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Synergistic Analgesic Effects of Petroleum Ether Extract of Oxalis Corniculata with Tramadol and Pentazocine in Mice

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ABSTRACT

Introduction*:* Opioids are the drug of choice for acute and chronic painful conditions not responding to other pain killers. But evidence shows that a small proportion of patients with chronic pain do not get complete pain relief with opioids, thus necessitating the need for newer modalities of treatment. Oxalis corniculata is a herbal plant used for pain medication. Beta sitosterol present in Oxalis corniculata is responsible for the analgesic action. Beta sitosterol is extracted through petroleum ether to form petroleum ether extract of Oxalis corniculata using Soxhlet apparatus. Oxalis corniculata was found to be acting through opioid receptors. In this study, we aim to evaluate the synergistic analgesic effects of Petroleum ether extract of Oxalis corniculata (PEOC) with Tramadol and Pentazocine in mice.

Methods*:* This study was conducted in Albino mice (Swiss strain) in the animal house of our institute. Animals were divided into seven groups of six mice each (Total = 42). Drugs such as Tramadol, Pentazocine and PEOC were given at a dose of 50mg/kg i.p., 10 mg/kg i.p., 150 mg/kg p.o. respectively. Analgesic activity is evaluated using "Hot plate test", "Tail immersion test", "Tail flick test", "Formalin induced paw licking test", and "Acetic acid induced writhing test".

Results*:* In Hot plate test at the end of 90 min, the reaction time was found to be increased in the Tramadol with extract (18.28+0.62) and the Pentazocine with extract (15.02+0.46 sec) than the other groups such as Tramadol, Pentazocine, PEOC, Olive oil and Distilled water group and was statistically significant. In tail immersion test, the tail withdrawal time was found to be better in the Tramadol with extract group (4.77+1.22 sec) and pentazocine with extract group (2.3+0.61 sec) compared to other groups. In Tail Flick test the tail flick latency was better in the Tramadol with extract group (10+0 sec) and Pentazocine with extract group (9.83+0.13 sec) compared to the control groups. In Formalin induced paw licking test, in both the phases (Phase I & II), the paw licking time was found to be reduced in the tramadol with extract group (44.83+15.67 sec & 16+4.78 sec) and pentazocine with extract group (66.33+7.57 sec & 44+8.61sec) compared to other groups. In acetic acid induced writhing test the number of writhing responses for a period of 30 minutes was found to be reduced in the tramadol with extract group (16.33+1.33), and pentazocine with extract group (22.17+3.04) compared to other groups.

Conclusion*:* Thus, from our study we conclude that Petroleum ether extract of Oxalis corniculata exhibits synergistic analgesic effect when given in combination with opioid analgesics such as tramadol and pentazocine in mice.

***Keywords*:** Opioids, necessitating, corniculate, Analgesic, tramadol.

INTRODUCTION:

Opioids are the drug of choice in severe painful conditions. Prolonged use of these drugs lead to sedation, tolerance, respiratory depression and even no response[1]. So there is a need for newer drug therapy. Oxalis corniculata (creeping woodsorrel), a weed grown in the paddy field was traditionally used for pain management with least side effects compared to the conventional drugs[2]. It contains phytosterols (β sitosterol) which is responsible for the analgesic action. It also possess anti-inflammatory, antidiabetic and antihypertensive[3] properties as well. Petroleum ether extract prepared from dried leaves of Oxalis corniculata possess β sitosterol and causes analgesia.

Srikanth M[4] in his study stated that β sitosterol

present in Oxalis corniculata shows the analgesic response. Also mice was found to be the best experimental model to demonstrate pain perceptions which was stated by Hickman DL[5]. Toxicity data was found to be non-toxic, proved by Mekap and Sahoo[6] in their study. Naloxone was found to reverse the antinociceptive response produced by petroleum ether extract of Oxalis corniculata which was confirmed by a previous study done by Dighe[7]. So, petroleum ether extract of Oxalis corniculata exhibiting analgesic action was found to act through opioid receptors.

The concept of opioid synergism was proven to show increased efficacy in chronic pain management. This forms a base for the present study showing synergism between Oxalis corniculata and opioid drugs such as tramadol and pentazocine which produces better analgesia compared to monotherapy.

