Analgesic and Anti-inflammatory action of *Opuntia elatior* Mill fruits

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ABSTRACT

Background: *Opuntia elatio* Mill is a xerophytic plant with potentially active nutrients. It is traditionally appreciated for its pharmacological properties; however, the scientific information on this plant is insufficient. **Objective:** The present study evaluates the antinociceptive and anti-inflammatory action of prickly pear. **Materials and Methods:** Writhing and tail-immersion tests were carried out to evaluate analgesic action, while the carrageenan-induced paw edema and neutrophil adhesion tests were conducted in Albino wistar rats to assess anti-inflammatory action. **Results:** ED_{50} values of the fruit juice in writhing, tail immersion, and paw edema test were 0.919, 2.77, and 9.282 ml/kg, respectively. The fruits of *Opuntia* produced analgesic and anti-inflammatory action in a dose-dependent manner. **Conclusion:** The results establish the folklore use of prickly pear may be due to the presence of betacyanin and/or other phenolic compounds.

Key words: Analgesic, anti-inflammatory, *Opuntia*, prickly pear

INTRODUCTION

Pain and inflammation are part of the body's immune response. They are a common symptom and affect a large number of patients with many types of disease. Because of the significant side effect profiles of steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), there is a greater interest in natural compounds, such as dietary supplement and herbal remedies, which have been used to reduce pain and inflammation. The cactus *Opuntia* (subfamily: *Opuntiodae*, family: Cactaceae) is a xerophytic plant; 200-300 species of the plant exist. In local parlance, cactus is called *Prickly Pear, Slipper Thorn*, and *Tuna* (English); in India, it has different vernacular names such as *Hathlo Thor* and *Chorhthlo* (Gujarati); *Haththathoira, Nagphana,* and *Nagphani* (Hindi); *Snuhi, Vajrakantaka,* and *Bahushala* (Sanskrit); *Nagadali* and *Nagakkali* (Tamil); and *Nagamulla* and *Nagajemudu* (Telugu). It has been established that all cacti found in India do not belong to one species (*O. dillenii*), but three to four species distributed over different regions in the country. *O. dillenii* Haw. is found mainly in the southern regions of India, while *O. vulgaris* Mill. (Syn *O. monocantha* Haw.) is distributed mainly in the northern regions; *O. elatior* Mill. is found in western India.[1,2] The presence of potentially active nutrients and their multifunctional properties make fruits and cladodes of *Opuntia* spp. ideal candidates for the production of phytopharmaceutical products. Although traditionally appreciated for its pharmacological properties by Native Americans, cactus/prickly pear is still rarely recognized as insufficient scientific information on these plants is available.[3] *Opuntia* species have been used as analgesic and anti-inflammatory, anticancer, antidiabetic, anti-hyperlipidemic and anti-hypercholesterolemic, antioxidant, antiulcer, antiviral, diuretic, immunomodulatory, neuroprotective, and monoamino-oxidase inhibitors; in addition, the species are nutritionally important, promote wound healing, and improve platelet function.[4,5] Canarian folk medicine has shown much evidence that the crude extract prepared from the fruits of *O. dillenii* is useful in the treatment of gastrointestinal and liver disturbances. Loro *et al.* investigated analgesic and anti-inflammatory effect of

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Received: 17-Jan-2014
Revised: 03-Mar-2014
Accepted: 26-Mar-2014

Access this article online	
Quick Response Code:	Website: www.jaim.in
	DOI: 10.4103/0975-9476.159025

O. dillenii extract (100-400 mg/kg) in rats and mice,[6] while Eun-Hee *et al.* also reported a potent anti-inflammatory action of ethanol extract of *O. ficus-indica*.[7] Based on previous studies and folkloric use, the aim of the present study was to evaluate the antinociceptive activity of prickly pear using the writhing and tail immersion tests. In addition, we investigated the anti-inflammatory effect on an acute inflammatory process by using the carrageenan-induced edema and neutrophil adhesion tests.

