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Original Research Article

Antinociceptive and Anti-inflammatory Activities of *Jatropha tanjorensis* Leaf Extract in Mice

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ABSTRACT

Traditional medicine has employed *Jatropha tanjorensis* to treat various diseases, especially those accompanied by pain, inflammation, and oxidative stress. This study investigated the antinociceptive and anti-inflammatory effects of *Jatropha tanjorensis* ethanol leaf extract on rodent models. Phytochemical and acute toxicity studies were determined by standard methods. Acetic acid-induced writhing and formalin-induced paw licking models were used to determine the antinociceptive efficacy, whereas formalin-induced hind paw oedema was employed for the anti-inflammatory study. In each of the assays, groups 2, 3, 4, and 5 received 100, 300 and 600 mg/kg of *J. tanjorensis* extract and aspirin (150 mg/kg) or Indomethacin (10 mg/kg) correspondingly while group 1 was administered 10 ml/kg physiological saline. *J. tanjorensis* extract, physiological saline, aspirin (150 mg/kg) or Indomethacin (10 mg/kg) were administered orally 1 hour before the induction of pain or inflammation. The most notable ($P < 0.05$) reduction of inflammatory response was shown by *Jatropha tanjorensis* leaf extract at 100 mg/kg with 80% inhibition of oedema. In addition, in comparison with the control group, the extract showed a significant ($P < 0.05$) decrease in paw licking and writhing in the mice. Flavonoids, steroids, terpenoids, tannins, and phenols were detected in the extract. The extract administered at a maximum dose of 2000 mg/kg did not cause any observable toxic effect. *J. tanjoreensis* leaves have potent antinociceptive and anti-inflammatory potentials. This validates its traditional usage in pain and inflammation.

Keywords: *Jatropha tanjorensis*, Nociception, Antinociceptive, Inflammation, Anti-inflammatory, Analgesic.

Introduction

Inflammation involves a wide range of physiological responses to viruses, dust particles, human pathogens, irritants and damaged cells.[1,2] Acute and chronic inflammation are the two main classifications for inflammations based on various inflammatory processes and cellular mechanisms.[2] Pain is described as an uncomfortable sensory and emotional experience related to actual or potential tissue damage.[1] Many illnesses, including cancer, autoimmune disorders, cardiovascular disease, arthritis, diabetes, eye disorder and neurological illnesses are all associated with inflammation.[1,2] Vasodilation (redness, heat, and swelling), inflammation, and pain are the primary indicators of inflammation. All of these signs are triggered by the production and physiological activity of prostaglandins which are produced when tissue is damaged.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, aspirin, ibuprofen, and naproxen, along with opioids and steroids, are commonly employed to manage inflammatory conditions. However, their clinical use is restricted due to possible side effects, including bleeding, peptic ulcers, mental dependence, tolerance, and addiction.[4]

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Researchers from all across the world are currently interested in developing novel plant-based medications with few side effects since plants are seen as creative reservoirs.[4] *Jatropha tanjorensis* is a member of the Euphorbiaceae family, widely known as "hospital too far," and is mostly used for fencing in Nigeria. It is also eaten as a vegetable and used as a herbal remedy.[5,6] Due to its presumed health benefits, accessibility, and cost, *J. tanjorensis* is given a lot of attention, and those who take it are believed to hardly ever become sick.[7] Different parts of *J. tanjorensis* have been traditionally utilized in rural areas of Nigeria to manage various health conditions, such as anaemia, malaria, hypertension, cardiovascular disorders, diabetes, urinary tract infections, and sexually transmitted diseases.[7,8] Previous studies have demonstrated that *J. tanjorensis* extracts have antibacterial, antiobesity, cardioprotective, hepatoprotective, antimalarial, and anti-anemic activities.[9-14] *J. tanjorensis* is also thought to be an important analgesic for the management of pain associated with various illnesses, such as cerebral malaria, arthritis, headaches, and rheumatism.[7] Given the surge in inflammation and pain caused by a range of ailments, a thorough scientific investigation is necessary to establish the plant's anti-inflammatory and analgesic potentials.

Therefore, the purpose of the study was to assess, using a mouse model, the antinociceptive and anti-inflammatory potentials of ethanol leaf extract of *Jatropha tanjorensis*.

Materials and Methods

Plant Collection and Identification

Jatropha tanjorensis leaves that were in good condition and fresh were collected in March, 2021 in the Azhata neighbourhood of Abuja. The plant was identified by Chijioke John Onyeukwu, Chief herbarium curator, at the Department of Plant Science and Biotechnology (formerly Botany), University of Nigeria, Nsukka, assigned the

herbarium number UNH no. 118, and deposited in the department's herbarium.