MATERIALS AND METHODS:

Study setting: The study was conducted in the Animal house, Department of Pharmacology, Sri Manakula Vinayagar Medical College and Hospital.

Study design: The study design is an experimental animal study

Study duration: The duration of the study is 1 year and 6 months from September 2022 to December 2023.

Ethical considerations: The ethical approval was obtained from Institutional Animal Ethics Committee (IAEC/SMVMCH/031/2022), Sri Manakula Vinayagar Medical College and Hospital. The care and maintenance for the animals were given as per CCSEA (Committee for Control and Supervision of Experimental Animals) guidelines. Experiment were canducted based on Good Laboratory Practice (GLP).

Sample size: The sample size of my study was calculated to be 42 based on the prevalence calculated from previous studies. There are total of seven groups containing six mice each.

Preparation of the petroleum ether extract using Soxhlet apparatus[8]:

The leaves of Oxalis corniculata were dried and powdered and extracted with solvents such as petroleum and ether to form petroleum ether extract using Soxhlet extraction method by a Soxhlet apparatus.

Animals:

Swiss albino mice weighing 25-30 gms and 10-12 weeks of age were procured from a registered CCSEA breeder. Animals are housed in groups of seven in polypropylene cages of six mice each and acclimatized for a period of one week. Room temperature is maintained at 24-27^{0}C. A 12:12 light dark cycle is maintained. The mice was provided with standard pellet diet and water ad libitum. The experiment was conducted throughout the light period between 10 and 12 hours.

Drugs and Chemicals:

Animals were provided with Standard Pellet diet (Pet care International, Tamil Nadu) and the drugs used are Injection Tramadol (Kalki enterprises, Puducherry), Injection Pentazocine lactate (Kalki enterprises, Puducherry), Olive oil (Vehicle), Petroleum ether extract of Oxalis corniculata (Mother Teresa Post Graduate and Research Institute) and chemicals such as 0.6% Acetic acid, 1% Formalin (Department of Pharmacology, SMVMCH, Puducherry).

METHODS:

A pilot study was done to determine the analgesic dose of Petroleum ether extract of Oxalis corniculata. The mice were divided into five groups of two mice in which group I receives Olive oil (10ml/kg p.o.), group II, III, IV and V receives petroleum ether extract of Oxalis corniculata at doses of 100mg/kg, 150mg/kg, 200mg/kg and 250mg/kg p.o. respectively.

Better analgesic dose was found to be 150mg/kg by using hot plate test.

Table 1: Grouping of animals:

Group	Number	Drug	Dose
I	6	Distilled water (Negative control)	0.23ml p.o.
II	6	Olive oil (Vehicle control)	0.23ml p.o.
III	6	Injection Tramadol	50mg/kg i.p[9]
IV	6	Injection Pentazocine	10mg/kg i.p[10]
V	6	Petroleum ether extract of Oxalis corniculata	150mg/kg p.o.

		(PEOC)	
VI	6	PEOC + Tramadol	Injection 150mg/kg p.o. + 50mg/kg i.p.
VII	6	PEOC + Pentazocine	Injection 150mg/kg p.o.+ 10mg/kg i.p.

I) Hot Plate test[11]:

Central nociceptive activity was evaluated using hot plate test. The test was performed using eddy's hot plate apparatus maintained at 55+0.2^{0}C. The mice was placed at the centre and the time till which the mice withholds the heat was measured as the reaction time. The threshold was maintained at 20 seconds. The onset of leaping/jumping/paw licking/biting were recorded as response, before drug administration and at 0, 30, 60, 90, 120 and 150min after drug administration.

II) Tail Immersion test[12]:

Tail immersion test was done with the help of a hot water bath maintained at 55^{0}C. The tip of the tail of the mice was exposed to the hot water bath and the threshold was maintained at 15

seconds. The tail flick latency of the mice was recorded before drug administration and at 60, 90, 120, 150 and 180 min after drug administration.

III) Tail Flick test[13]:

Tail Flick test was done using a Tail flick Analgesiometer, comprises of a holder for the restrained mice and a nichrome wire which was the source of radiant heat. The mice was restrained with the help of a mice restrainer. The middle part of the tail was exposed to heat and the threshold was maintained at 10-15 seconds. The duration of the tail flick latency was recorded before drug administration and at 0, 30, 60, 90, and 120 min after drug administration.