MATERIALS AND METHODS

Collection, authentication, and preparation of fruit juice

The fruits of *O. elatior* Mill. were collected from roadside weed near Atkot, Ta: Jasdan, Dist: Rajkot, Gujarat, India, at Latitude (22° 1' 48"N), Longitude (71° 12' 0"E), and Elevation 193 M (633 ft); the fruits were authenticated by Raw Materials Herbarium and Museum, National Institute of Science and Communication and Information Resources (NISCAIR), New Delhi. The herbarium (specimen voucher No.: rbpmpc/museum/herbarium/07-08/01) was preserved in the museum of Department of Pharmacognosy, Smt. R. B. Patel Mahila Pharmacy College, Atkot. Mature fruits of *O. elatior* Mill. were collected and immediately taken to the laboratory. Spines and glochides were removed from the fruits by heating on a wire gauge burner and then washed with water. The fruits were peeled manually and the pulp homogenized for 5 minutes using boss portable blender (Boss appliances, Daman). After homogenization, the fruit juice was filtered through glass filter G_4 (Borosil Glass Works Ltd., Mumbai), and the filtered *Opuntia* fruit juice (OFJ) was used for various estimation and biological studies.

Phytochemical analysis

Identification of betalains was performed by spectrophotometric, high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectroscopy (LC-MS) analyses, and the findings were recently published by Chauhan *et al.*[8]

Animals

Albino wistar rats of either sex (180-250 g body weight) were used in this study. They were housed at ambient temperature (22 ± 1°C), relative humidity (55 ± 5%), and 12h/12h light-dark cycle. Animals had free access to Amrut brand rat pellet diet supplied by Pranav Agro Industry, Baroda, and water was given *ad libitum*. The experiment protocol was approved by the Institutional Animal Ethics Committee (IAEC) as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, vide certificate no. IAEC/RBPMPC/09-10/01 dated 18/07/2009.

Acute toxicity study

Acute toxicity studies for the fruit juice were performed according to the acute toxic classic method as per guidelines 423 prescribed by the Organisation for Economic Co-operation and Development OECD. Female albino rats were used for acute toxicity study. The animals were kept fasting overnight and provided with only water. The animals were divided into two groups containing five animals each. Each group was then administered with water and OFJ at the dose of 20 ml/kg p.o. The animals were observed for 30 min and then periodically for the first 24 h, with special attention during the first 4 h; thereafter, the animals were observed daily for 14 days. Observations such as sedation, convulsions, tremors, lethargy, and death were systemically recorded with individual records of each animal.

Antinociceptive tests

Writhing test

Abdominal constriction induced by intra-peritoneal injection of acetic acid (0.75%) was carried out according to the procedures described previously by Koster *et al.*[9] The OFJ was tested at doses 5, 10, and 15 ml/kg. Diclofenac sodium, a reference peripheral analgesic compound, was used at 10 mg/kg. Each group was composed of six rats. The number of writhings and stretchings was recorded and the percentage protection was calculated by the following equation:

$$\text{Percentage of protection} = \frac{\left[\begin{matrix}\text{Control mean} - \\ \text{Treated mean}\end{matrix}\right]}{\text{Control Mean}} \times 100$$

Tail immersion test

Tail immersion test was conducted as described by Aydin *et al.*[10] This involved immersing the extreme 3 cm of the rat's tail in a water bath containing water at a temperature of 55 ± 0.5 °C. Within a few minutes, the rat reacted by withdrawing its tail. The reaction time was recorded with a stopwatch. The average of the two values was the initial reaction time (Tb). The test groups were administered OFJ (5, 10, and 15 ml/kg, p.o.) and tramadol (10 mg/kg, p.o.). The reaction time (Ta) for the test groups was taken at intervals of 0.5, 1, 2, 4, 5, and 6 h after a latency period of 30 min following the administration of the OFJ and tramadol.[11]

Anti-inflammatory tests

Carrageenan-induced rat paw edema

Pedal inflammation in rats was produced according to the method described by Winter *et al.*[12] Following an overnight fast, OFJ (5, 10, and 15 ml/kg, p.o.) was

administered to animals in different groups by using an oral cannula. At the same time, animals in the reference standard group received diclofenac sodium (10 mg/kg, p.o.), while those in the control group received saline solution (10 ml/kg, p.o.). The paw size was measured in cm by wrapping a piece of cotton thread around the paw of each rat and measuring the circumference on a meter rule.[13,14] Inhibitory activity was calculated at every one-hour interval following carrageenan injection by using the following formula:

$$\text{Percentage Inhibition} = \frac{\left[\begin{array}{l}(\text{Ct}-\text{Co})\,\text{control} - \\ (\text{Ct}-\text{Co})\,\text{treated}\end{array}\right]}{(\text{Ct}-\text{Co})\,\text{control}} \times 100$$

Where, Ct is paw size at time (t) after carrageenan injection and Co is paw size before carrageenan injection.

