IJPSR (2019), Volume 10, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 July 2018; received in revised form, 30 September 2018; accepted, 01 October 2018; published 01 April 2019

ANTINOCICEPTIVE EFFECTS OF METHANOLIC EXTRACTS OF *POTENTILLA ANSERINA* IN ANIMAL MODELS

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Keywords:

Potentilla anserina, Indomethacin, Acetic acid

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ABSTRACT: *Potentilla anserina* (Rosaceae) is a traditional medicinal plant in India, and it is available throughout the Northern hemisphere. This study was intended to evaluate the antinociceptive activity of methanolic extract of *Potentilla anserina* in acetic acid-induced writhing test in mice and Eddy's Hot Plate method in Albino rats at the dose level of 75, 150 and 300 mg/kg p.o and the study was compared with the standard drug Indomethacin 10 mg/kg. The data were expressed as mean ± S.E.M. The statistical analysis was done using ANOVA followed by Dunnett‟s post hock test. The methanolic extract of *Potentilla anserina* showed significant antinociceptive activity in the acetic acid-induced writhing method the PAME (75, 150, 300 mg/kg, p.o) 1hr before a pain stimulus significantly reduced the nociceptive response. In the hot plate method, there was no significant difference in nociceptive behavior. The antinociceptive activity could be associated with the presence of several flavonoid-based bioactive compounds and their synergistic action with non-volatile bioactive compounds.

INTRODUCTION: Traditional medicinal herbs are being used extensively in various part of the world, including India, to treat different types of ailments as alternative medicine. The major importance of these herbal medicines has less toxicity compared to synthetic ones. Medicinal plants and their derivatives represent a common alternative for the treatment of diseases [1, 2]. The extracts are exhaustively used to treat various disorders, although there is relatively little knowledge about their mode of action.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(4).1760-64

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(4).1760-64

Potentilla anserina (Rosaceae) is traditional medicinal plant available in India and Northern hemispheres often on river shores and grassy habitats. Plants which are reported to have anti-inflammatory and antinociception activity include *Syzygium cerasoideum* [3], *Potentilla reptans* [4], *Inula britannica* [5], *Coriandrum sativum* [6], *Clinacanthus nutans* [7], *Borreria verticillata* [8], *Sonchus asper* [9], *Inula helenium* [10], *Erigeron acer* [11], *Rhus coriaria* [12], *Ducrosia anethifolia* [13], *Eryngium pyramidal* Boiss [14], *Pimpinella anisum* [15], *Tanacetum balsamita* [16], *Echinophora platyloba* [17] and *Lemon verbena* [18], *etc*. There is a growing interest in the pharmacological evaluation of various plants used in traditional Indian systems of medicine. Thus the present investigation was carried out to evaluate the antinociceptive potential of methanol extracts of the whole plant of *Potentilla anserina* Linn.

It is used as astringent, anti-inflammatory, antispasmodic, hemostatic, and for treating diarrhea, leucorrhoea, dysmenorrhoea, arthritis, cramps, kidney stones, and bleeding piles. It is also used as mouth wash in pyorrhoea, gingivitis and sore throat [19]. *Potentilla anserina* Linn. have revealed the presence of various phytoactive constituents such as alkaloids, saponins, flavonoids, glycosides, tannins, phenolic compounds, and steroids.

Earlier studies indicate *β*-sitosterol, flavonoids, phenolic compounds, and tannins may be responsible for the antinociceptive activity. These plant extracts also contain similar phytoconstituents which was responsible for the activity.

From the literature survey, it may be revealed that still there is lacking scientific data on the analgesic effect of *Potentilla anserina*. Given the fact that (i) pain transmission is a complex process that involves activation of a plethora of signaling cascades by various mediators through numerous receptors at the peripheral and central levels and (ii) currently available analgesics are associated with adverse effects that may overshadow their effectiveness, the present study was conducted to evaluate the analgesic effect in experimental animals using methanol extract.

MATERIALS AND METHODS:

Plant Material and Extract Preparation: [20] The whole plant of *Potentilla anserina* L. (Rosaceae) was collected from Tirupati, India and was authenticated by Dr. K. Madhava Chetty, Sri Venkateshwara University, Tirupati, India. The authenticated methanolic extract of the whole plant done by using Soxhlet apparatus.

The methanol extract was evaporated under reduced pressure and temperature less than 50 ºC to obtain a dark green viscous mass. The extract was then stored at a temperature of 2 - 4 ºC for phytochemical and pharmacological evaluations.

