiola rosea* by Acetic Acid Induced Writhing Response in Mice**

Treatments	Dose (mg/kg)	No of abdominal writhing	% Inhibition
Control	1ml/kg	0.88±1.995	-
Indomethacin	25mg/kg	11.50±0.8018**	62.76
<i>R.rosea</i> extract	50mg/kg	23.88±1.420**	22.67
<i>R.rosea</i> extract	200mg/kg	15.63±1.068**	49.38

Data presented as mean ± SEM, n = 8 for all groups.\*= p< 0.01 (significant) when last three groups are compared to control in Dunnett's multiple comparison test.

### 4. Tail immersion method

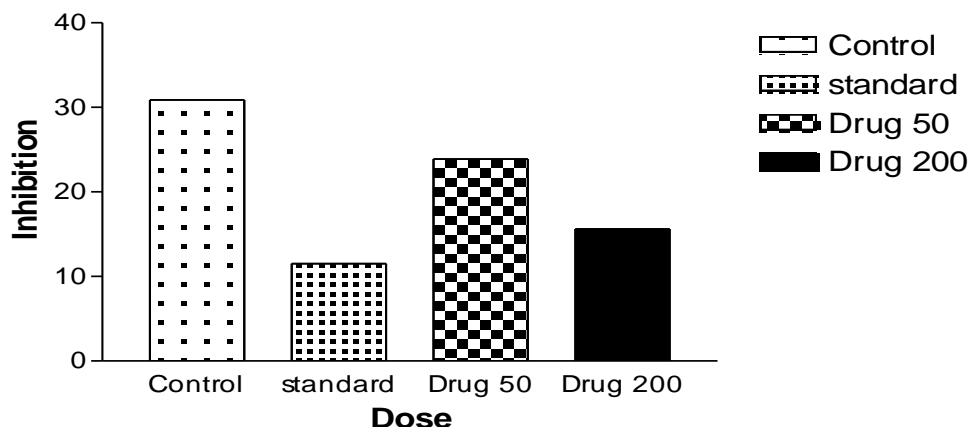
The methanolic extract of the plant *Rhodiola rosea* L. rhizomes at the doses of 50 and 200

mg/kg body weight and Morphine 5 mg/kg body weight induced a significant (p<0.05) decrease in the reduction of painful

sensation when compared to control untreated groups in tail immersion method. The 200 mg/kg dose produced significant ( $p < 0.05$ ) analgesic activity and reduced the painful sensation by 44.59%, whereas morphine caused 52.87% reduction when used as a reference drug. There was a

significant reduction of painful sensation due to tail immersion in warm water, after a latency period of 0.5 h following oral administration of the plant extract at the dose of 200 mg/kg. Result of tail immersion is written on table-4 and plotted in (Fig. 4).

**Dose response comparison by using Acetic acid induced writhing reflex method**



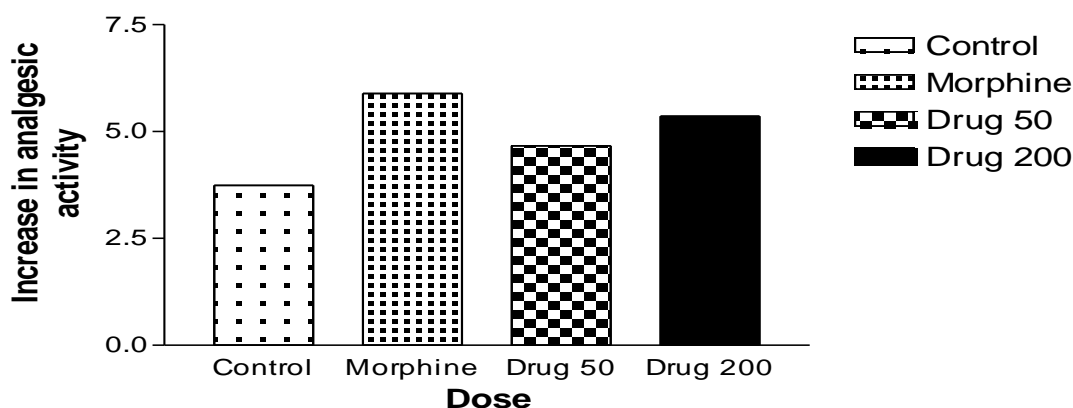
**Figure 6: Dose response comparison of *R.rosea* extracts by using Acetic acid induced writhing reflex method**