Neutrophil adhesion test

The study was carried out as described by Wilkinson and Ghule *et al.*[15,16] Albino wistar rats of either sex were used in the study. The animals were randomly divided into four groups ($n = 6$) and treated accordingly.

Group A: Control (treated with vehicle, p.o., for 14 days)
Group B: OFJ (5 ml/kg, p.o., for 14 days)
Group C: OFJ (10 ml/kg, p.o., for 14 days)
Group D: OFJ (15 ml/kg, p.o., for 14 days).

On day 14, blood samples were collected from the retro-orbital plexus in heparinized vials and analyzed for total leukocyte count (TLC). The product of TLC and percent neutrophils gave the neutrophil index of blood sample. Percent neutrophil adhesion was calculated using the following formula:

$$\text{Neutrophil adhesion}\,(\%) = \frac{\text{NIu} - \text{NIt}}{\text{NIu}} \times 100$$

Where,
NIu = Neutrophil index of untreated blood sample
NIt = Neutrophil index of treated blood sample.

Statistical analysis

All the values are expressed as Mean ± SEM (standard error of mean). The data were analyzed by one-way ANOVA followed by Tukey's multiple comparison tests. A level of $P < 0.05$ was considered as statistically significant. A level of significance was noted and interpreted accordingly by using software GraphPad Prism free trial version 5. Regression analyses were used to calculate ED_{50} for the antinociceptive test and carrageenan-induced paw edema.

RESULTS

The OFJ (20 ml/kg) showed no significant change in various autonomic and behavioral responses of rat compared to the control animals. No mortality was recorded until 48 h in the animals treated with OFJ up to 20 ml/kg oral dose, and therefore, considered to be safe. The dose of OFJ was selected after carrying out acute toxicity studies. According to the finding, the maximum dose (20 ml/kg) was safe and based on that we selected three different doses for the study: low (5 ml/kg), medium (15 ml/kg), and high (15 ml/kg). The phytochemical analysis indicated the presence of color pigment betacyanin as the active principle, in addition to being a good source of sugar content and low acidity which make the fruit sweet and delicious. The total betacyanin content (47.1 mg/100 ml) equivalent to betanin obtained from the fruits of *O. elatior* Mill. was higher than that in *O. ficus-indica* and *O. undulate* Griff., while it was lower than that in *O. stricta* Haw.[8]

Antinociceptive action

Effect on acetic acid-induced writhing

Figure 1 presents the results of the acetic acid-induced writhing in rats. The OFJ (5, 10, and 15 ml/kg, p.o.) inhibited the writhing responses of rat caused by the intraperitoneal administration of acetic acid. The mean numbers of writhes was significantly ($P < 0.001$) reduced in OFJ-treated groups after 10 min when compared with the control group. Figure 2 illustrates the percentage inhibition of nociceptive responses. Maximum inhibition was found to be 89.67 ± 1.79% at the dose of 15 ml/kg after 20 min. The analgesic effect of the OFJ in this model was dose-dependent, with the ED_{50} being 0.919 ml/kg, which was equivalent to 1 ml/kg. At the dose of 15 ml/kg, the fruit juice exerted better analgesic action than diclofenac sodium after 20 min in acetic acid-induced writhing in rat.