IV) Formalin induced paw licking test[14]:

0.1ml of 1% formalin was injected into the right hind paw of the mice. The time taken to lick the paw was recorded as the reaction time. The paw licking was calculated in two phases namely phase I which was immediate mediated by nociceptive receptors within 0-5 min after drug administration. Phase II was delayed by 15-30 min which was mediated by inflammation. Opioids drugs have better action in phase I and NSAIDs have better action in phase II. Reduction in the reaction time i.e. paw licking time in both the phases indicates the analgesic effect.

V) Acetic acid induced writhing test[15]:

The mice were treated with the drugs 1 hr before, and then 0.6% of glacial acetic acid was prepared and 0.1 ml was injected intraperitoneally into the mice. The mice shows a characteristic stretching response known as 'writhing response'(arching of back, extension of hindlimbs, contracture of abdominal musculature). The pain was due to the activation chemosensitive nociceptors. The number of writhing responses for a period of 30 mins after drug administration was recorded as the reaction time. Reduction in the number of writhing responses indicates the analgesic effect.

Analysis:

Data was entered in Microsoft Excel. Data was summarized as mean + SEM (standard error of mean). Analysis was done using appropriate statistical test namely one way ANOVA followed by Tukey's post hoc test. Analysis was done using SPSS version 24.0., $P < 0.05$ was considered statistically significant.

RESULTS:

I) Hot Plate test:

Table 2 shows that the results of the tramadol with extract group at

the end of 90 minutes (18.28 $\pm$ 0.62 sec) was found to be better and it was statistically significant ($p < 0.05$) when compared to Distilled water group, Olive oil group, tramadol group, pentazocine group, and the extract group. This shows that there was a better efficacy in tramadol with extract group compared to other groups. Whereas the results of the pentazocine with the extract group at the end of 90 minutes (15.02 $\pm$ 0.46 sec) was better and statistically significant when compared to the Distilled water group and the Olive oil group. There was a decrease in efficacy when compared to tramadol with extract group.

Table: 2 – Evaluation of Synergistic analgesic activity of Oxalis corniculata using hot plate test in mice. (n=42)

Group	Drug	Dose	Time of onset of paw licking/leaping/jumping in mice (seconds)						
			Before drug adm.	After drug administration					
				0 min	30 min	60 min	90 min	120 min	150 min
I	Distilled water	0.23ml (p.o)	3.43 ±0.27	3.23±0.47	5.63±0.74	7.4±0.34	4.97 ±0.35	3.53±0.25	2.55±0.28
II	Olive oil	0.23ml (p.o)	3.57 ±0.31	3.45±0.74	6.58±0.94	10.63±1.22	7.35 ±0.80	4.02±0.25	3.12±0.25
III	Tramadol	50mg/kg (IP)	3.22 ±0.30	2.92±0.29	4.18±0.51	8.57±1.21	11.43 ±0.92*	6.02±0.41	4.95±0.37
IV	Pentazocine	10mg/kg (IP)	4±0.36	3.97±0.36	5.37±0.43	9.08±2.10	11.2 ±2.02*	9.98 ±1.11*#$	7.59 ±1.09*#
V	PEOC	150mg/kg (p.o)	3.1 ±0.22	3.57±0.37	5.77±0.59	8.73±0.98	13.77 ±0.48*#	6.7±0.79	4.52 ±0.38@
VI	Tramadol + PEOC	50mg/kg IP+150 mg/kg p.o	2.87 ±0.33	3.07±0.40	4.95±0.35	7.72±0.90	18.28 ±0.62*#$@ Ω	9.32 ±1.16*#$	5.75±0.61*
VII	Pentazocine + PEOC	10mg/kg IP+150 mg/kg p.o	3.58 ±0.38	6.38± 0.50*#$@ Ω¥	9.5± 0.48*#$@ Ω¥	12.47±0.83	15.02 ±0.46*#	10.87 ±0.61*#$Ω	6.73 ±1.04*#

PEOC – Petroleum ether extract of Oxalis corniculata p.o. – peroral, IP - Intraperitoneal

* p<0.05 compared to distilled water; # p<0.05 compared to olive oil; $ p<0.05 compared to tramadol;

@ p<0.05 compared to Pentazocine; Ω p<0.05 compared to PEOC; ¥ p<0.05 compared to Tramadol + PEOC

II) Tail Immersion test:

Table 3 shows that the tramadol with extract group at the end of 90 minutes (4.77 + 1.22 sec) was found to be better ($p < 0.05$) when compared to Distilled water group, Olive oil group, pentazocine group, and the extract group.The results of the pentazocine with the extract group at the end of 120 minutes (2.3 ± 0.61sec) was better and statistically significant when compared to the Distilled water group, Olive oil group, tramadol group, pentazocine group, extract group and the tramadol with extract group.