Animals
The Swiss mice employed in this investigation were male and female. The mice were purchased from Kaduna. For two weeks, they were acclimated in the Department of Biochemistry's animal house at Veritas University, Abuja. The experiment was conducted in conformity with the internationally recognized standards for the care and use of laboratory animals, in line with the Canadian Council on Animal Care (CCAC) guidelines for animal use protocol evaluation (1997) and the ethical codes of Veritas University governing laboratory animal use.

Extraction process
After the leaves were cleaned of contaminants under running water, they were left to air dry at room temperature in an open laboratory. The leaves were pulverised using an electric blender. The plant extraction was carried out using a cold maceration protocol, as described by Yusuf *et al*.[15] The leaves (300 g) were extracted by macerating in 1500 ml 100% ethanol for 72 hours. This was followed by filtering using Whatman filter paper and muslin cloth. A rotary evaporator was utilized to concentrate the filtrate at an optimum temperature of 60 ºC and 120 revolutions per minute. Following completion of the procedure, the concentrate was placed in a clean sample bottle and stored at 4 ºC until needed.

Antinociceptive effect of the extract: Acetic acid-induced writhing
This study employed the procedure outlined by Soyocak *et al*.[1] A total of 25 mice were randomly divided into five groups, with five mice per group. One hour before the injection of 0.7% acetic acid (10 ml/kg, i.p.), Groups 5 and 1 received aspirin (150 mg/kg, p.o.) and vehicle (0.9% normal saline, p.o.) respectively. Groups 2 to 4 were administered the extract orally at dosages of 100, 300, and 600 mg/kg, respectively. The mice were put in separate observation cages, and each mouse's frequency of abdominal writhings - abdominal muscle contractions accompanied by hindlimb stretching - was tallied over ten minutes. The count of writhes was recorded five minutes post-acetic acid administration. Five minutes post-acetic acid injection, the frequency of writhes was tallied. A decrease in writhes compared to the control group of mice was observed as evidence of antinociception, quantified as a percentage inhibition of writhes using the following formula:

$$\%\ Inhibition = \frac{\textbf{Average paw inflammation of control} - \textbf{Average paw inflammation of test}}{\text{Average paw inflammation of control}} \times 100$$

Anti-inflammatory efficacy of the extract: formalin-induced paw licking and paw edema in mice
The extract's anti-inflammatory properties were evaluated utilizing the formalin-induced paw edema techniques that have been previously described.[1,16,17,18] Twenty-five mice were randomly assigned to five groups, with five mice in each group. The extract was given orally to Groups 2, 3, and 4 at doses of 100 mg/kg, 300 mg/kg, and 600 mg/kg, respectively. Groups 1 and 5 received Indomethacin (10 mg/kg, orally) and 0.9% normal saline (10 ml/kg, orally), respectively. An injection of 0.02 ml of 2.5% formalin was given to each mouse's right hind paw's sub-plantar tissues one hour after therapy was given to cause acute inflammation. After the formalin injection, each animal was kept in a clear cage for five minutes, and the duration (in seconds) that the animal spent biting and licking its injected hind paw was noted as a sign of nociceptive behaviour. The neurogenic pain response is represented by the nociceptive scores, which typically peak 0–5 minutes after formalin injection. Using a Vernier calliper, the mice's paw volume was measured, and the mice were monitored before and after the injection of formalin for 30, 60, 120, and 180 minutes.
The following formula was used to calculate the percentage inhibition of edema:

$$\%\ Inhibition = \frac{\textbf{Average paw inflammation of control} - \textbf{Average paw inflammation of test}}{\text{Average paw inflammation of control}} \times 100$$

Acute toxicity study
Following the OECD 425 guideline, an acute toxicity test was performed using a limit dose of 2000 mg/kg.[19] A total of five female mice were fasted for 24 hours, although they were allowed free access to water during this period. The animals were administered the extract at a dose of 2000 mg/kg, dissolved in 10 ml of physiological saline, and observed individually for various behavioural characteristics, including alertness, restlessness, irritability, and fearfulness. Neurological assessments included spontaneous activity, reactivity, touch response, pain response, and gait. Autonomic functions such as defecation and urination were also monitored. Physical conditions like lacrimation, loss of appetite, tremors, hair erection, salivation, and diarrhoea were recorded. The animals were monitored for morbidity or mortality for 14 days, with observations made continuously for the first two hours post-dosing, periodically during the first 24 hours (with special attention during the initial 4 hours), and daily thereafter.

Phytochemical screening
Using standard protocols, *J. tanjorensis* extract was subjected to phytochemical screening for alkaloids, tannins, saponins, flavonoids, terpenoids, glycosides, and steroids.[20,21]

Statistical analysis
The data were analyzed using SPSS version 23, employing a one-way analysis of variance (ANOVA) followed by a Duncan post-hoc test to assess the significance of variations in the mean values of the measured parameters between the control groups. A P-value of less than 0.05 was considered statistically significant.