Drugs and Chemicals: The methanolic extract of *Potentilla anserina* at doses of 75, 150 and 300 mg/kg were prepared by suspending this remainder in the 2% gum acacia and given to the animals orally. The reference drugs used in the study were Indomethacin (10 mg/kg) is administered orally by dissolving in 0.9% normal saline.

Animals: Adult rats of either sex, weighing 200-250g and mice of 20-25g were obtained from the animal house of Dayananda Sagar University, Bengaluru. They were housed in an artificial regulated room on a 12h light; 12h dark cycle with 25 ± 2 ºC and had water *ad libitum*. The IAEC approved the experimental protocol, DSU 606/20/c/CPCSEA and experiments were conducted according to the CPCSEA, India guidelines on the use and care of experimental animals.

Experimental Design:

Acetic Acid-Induced Writhing Test in Mice: [21] The procedure described by Koster *et al*., was used to evaluate the antinociceptive activity Albino mice of either sex selected by random sampling technique weighing between 20-25g body weight selected for the study. They are divided into five groups each composed of six animals.

Group I: Control (0.5% CMC-Na 20 ml/kg p.o.)

Group II: Standard (Indomethacin 10 mg/kg p.o.)

Group III: Animals received PAME at the dose of 75 mg/kg b.w. p.o

Group IV: Animals received PAME at a dose of 150 mg/kg b.w. p.o

Group V: Animals received PAME at the dose of 300 mg/kg b.w. p.o

Mice were given an intraperitoneal injection of 1% acetic acid (10 ml/kg) 60 min to induce the characteristic writhings after the last administration. The number of abdominal constrictions produced in these animals was counted cumulatively for 15 min after the injection. Antinociceptive activity indicated by a reduction in the mean of the number of abdominal constrictions in the test group compared to the control group was calculated as percent inhibition of abdominal constrictions (percent of inhibitory level) using the following formula:

Mean of (Control-Test) / Control group × 100%

Eddy's Hot Plate Model in Rats: [22] The procedure described by Prabodh Bora *et al*., was used. In this model, the animals were divided into five groups of six animals each.

Group I: Control (Saline 0.9%)

Group II: Standard (Indomethacin 10 mg/kg p.o.)

Group III: Animals received PAME at a dose of 75 mg/kg p.o.

Group IV: Animals received PAME at a dose of 150 mg/kg p.o.

Group V: Animals received PAME at a dose of 300 mg/kg p.o.

Animals were placed individually on a hot plate metallic surface (Insight, Brazil-model EFF-361) maintained at 54 +/- 1C, and the time between placement of the animal on the hot plate and occurrence of either licking of the hind paws, shaking or jumping off the surface was recorded in terms of the reaction time(s). The reaction time was measured 1h following treatment.

Statistical Analysis: The data obtained were analyzed using Sigmastat software (3.5) and expressed as a mean ± SEM. The statistically significant differences between groups were calculated by ANOVA, followed by Dunnet's test. The $p<0.05$ selected as the level of statistical significance.

RESULTS:

Effect of *Potentilla anserina* Extract on the Writhing Response in Mice: The PAME administered orally at different doses (75, 150 and 300 mg/kg) caused significant inhibition (30%, 52.09%, and 54.1% respectively) compared to the control of the writhing responses induced by the acetic acid. The decrease in the number of writhing was dose-dependent. Indomethacin (10 mg/kg,p.o) produced a 72.6% reduction compared to the control **Table 1**.

TABLE 1: EFFECT OF *POTENTILLA ANSERINA* EXTRACT ON THE WRITHING RESPONSE IN MICE

Group	Dose (mg/kg p.o.)	Writhing Num.	Inhibition of writhing Num. (%)
1	Control	30 ± 3	-
2	Indomethacin (10 mg/kg)	7.0 ± 0.9	72.6 ± 0.7
3	PAME (75 mg/kg)	26 ± 2.0	30.10 ± 2.9
4	PAME (150 mg/kg)	15 ± 0.5	52.09 ± 1.4
5	PAME (300 mg/kg)	17 ± 0.7	54.1 ± 1.8

PAME- *Potentilla anserina* methanolic extract**,** values are expressed as mean ± SEM

Effect of *Potentilla anserina* Extract on Hot Plate Test in Rats: The PAME administered orally at different doses (75, 150 and 300 mg/kg) caused significant inhibition (11.7%, 13.65% and 16.08% at 60 min and 12.3%, 12.6% at 90 min respectively compared to control but no significant at high dose (300 mg/kg) at 90 min **Table 2**.