Table: 3 – Evaluation of Synergistic analgesic effects of Oxalis corniculata using tail immersion test in mice. (n=42)

Group	Drug	Dose	Tail withdrawal time (seconds)					
			Before drug adm.	After drug administration				
				60 min	90 min	120 min	150 min	180 min
I	Distilled water	0.23ml (p.o)	0.4±0.05	0.58±0.05	1.04±0.07	0.69±0.07	0.73±0.03	0.57±0.07
II	Olive oil	0.23ml(p.o)	0.38±0.05	0.47±0.04	1.19±0.13	0.91±0.12	0.58±0.06	0.39±0.04
III	Tramadol	50mg/kg (IP)	0.53±0.05	2.4±0.14*#	3.02±0.54	0.67±0.11	0.43±0.06	0.37±0.06

IV	**Pentazocine**	**10mg/kg (IP)**	**0.35±0.06**	**0.97±0.17$**	**1.2±0.17**	**0.7±0.07**	**0.55±0.06**	**0.43±0.05**
V	**PEOC**	**150mg/kg (p.o)**	**0.62±0.07@**	**1.55±0.11*#$**	**1.99±0.29**	**0.94±0.11**	**0.7±0.12**	**0.41±0.07**
VI	**Tramadol + PEOC**	**50mg/kg IP+150 mg/kg(p.o)**	**0.65 ±0.06#@**	**2.03 ±0.31*#@**	**4.77 ±1.22*#@Ω**	**0.67±0.11**	**0.48±0.04**	**0.35±0.04**
VII	**Pentazocine + PEOC**	**10mg/kg IP+150 mg/kg(p.o)**	**0.53±0.07**	**1.17 ±0.13$¥**	**3.1±0.51**	**2.3 ±0.61*#$@Ω¥**	**1.7 ±0.41*#$@Ω¥**	**0.95 ±0.25#$@Ω¥**

PEOC – Petroleum ether extract of Oxalis corniculata

p.o. – peroral IP – Intraperitoneal

* p<0.05 compared to distilled water;

# p<0.05 compared to olive oil;

$ p<0.05 compared to tramadol; @ p<0.05 compared to Pentazocine; Ω p<0.05 compared to PEOC; ¥ p<0.05 compared to Tramadol + PEOC

III) Tail Flick test:

Table 4 shows that the tramadol with extract group at the end of 90

minutes (10 ± 0 sec) was found to be better ($p < 0.05$) when compared to Distilled water group, and the Olive oil group. The pentazocine with the extract group at the end of 90 minutes (9.83 ± 0.13 sec) was better and statistically significant when compared to the Distilled water group and the Olive oil group.

Table: 4 – Evaluation of Synergistic analgesic effects of Oxalis corniculata using tail flick test in mice. (n=42)

			Time taken to withdraw the tail (seconds)					
			Before drug	**After drug administration**				
Group	**Drug**	**Dose**		**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
I	**Distilled water**	**0.23 ml (p.o)**	**4.03 ±0.37**	**4.73±0.51**	**5.7±0.47**	**4.82±0.32**	**4.78±0.45**	**4.5±0.25**
II	**Olive oil**	**0.23ml po**	**3.45 ±0.32**	**4.75±0.30**	**5.38±0.38**	**6.75±0.35***	**6.75±0.76***	**4.97±0.42**
III	**Tramadol**	**50mg/kg (IP)**	**4.73 ±0.40**	**5.32±0.69**	**5.97±0.27**	**8.4±0.36***	**9.3 ±0.40*#**	**5.32 ±0.47**
IV	**Pentazocine**	**10mg/kg (IP)**	**3.47 ±0.26**	**5.12±0.42**	**5.92±0.44**	**8.2±0.21***	**8.83 ±0.15*#**	**6.23 ±0.29**
V	**PEOC**	**150mg/kg (p.o)**	**3.68 ±0.23**	**4.03±0.35**	**5.4±0.70**	**7.13±0.84***	**9.2±0.59*#**	**5.58 ±0.46**
VI	**Tramadol +PEOC**	**50mg/kg IP + 150 mg/kg p.o**	**4.17 ±0.38**	**5.4±0.28**	**7.8 ±0.36*#Ω**	**9.93 ±0.07*#Ω**	**10±0*#**	**7.13 ±0.63*#**
VII	**Pentazocine + PEOC**	**10mg/kg IP+ 150 mg/kg p.o**	**3.43 ±0.29**	**4.28±0.29**	**5.82 ±0.15¥**	**8.52±0.38***	**9.83 ±0.13*#**	**6.7 ±0.41***