Results and Discussion

As an alternative to conventional treatment, herbal therapies have drawn more attention, and there is currently a rise in the demand for them. The *Jatropha tanjorensis* ethanol leaf extract was evaluated for its antinociceptive and anti-inflammatory activity in a rodent model using assays that cause writhing in response to acetic acid, paw licking, and hind paw edema in response to formalin. The experimental screening method is important for determining the safety and efficacy of traditional and herbal products as well as for establishing the active components of the herbal products.
An established model for examining the peripheral analgesic efficacy of test compounds in mice is acetic acid-induced writhing.[21] By releasing endogenous chemicals such as serotonin, histamine, prostaglandins, bradykinins, substance P31, and activating non-selective cation channels, acetic acid causes pain.[23,23] Through the activation of spinal cord microglia and mitogen-activated protein (MAP) kinases, acetic acid elicits central pain. Additionally, it regulates central pain via a variety of intricate mechanisms, such as the serotonergic, opiate, dopaminergic, and descending noradrenergic systems.[24] Consequently, despite the variety of processes involved, this model of inflammatory pain is well controlled by agents that suppress prostaglandin formation. When compared to control group 1, *Jatropha tanjorensis* extract resulted in a statistically significant ($P < 0.05$) decrease in the average number of writhes elicited by acetic acid in the acetic acid-induced writhing test (Table 1). Groups 2, 3, and 4 caused writhing inhibition of 48.31%, 42.69%, and 49.44%, respectively, which was similar to that of aspirin at 53.36% (Table 1). Therefore, the findings showed that *Jatropha tanjorensis* exhibited a considerable antinociceptive effect in acetic acid-induced abdominal writhing at all tested dosages.
Mice that are given formalin develop paw edema and licking that closely mimics human arthritis. Consequently, it is among the most effective techniques for determining if potential drugs could treat chronic inflammation.[17]

Formalin initially triggers an acute inflammatory infiltration in the temporomandibular joint (TMJ) of mice, subsequently evolving into a chronic disease. It also leads to hyperplasia and persistent growth of the

synovial lining, which ultimately results in the development of villous regions.[17,25]

Formalin injection causes biphasic pain patterns: the first phase, known as the neurogenic phase, starts immediately after the formalin is administered and is characterized by the direct stimulation of peripheral nociceptors through the C fibres to the spinal cord's dorsal horn after substance P, a neurotransmitter, is secreted. The second phase, known as the prostaglandin-induced phase, starts 15 minutes after noxious stimulation and includes the release of serotonin, histamine, bradykinin, nitric oxide (NO), cytokines, and prostaglandins from tissue that has been damaged by the formalin.[23,24]

The effect of *J. tanjorensis* on inflammation was assessed in mice using models of formalin-induced hind paw oedema. At 100 mg/kg, *Jatropha tanjorensis* leaf extract was found to have an effect on paw licking induced by formalin. In comparison with the control, the extract reduced the time spent in paw licking and inhibited pain by 24.78% at 100 mg/kg dose level, although at a lesser rate than indomethacin (49.13%) (Table 2). The plant extract also demonstrated a significant ($P < 0.05$) anti-oedematogenic effect in the late phase as compared to the control on formalin-induced oedema of the hind paw in mice. This is an indication of anti-inflammatory action. When compared to the group treated with indomethacin (30%; 180mins), the group treated with the lowest dose (extract; 100 mg/kg) had the highest antioedematogenic action, with 80% suppression of oedema at 180mins (Table 3). Studies have shown that the formalin-induced inflammation model is an effective way to predict anti-inflammatory efficacy.[11,12,13] These findings suggest that *Jatropha tanjorensis* is effective for the treatment of acute inflammatory conditions *in vivo*. The anti-inflammatory properties of *Jatropha tanjorensis* leaves have been demonstrated in an earlier in vitro investigation.[25]

Preliminary phytochemical screening of *Jatropha tanjorensis* revealed the presence of steroids, flavonoids, terpenoids, tannins, alkaloids, and phenols, while saponins were absent. Previous research on the phytochemical composition of *J. tanjorensis* has identified flavonoids, terpenoids, alkaloids, tannins, saponins, and anthraquinones.[8,11,12] There is increasing evidence that flavonoids, phenols, tannins, and terpenoids have antinociceptive and anti-edema properties.[1,4,16,17] These bioactive ingredients may be the source of the plant's apparent medicinal effect. Through inhibition of prostaglandins-producing enzyme activity, *J. tanjorensis* extract may elicit an anti-inflammatory response.[3,17,26]

Flavonoids have been demonstrated to inhibit the activity of three key enzymes involved in the synthesis of various inflammatory mediators: lipoxygenase, cyclooxygenase, and inducible nitric oxide synthase isomers.[17,27] Additionally, flavonoids can competitively bind to the catalytic site of ATP, thereby inhibiting the activity of the regulatory enzyme protein kinase, which helps reduce the inflammatory response.[17]