**Table 4: Analgesic activity of *Rhodiola rosea* extracts by tail immersion methods in mice**

Treatment group	Dose (mg/kg)	0 min	30 min	1 hr.	2 hr.	% Inhibition
Control	1ml/kg	3.500±0.1890	3.750±0.1402	3.838±0.1700	3.875±0.1176	-
Morphine	5mg/kg	3.925±0.2210	6.275±0.1306	6.725±0.1612**	6.650±0.1535**	52.87
<i>R. rosea</i> extract	50mg/kg	4.350±0.1711	4.825±0.1013	4.925±0.0839	4.575±0.1236	5.17
<i>R. rosea</i> extract	200mg/kg	3.925±0.2358	5.713±0.1481	5.900±0.1086*	5.888±0.1076*	44.59

The data represent the mean±SEM (n=8). \*:  $P < 0.05$ , \*\*:  $P < 0.01$ , compared to corresponding control. Control: 1ml/kg (p.o); Standard drug: Morphine (s.c); Test drug: Methanolic extract of *Rhodiola rosea* L. (p.o).

**Dose response comparison by using Tail immersion method**



**Figure 7: Dose response comparison of *R. rosea* extracts by using tail immersion method**

## DISCUSSION

The acute toxicity study of the four different doses of *Rhodiola rosea* extract shows no lethality within 24 hrs and there are no behavioral changes take place within 14 days after administer 2000mg/kg dose of the extract. So we can conclude that the extracts are safe for further work. Inflammation has different phases the first phase is caused by an increase in vascular permeability, the second one by infiltrate of leucocytes and the third one by granuloma formation. We determined anti-inflammatory activity by using inhibition of carrageenan-induced inflammation which is one of the most feasible methods to screen anti-inflammatory agents. The development of carrageenan-induced edema is bi-phasic; the first phase is attributed to the release of histamine, serotonin and kinins and the second phase is related to the release of prostaglandins and bradykinins [13-16]. We observed that *R.rosea* (50mg/kg) and *R.rosea* (200mg/kg) showed significant inhibition against carrageenan-induced paw edema in the dose dependent manner This response tendency of the extract in carrageenan induced paw edema revealed good peripheral anti-inflammatory properties of the methanolic extract. This anti-inflammatory effect of *R.rosea* (50mg/kg) and *R.rosea* (200mg/kg) may be due to the presence of flavonoids. It has been reported that a number of flavonoids possess anti-inflammatory [17] and analgesic [18] activities. Flavonoids are known to inhibit the enzyme prostaglandin synthetase, more specifically the endoperoxidase and reported to produce anti-inflammatory effect. Since, prostaglandins are also involved in the pain perception; inhibition of their synthesis might be the possible reason for the analgesic activity of the methanolic extract. The presence of flavonoid identified might be responsible for the analgesic and anti-inflammatory activities in methanolic extract.

## CONCLUSION

Thus, it is concluded that the methanolic extract of rhizomes of *Rhodiola rosea* produces significant analgesic and anti-inflammatory activities in dose dependent manner. Flavonoids are known to inhibit the enzyme prostaglandin synthetase, more

specifically the endoperoxidase and reported to produce anti-inflammatory effect. Since, prostaglandins are also involved in the pain perception; inhibition of their synthesis might be the possible reason for the analgesic activity of the methanolic extract. The presence of flavonoid identified might be responsible for the analgesic and anti-inflammatory activities in methanolic extract.

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