PEOC – Petroleum ether extract of Oxalis corniculata

p.o. – peroral, IP – Intraperitoneal

* p<0.05 compared to distilled water;
# p<0.05 compared to olive oil;
$ p<0.05 compared to tramadol; @ p<0.05 compared to Pentazocine; Ω p<0.05 compared to PEOC; ¥ p<0.05 compared to Tramadol + PEOC

IV) Formalin induced paw licking test:

Table 5 shows that the tramadol with extract group at Phase I (44.83 ± 15.67 sec) was found to be better ($p < 0.05$) when compared to Distilled water group, Olive oil group, and the Pentazocine group. At Phase II the results of the tramadol with extract group (16 ± 4.78 sec) was found to be better when compared to Distilled water group, Olive oil group, pentazocine group and the extract group. The pentazocine with the extract group at Phase I (66.33 ± 7.57 sec) was better when compared with Distilled water group and in Phase II it was better when compared with Distilled water group, Olive oil group, pentazocine group and the extract group

Table: 5 – Evaluation of Synergistic analgesic activity using formalin induced paw licking test in mice. (n=42)

Group	Drug	Dose	Paw licking time (in seconds)	
			Phase I (0-5 min)	Phase II (15-30 min)
I	Distilled water	0.23 ml (p.o)	130.83+18.17	170.83+18.90
II	Olive oil	0.23 ml (p.o)	114.67+14.25	160.33+21.39
III	Tramadol	50mg/kg (IP)	68.17+3.18*	42+1.39*#
IV	Pentazocine	10mg/kg (IP)	109.67+9.63	133.67+10.50$
V	PEOC	150mg/kg (p.o)	62.33+12.54*	118.67+24.83$
VI	Tramadol + PEOC	50mg/kg (IP) + 150mg/kg (p.o)	44.83±15.67*#@	16±4.78*#@Ω
VII	Pentazocine + PEOC	10mg/kg (IP) + 150mg/kg (p.o)	66.33±7.57*	44±8.61*#@Ω

PEOC – Petroleum ether extract of Oxalis corniculata

p.o. – peroral, IP – Intraperitoneal

* p<0.05 compared to distilled water; # p<0.05 compared to olive oil; $ p<0.05 compared to tramadol;

@ p<0.05 compared to Pentazocine; Ω p<0.05 compared to PEOC; ¥ p<0.05 compared to Tramadol + PEOC

V) Acetic induced writhing test:

Table 6 shows that the tramadol with extract group (16.33 ± 1.33 sec) was found to be better ($p < 0.05$) when compared to Distilled water group, Olive oil group, tramadol group, pentazocine group, and the extract group. the pentazocine with the extract group (22.17 ± 3.04 sec) was found to be better when compared to the Distilled water group, Olive oil group, tramadol group, pentazocine group and the extract group.

Table: 6 – Evaluation of Synergistic analgesic effects of Oxalis corniculata using acetic acid induced writhing test in mice. (n=42)

Group	Drug	Dose	Writhing response for a period of 30 mins
			No. of writhings
I	Distilled water	0.23 ml (p.o)	79.83+1.52

II	**Olive oil**	**0.23 ml (p.o)**	**66.5+2.01***
III	**Tramadol**	**50mg/kg (IP)**	**37.33+2.26*#**
IV	**Pentazocine**	**10mg/kg (IP)**	**43+3.24*#**
V	**PEOC**	**150mg/kg (p.o)**	**57+2.25*$@**
VI	**Tramadol + PEOC**	**50mg/kg (IP)+ 150mg/kg (p.o)**	**16.33±1.33*#$@Ω**
VII	**Pentazocine + PEOC**	**10mg/kg (IP) + 150mg/kg (p.o)**	**22.17±3.04*#$@Ω**