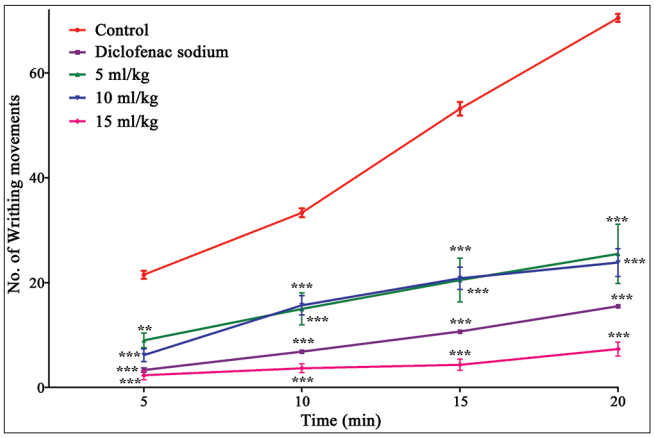

Figure 1: Influence of OFJ on acetic acid–induced writhing in rat. Values are Mean ± SEM ($n = 6$); analyzed by one-way ANOVA followed by Tukey's multiple comparison test, ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$ for change difference *vs* vehicle control group

Effect on tail immersion test

Table 1 presents the results of latency period (hour) and percentage analgesic action of OFJ in tail immersion test. After a latency period of 0.5 h, the OFJ (15 ml/kg) demonstrated significant reduction ($P < 0.001$) in painful sensation due to tail immersion in warm water compared to the control group. The maximum inhibitory effect of the fruit juice was 45.41 ± 0.89%, 1 h post-dosing at 15 ml/kg. The maximum antinociceptive action of the OFJ (15 ml/kg) was found to be 65.56 ± 1.52% at 3 h which is as effective as that of tramadol (10 mg/kg) 62.32 ± 6.29%. The OFJ significantly ($P < 0.001$) increased the reaction time of rats in a dose-dependent manner, with the ED_{50} being 2.77 ml/kg after a latency period of 3 hour.

Anti-inflammatory action

Carrageenan-induced rat paw edema

Figure 3 presents the percentages of inflammation calculated for each group; percentages of inhibition at 3 hour are reported in Table 2 and those over 5 hours are given in Figure 4. In control animals, the subplantar injection of carrageenan produced a local edema that increased progressively to reach the maximum intensity at 5 h after the injection of the phlogistic agent (90.68 ± 4.21%). OFJ at oral doses of 10 ml/kg and 15 ml/kg showed significant suppression of carrageenan-induced rat paw edema after 2 h when compared with the control group ($P < 0.01$ and $P < 0.001$, respectively). Diclofenac sodium also showed a clear inhibition of the inflammation induced by carrageenan after 2 h when compared with the control group ($P < 0.001$). Pretreatment by OFJ significantly reduced ($P < 0.001$) the carrageenan-induced edema in a dose-dependent manner, 3 h after carrageenan injection, to reach the maximal inhibition at this time with the dose of 15 ml/kg (54.69 ± 5.98%) and ED_{50} at 9.282.

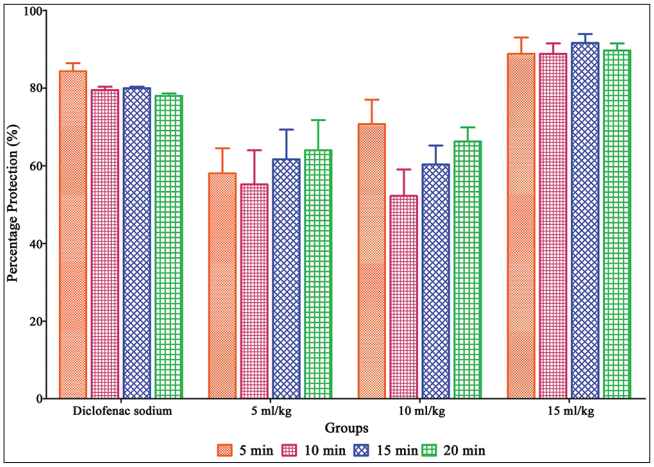

Figure 2: Percentage protection OFJ and diclofenac sodium on acetic acid–induced writhing in rat. Values are Mean ± SEM ($n = 6$); analyzed by one-way ANOVA followed by Tukey's multiple comparison test

Neutrophil adhesion test

Figure 5 presents the percentage of neutrophil adhesion which was estimated on day 14. Pretreatment with OFJ at doses 10 and 15 ml/kg, p.o., induced a significant ($P < 0.001$) decrease in the *in vitro* neutrophil adhesion to nylon fibers with respect to that of the control group, which correlated with the decrease