TABLE 2: EDDY'S HOT PLATE METHOD

Group	Dose (mg/kg p.o.)	Reaction time				
		0 min	30 min	60 min	90 min	120 min
1	Control	3.98 ± 0.15	4.10 ± 0.07	4.60 ± 0.17	4.3 ± 0.55	3.09 ± 0.11
2	Indomethacin (10 mg/kg)	12.6 ± 0.42	14.6 ± 0.81	17.2 ± 0.64	4.2 ± 1.4	13.6 ± 0.9
3	PAME (75 mg/kg)	4.55 ± 0.85	8.12 ± 0.75	11.7 ± 0.56	12.3 ± 0.12	12.5 ± 0.15
4	PAME (150 mg/kg)	7.80 ± 0.24	11.7 ± 0.75	13.65 ± 0.75	12.6 ± 0.07	13.02 ± 0.01
5	PAME (300 mg/kg)	10.0 ± 0.62	13.8 ± 0.69	16.08 ± 0.36	-	-

PAME- *Potentilla anserina* methanolic extract

DISCUSSION: Herbal remedies are used frequently in healthy as well as diseased persons. Some herbals have been developed as analgesics amongst them a very little has studied for the molecular mode of action. In recent some studies *Potentilla anserina* shown different pharmacological actions, even there are less knowledge and significant results about the anti-inflammatory activities. To evaluate for a possible central antinociceptive effect of the methanolic extract the hotplate and writhing tests are used for evaluation of the central pain at the supraspinal and spinal levels [23], respectively, possibly acting on a descending inhibitory pain pathway [24]. Anti-nociceptive activity *via* activation of opioid receptors and modulation of the L-arginine/NO-dependent / cGMP-independent pathway [7]. The involvement of capsaicin receptors, also known as

transient receptor potential vanilloid type 1 (TRPV1) receptors, in the modulation of nociceptive transmission has been well documented [25]. Some activators such as prostaglandins and bradykinin modulate the activity of the receptor indirectly by activating different protein kinases inside the cell. Interestingly, Caterina *et al*., [26] have earlier demonstrated that mice lacking TRPV1 receptor showed normal responses to noxious mechanical stimuli but exhibited no vanilloid-evoked pain behavior. Moreover, these mice were also impaired in the detection of painful heat and showed little thermal hypersensitivity in the setting of inflammation. These findings indicate the important role of TRPV1 receptors in the modulation of different modalities of pain sensation and for tissue injury-induced thermal hyperalgesia.

Nonopioid analgesics are among the most widely used treatments for pain [27]. Other than the inhibition of COX and prostaglandin synthesis, accumulating evidence has demonstrated the multiple actions of analgesics with other systems during pain. The involvement of noradrenergic system in nociception at spinal and supraspinal levels has been proven to be mediated through activation of α-adrenoceptors and descending inhibitory pathways [28]. Yohimbine, the α2 adrenoceptor antagonist, has been reported to antagonize the antinociceptive effects of nonopioid octacosanol when assessed using the mouse abdominal constriction test [29].

The μ receptor has generally been regarded as the receptor type associated with pain relief and is potent in regulating thermal pain [30]. Nonanalgesic effects mediated by the μ receptors include respiratory depression, inhibition of intestinal motility and most importantly for therapeutic considerations is its induction of physical dependence. Activation of μ2 opioid subtype leads to spinal analgesia and commonly through constipation adverse effect [31]. Therefore, taking all these data together we believe that the antinociceptive activity of methanol extract is most likely to be mediated peripherally and centrally and indicates morphine-like mechanisms by binding with opioid receptors.

CONCLUSION: In the present study, *Potentilla anserina* showed significant results in experimental analgesia. It can be interpreted that PAME possesses good antinociceptive property which may be due to peripheral inhibition by prostaglandin synthesis inhibition and central inhibitory mechanisms and may show a healthful benefit in the management of pain.

ACKNOWLEDGEMENT: We are thankful to Dayananda Sagar University and Oxbridge College of Pharmacy, Bengaluru for their support.

CONFLICT OF INTEREST: The authors declare no potential conflicts of interest concerning the research, authorship, and publication of this paper.

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How to cite this article:
Sadik S, Geetha KM, Vasia and Reddy AM: Antinociceptive effects of methanolic extracts of *Potentilla anserina* in animal models. Int J Pharm Sci & Res 2019; 10(4): 1760-64. doi: 10.13040/IJPSR.0975-8232.10(4).1760-64.