PEOC – Petroleum ether extract of Oxalis corniculata

p.o. – peroral, IP – Intraperitoneal

* p<0.05 compared to distilled water; # p<0.05 compared to olive oil; $ p<0.05 compared to tramadol;

@ p<0.05 compared to Pentazocine; Ω p<0.05 compared to PEOC; ¥ p<0.05 compared to Tramadol + PEOC

DISCUSSION:

Our study focusses on synergism between Oxalis corniculata acting through opioid receptors and other opioid drugs such as tramadol and pentazocine. Our study shows that Oxalis corniculata exhibits synergistic analgesic action with tramadol and pentazocine in mice using hot plate test, tail immersion test, tail flick test, formalin induced paw licking test, and acetic acid induced writhing test.

Dighe stated that Oxalis corniculata produced antinociception in mice using hot plate test. They have not tried to explain about the synergism between the Oxalis corniculata and the opioid drugs but it was explored in our study which shows increased efficacy and duration of action of opioids compared to the above stated study. Also we have selected two standard opioid drugs with different receptor action to explain the concept of synergism.

Kim[16] in his study proved that there is synergism between two opioid drugs. In our study, Oxalis corniculata and the opioid drugs act through different receptors and through different routes namely, oral and intraperitoneal respectively exhibited synergism and it was statistically significant. Foroud M[17] explained that when two opioid drugs given in combination exerted increased antinociceptive effect but they did not clearly explain that the maximal effect is due to additive mechanism or synergism. In our study there was mechanism of synergism involved and it was statistically significant.

Miranda HF[18] in their study used only hot plate test and acetic acid induced writhing test to estimate analgesia, whereas we have used five different tests to evaluate the central and peripheral analgesic activity. Study done by Yeh YC[19] states that the effects are mostly additive rather than synergy. In our study the pain relief produced by the PEOC and opioid drugs (tramadol and pentazocine) combination were adequate in all the five tests. Also we found that the mechanism involved behind the increased analgesic activity was found to be synergism.

Oxalis corniculata is a medicinal plant used as a pain medication in traditional medicine. Oxalis corniculata acts through opioid type of receptors, confirmed by administration of Naloxone. Beta-sitosterol which is a phytosterol present in Oxalis corniculata was found to be causing antinociceptive effects by inhibition of supraspinal pathway (µ1, k3, ð1) of opioid receptors[20],[21] .Hot plate test follows the supraspinal pathway whereas the tail flick test follows the spinal pathway of pain sensation. The results of the hot plate test shows that the synergistic analgesic effects produced by the petroleum ether extract of Oxalis corniculata with tramadol and pentazocine was found to be better when compared to the tail flick test in mice. From this we conclude that the petroleum ether extract of Oxalis corniculata was found to be causing antinociception in mice mainly by inhibiting supraspinal pain pathway of pain sensation with little effect of spinal pathway of pain sensation.

Animals (mice) selected for the study have more genetic similarity with human beings[22] .We have used two standard opioid drugs tramadol (μ receptor) , pentazocine (κ receptor) and the analgesic dose of the petroleum ether extract of Oxalis corniculate was obtained from the pilot study.

The exact molecular mechanism of action of petroleum ether extract of Oxalis corniculata was not evaluated and the synergism explained in our study was not quantified. Different doses of Oxalis corniculata were not tried in our study to prove the mechanism of synergism. No separate parameters were used to measure the intensity of pain response. The dose of Oxalis corniculata and the toxicological data available were only for experimental laboratory animals. Due to similarity in genetic makeup with humans, further studies can be done using the petroleum ether extract of Oxalis corniculata in clinical trials to evaluate the effective analgesic dose in humans. Also the concept of synergism can be applied with other opioid drugs with different receptor action to improve the efficacy and duration of action of opioids with least adverse effects.

CONCLUSION:

Thus, from our study we conclude that Petroleum ether extract of Oxalis corniculata exhibits synergistic analgesic effect when given in combination with opioid analgesics such as tramadol and pentazocine in mice.

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