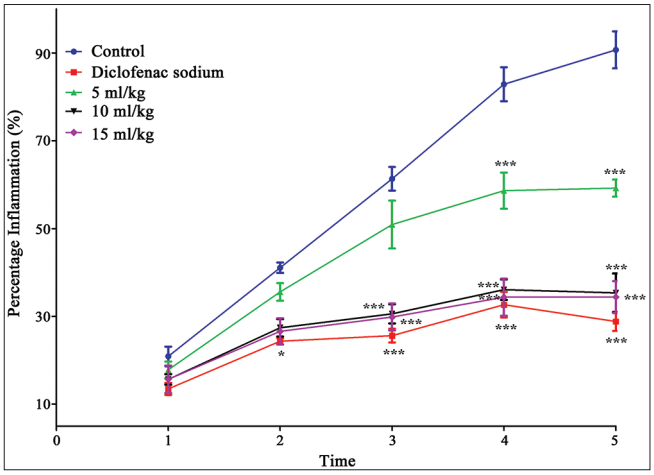

Figure 3: Influence of OFJ on percentage inflammation in carrageenan-induced rat paw edema. Values are Mean ± SEM ($n = 6$); analyzed by one-way ANOVA followed by Tukey's multiple comparison test, ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$ for change difference *vs* vehicle control group

Table 1: Analgesic effect of OFJ by tail immersion test

Latency period (h)	Control		Tramadol (10 mg/kg)		*Opuntia* fruit juice (ml/kg)					
					5		10		15	
	Min	%	Min	%	Min	%	Min	%	Min	%
0	1.582±0.02	-	1.87±0.01	-	1.67±0.01	-	1.58±0.02	-	1.74±0.01	-
0.5	1.567±0.05	0.97±2.72	2.31±0.08***	23.49±3.81	1.873±0.02	12.18±1.14	1.852±0.11	17.37±7.71	2.12±0.01***	21.87±1.17
1	1.59±0.09	0.85±6.93	2.527±0.14***	35.13±7.68	2.1±0.01***	25.76±0.73	2.12±0.06***	34.35±4.41	2.53±0.02***	45.41±0.89
2	1.593±0.04	0.79±2.75	2.797±0.06***	49.57±3.48	2.34±0.03***	40.11±1.56	2.32±0.02***	46.95±2.32	2.58±0.01***	48.29±0.69
3	1.587±0.10	0.36±6.18	3.035±0.12***	62.32±6.29	2.57±0.03***	53.9±1.89	2.46±0.003***	55.79±1.69	2.88±0.01***	65.56±1.52
4	1.57±0.08	0.56±5.49	3.407±0.09***	82.2±4.94	2.858±0.01***	71.17±0.83	2.803±0.13***	77.62±8.60	3.22±0.01***	85.1±1.46
5	1.547±0.09	2.15±5.53	3.63±0.01***	94.14±0.89	2.88±0.01***	72.47±0.82	2.94±0.05***	86.22±4.01	3.37±0.01***	93.71±1.24
6	1.588±0.17	0.56±10.73	3.72±0.004***	98.97±1.25	2.94±0.01***	76.06±0.59	3±0.05 ***	90.01±3.78	3.44±0.01***	97.74±1.54

Values are in minutes and percentage mean ± SEM ($n=6$); analyzed by one-way ANOVA followed by Tukey's multiple comparison test, ***$P<0.001$ for change difference *vs* vehicle control group, OFJ: *Opuntia* fruit juice, SEM: Standard error of mean

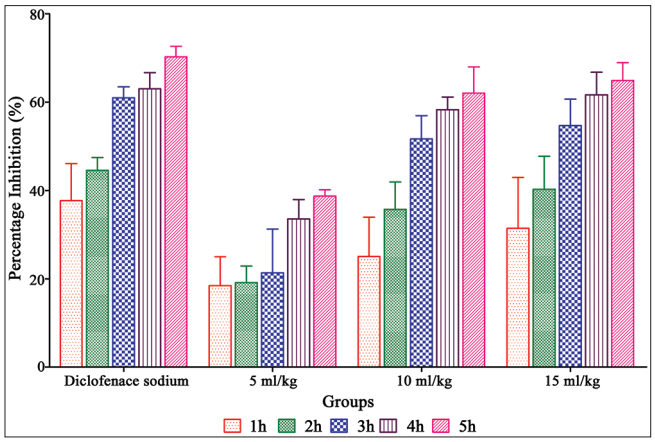

Figure 4: Percentage inhibition produced by OFJ and diclofenac sodium on carrageenan-induced rat paw edema over 5 hour. Values are Mean ± SEM (n = 6); analyzed by one-way ANOVA followed by Tukey's multiple comparison test