Similarly, terpenoids may prevent inflammation by blocking the action of cytokines (IL-2, IL-4, and IL-6) and inducible nitric oxide synthase enzymes, prostaglandin synthesis, cyclooxygenase enzymes, and tumor necrosis factor (TNF-).[17,25] Additionally, tannins' anti-inflammatory effect is linked to their ability to inhibit inflammatory mediators such as the COX-2 enzyme, histamine and prostaglandins.[17,28] *Jatropha tanjorensis* leaf extract may therefore, have antinociceptive and anti-inflammatory properties due to the presence of flavonoids, phenols, terpenoids, and tannins.

The administration of *J. tanjorensis* extract did not cause any observable toxic effect at a maximum dose of 2000 mg/kg body weight administered. Thus, *Jatropha tanjorensis* leaf extract is relatively safe. This is similar to the previous work which revealed that *Jatropha tanjorensis* is not toxic to health as no mortality was recorded after 48 hours of administration at a maximum dose of 2000 mg/kg body weight.[9]

Furthermore, additional comprehensive molecular study is required to validate the mode of antinociceptive and anti-inflammatory effects.

Table 1: Percentage inhibition of *Jatropha tanjorensis ethanol leaf extracts* on acetic acid induced mouse writhing

Dose	Mean writhing	% Inhibition
Control (Normal saline)	59.33±8.65	-
100 mg/kg JT	30.67±7.42*	48.31
300 mg/kg JT	34.00±6.11	42.69
600 mg/kg JT	30.00±4.04*	49.44
ASA 150 mg/kg	27.67±4.37*	53.36

Values are shown as mean ± SEM (n = 5). JT, *Jatropha tanjorensis*; ASA, Aspirin. $P < 0.05$ was accepted as significant when compared to the Control group.

Table 2: Activity of *J. tanjorensis* ethanol leaf extract on formalin induced paw licking

Dose	Mean Paw Licking	% Inhibition of Paw Licking
Control (10 ml saline)	76.67±4.48	-
100 mg/kg JT	57.67±1.45	24.78
300 mg/kg JT	109.00±14.29	-42.17
600 mg/kg JT	124.33±10.49	-47.66
Indo 150 mg/kg	39.00±4.16*	49.13

Values are represented in mean ± SEM (n=5). JT, *Jatropha tanjorensis*; Indo, indomethacin. $P < 0.05$ was accepted as significant when compared to the Control group.

Table 3: Anti-inflammatory Activity of *J. tanjorensis* Ethanol Leaf Extract on Formalin-induced Hind Paw Oedema

	Mean paw volume (ml)

Time/Dose	Control (saline)	100 mg/kg JT	300 mg/kg JT	600 mg/kg JT	Indomethacin 10 mg/kg
0 minutes	0.30±0.03	0.29±0.00	0.26±0.00	0.27±0.02	0.26±0.01
30 minutes	0.37±0.02	0.31±0.00	0.35±0.03	0.32±0.00	0.32±0.00
60 minutes	0.37±0.01	0.31±0.01	0.31±0.01	0.29±0.00	0.31±0.01
120 minutes	0.37±0.03	0.36±0.02	0.32±0.01	0.35±0.04	0.32±0.01
180 minutes	0.4±0.00	0.31±0.01*	0.33±0.02	0.32±0.01*	0.33±0.01
Mean increase in paw volume (ml)					
0 minutes	0.30±0.03	0.29±0.00	0.26±0.00	0.27±0.02	0.26±0.01
30 minutes	0.07±0.02	0.02±0.01	0.09±0.01	0.05±0.01	0.06±0.01
60 minutes	0.07±0.02	0.02±0.00	0.05±0.00	0.02±0.01	0.05±0.01
120 minutes	0.07±0.06	0.07±0.03	0.06±0.02	0.08±0.03	0.06±0.01
180 minutes	0.1±0.01	0.02±0.04*	0.07±0.01	0.05±0.02*	0.07±0.01
% inhibition in edema (%)					
0 minutes	-	-	-	-	-
30 minutes	-	71.43	-28.57	28.57	14.28
60 minutes	-	71.43	28.57	71.43	28.57
120 minutes	-	-	14.29	-14.29	14.28
180 minutes	-	80.00	30.00	50.00	30.00

Values are represented in mean ± SEM (n=5). JT, *Jatropha tanjorensis*; Indo, indomethacin. P < 0.05 was considered significant relative to control.

Conclusion

The research findings established that *Jatropha tanjorensis* extract is reasonably safe at a maximal dosage of 2000 mg/kg and showed antinociceptive and anti-inflammatory potentials. The findings support traditional medicine's usage of *J. tanjorensis* for pain relief and anti-inflammatory effects.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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