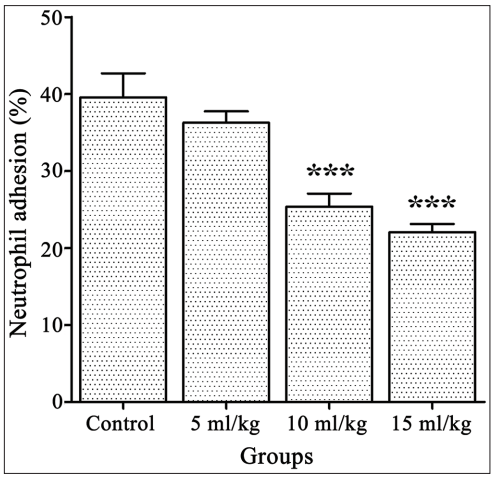

Figure 5: Effect of OFJ on neutrophil adhesion test. Values are Mean ± SEM (n = 6); analyzed by one-way ANOVA followed by Tukey's multiple comparison test, ***P < 0.001 for change difference vs vehicle control group

Table 2: Effect of OFJ on carrageenan-induced rat paw edema at 3 hour

Group	Dose	Inhibition (%) (mean±SEM)	ED_{50}
Control (Saline)	-	-	9.282±0.9117 ml/kg
Diclofenac sodium	10 mg/kg	60.99±2.48	
Fruit Juice	05 ml/kg	21.35±9.90	
Fruit Juice	10 ml/kg	51.69±5.25	
Fruit Juice	15 ml/kg	54.69±5.98	

OFJ: *Opuntia* fruit juice, SEM: Standard error of mean, ED: Effective dose

in percentage of neutrophils. However, fruit juice at a dose of 5 ml/kg did not show any significant change in neutrophil adhesion when compared with the respective control group.

DISCUSSION

This study investigated the potential of antinociceptive as a central analgesic by using tail immersion test and peripheral analgesic by using acetic acid-induced writhing test in the fruits of *O. elatior* Mill. The antinociceptive tests used in the present work were chosen to test different nociceptive stimuli, namely, cutaneous thermal(tail immersion) and chemical visceral (writhing) stimuli. The results indicate that the oral administration of the fruit juice of *O. elatior* Mill. exhibited central and peripheral analgesic properties since it exerted a significant and dose-dependent protective effect on chemical (acetic acid injection) and thermal painful stimuli. Such an effect on the two stimuli is characteristic of central analgesics such as morphine and tramadol, while peripheral analgesics such as diclofenac sodium and aspirin are known to be inactive on thermic painful stimuli.

The results demonstrate that the fruits of *O. elatior* Mill. attenuated the nociceptive responses to chemical stimuli in the acetic acid-induced abdominal constriction. The mean number of abdominal contractions was reduced from 25 to 7 at the respective doses of 5 and 15 ml/kg. Diclofenac sodium, the peripheral analgesic drug, also produced a similar antinociceptive action. It has been postulated that acetic acid acts indirectly by inducing the release of endogenous mediators, which stimulate the nociceptive neurons sensitive to non-steroidal anti-inflammatory drugs and opioids.[17,18] This test is generally used for the screening of central and peripheral analgesic effects.[9,11] The centrally acting protective effect of the extract was also corroborated in our study by the tail immersion test results.

The analgesic efficacy and potency of acutely administered tramadol is comparable to that of codeine, pentazocine, or dextropropoxyphene,[19] while its analgesic and antinociceptive potency is only 5 to 10 fold lower than that of morphine.[20] It is believed that tramadol works by μ-opioid receptors[21] despite its relatively low binding affinity.[19] Thus, it is speculated that nonopioid mechanisms are involved in tramadol analgesia. In accordance with the recognized implication of noradrenaline and serotonin in pain modulation, tramadol has been shown to inhibit the re-uptake of noradrenaline and serotonin, thereby increasing the concentration of these two neurotransmitters in specific areas of the brain, thus raising the pain threshold.[22]

Lyophilized aqueous extract (100-400 mg/kg, i.p.) of the fruits of *O. dillenii* (Ker-Gawl) Haw was evaluated for analgesic activity using writhing and hot plate test in mice and rat, respectively, as well as anti-inflammatory activity using carrageenan-induced paw edema in rats; the results exhibited a dose-dependent action.[6] Considering all these factors, it seems that the fruit juice of *O. elatior* Mill. contains morphine- and tramadol-like components and

other peripherally acting principles. Based on this study, we conclude that the fruits of *O. elatior* Mill. is endowed with central and peripheral analgesic properties, which might be due to the presence of phenolics and betanin content. In future experiments, studies with purified fractions of the fruit would be conducted carried out to derive the mechanism involved in its analgesic action.

Anti-inflammatory drugs suppress the inflammatory response by inhibiting infiltration and activation of inflammatory cells as well as their synthesis, or release of mediators and the effects of inflammatory mediators. Carrageenan rat paw edema is a suitable test for evaluating anti-inflammatory drugs and has been frequently used to assess the anti-edematous effect of natural products.[23] Carrageenan-induced inflammation is useful in detecting orally active anti-inflammatory agents. Edema formation due to carrageenan in the rat paw is a biphasic event. The initial phase is attributed to the release of histamine and serotonin. The edema produced at the peak (3 h) is thought to be due to the release of kinin-like substances, especially bradykinin. The second phase is sensitive to most clinically effective anti-inflammatory drugs.[24-27] It is a well-established fact that NSAIDs exert their anti-inflammatory activity by the inhibition of prostaglandin biosynthesis. The anti-edematogenic mechanism of the action of *O. elatior* Mill. fruit may also be related to prostaglandin synthesis inhibition. Inflammation pain results from the release of hyperalgesic mediators - prostaglandins and catecholamines - which are supposed to act by regulating the sensitivity of pain receptors.[28,29]

Neutrophils are present in much larger numbers than any other inflammatory cell in the circulation and in tissue stores, particularly the lung. Neutrophils are one of the first inflammatory cells to be recruited into the airways after either allergen exposure or injury.[30] In acute inflammation, activated neutrophils are the major effector cells of this inflammatory response, releasing interleukins, tumor necrosis factor α, leukotriene B_4, platelet activating factor (PAF), proteases, and products of the respiratory burst reaction.[31,32] A number of cellular adhesion molecules are involved in the adhesion of neutrophils to the site of tissue inflammation. Neutrophils must adhere to the endothelium and subsequently migrate through the vessels before entering the tissue. Neutrophil rolling and arrest on the endothelium is mediated through successive interactions of selectins and β_2-integrins.[30] Neutrophil adhesion to endothelium is enhanced by the activation of adenosine A_1 receptors. Binding of neutrophils to the adenosine A_2 receptor results in the inhibition of the respiratory burst reaction and decreased binding to fibrinogen.[33-35] In the present study, fruit juice of *O. elatior* Mill. significantly reduced the percentage of neutrophil adhesion. This may help in decreasing the release of various cytokines and might be able to bind to A_1 and/or A_2 receptor on the endothelium and trigger anti-inflammatory action.

CONCLUSION

The data suggests that fruits of *O. elatior* Mill. has potential analgesic and anti-inflammatory properties. The fruit juice was reddish purple due to the presence of betanin in high concentration. Therefore, betanin might be responsible for this action due to its anti-oxidant and/or other properties.

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How to cite this article: Chauhan SP, Sheth NR, Suhagia BN. Analgesic and Anti-inflammatory action of *Opuntia elatior* Mill fruits. J Ayurveda Integr Med 2015;6:75-81.

Source of Support: Nil, **Conflict of Interest:** None declared.

Tribute to Professor Pratip Kumar Debnath

Professor Pratip Kumar Debnath, a senior scholar of Bengal School of Ayurveda passed away on 25th April 2015. Born in a family of Vaidyas, Dr. Debnath taught Kaychikitsa and contributed to clinical research of Ayurveda. He was associated with several academic and research institutes. J-AIM pays homage to Prof. Debnath.