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Ethanollic Root Extract of *Jatropha curcas* L. relieves Hyperalgesia in Arthritis Model in Rats

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Abstract

This work evaluated the analgesic property of ethanolic extract of *Jatropha curcas* in arthritic/skeletal pain models. Acute skeletal hyperalgesia was induced in knee joints of rats with 3% carrageenan-kaolin mixture. Twelve hours later, the rats were grouped and treated orally with 30, 100 and 300 mg/kg *Jatropha curcas* or morphine (1, 3 and 10 mg/kg). Pain thresholds were measured by knee compression in the ipsilateral limb. In a separate experiment to determine the effect of ethanolic root extract of *Jatropha curcas* (30-300 mg/kg, *p.o.*) and morphine (1-3 mg/kg, *p.o.*) on chronic skeletal hyperalgesia, the extracts and morphine treatments were administered 2 weeks after the induction of the pain with 3% carrageenan-kaolin mixture. The effects of *Jatropha curcas* on chronic skeletal hyperalgesia in both the ipsilateral and contralateral paws was assessed in the Randall-Selitto test.

Jatropha curcas ($P < 0.05$) and morphine ($P < 0.05$) significantly reduced acute knee hyperalgesia in the ipsilateral limb. Chronic skeletal hyperalgesia was dose-dependently inhibited by the extract of *J. curcas* and the standard drug morphine in the ipsilateral and contralateral paws. Ethanolic root extract of *Jatropha curcas* relieves skeletal pain in rats.

Keywords: Hyperalgesia, *Jatropha curcas*, kaolin, carrageenan

1. Introduction

Jatropha curcas (Euphorbiaceae) is a multipurpose species with many attributes and considerable potential. The genus name, *Jatropha* derived from the Greek word *jatro*'s (doctor) and *trophe*' (food), which connotes its medicinal uses. *J. curcas* exhibits articulated growth, with a morphological discontinuity at each increment. Normally, five roots are formed from seedlings, one central and four peripheral. A tap root is not usually formed by vegetatively propagated plants.

The plant enjoys some agricultural usefulness such the prevention of soil erosion and shifting of sand dunes. The various parts of *J. curcas* are used medicinally for human and veterinary purposes. The seed oil can be applied to treat eczema and skin diseases as well as to soothe rheumatic pain. Ethanolic root extract has demonstrated analgesic properties in paclitaxel-induced neuropathic pain in rats⁴. Despite the plants usefulness as food and medicine, it is not without toxic effects. The toxicity of the plant has been associated with the presence of the toxalbumine, curcine, a cyanic acid related to ricinacid, and phorbol esters. In this respect, the molluscicidal, insecticidal and fungicidal properties of the esters have been demonstrated. The agricultural importance of the toxic nature of the plant is its application to reclaim land and grown as a live fence to exclude farm animals.

Traditionally, topical application of root powder of *J. curcas* in the form of a paste is used to treat inflammatory diseases such as gout. In light of the above, ethanolic root extract of *J. curcas* was investigated on arthritis pain in rats.

2. Materials and Methods

2.1 Collection and preparation of ethanolic extract of roots of *Jatropha curcas*: Roots of *Jatropha curcas* were harvested from Kete-Krachi in the Volta region of Ghana. The plant was identified by a botanist in the School of Biological Sciences, University of Cape Coast and a specimen kept in the herbarium of the School of Biological Sciences. The roots were air dried under a shade for fourteen days and pulverised into fine powder. A quantity of 0.2 kg of the

powdered material was macerated with 70 % (v/v) ethanol for five days in cylindrical jars. The filtrate was concentrated with a rotary evaporator at a temperature of 50 °C. The concentrate was dried over hot water bath to yield a solid mass of ethanol extract of roots of *Jatropha curcas* [percentage yield of 39.5 % (w/w)]⁴.

2.2 Drugs and chemicals: Carrageenan sulphate and kaolin were obtained from Sigma-Aldrich Inc., St. Louis, MO, USA, morphine hydrochloride was obtained from Phyto-Riker, Accra, Ghana.

2.3 Animals and Husbandry: Sprague-Dawley rats (200–250 g) of both sexes were obtained from the animal house of Biological sciences and kept in stainless steel cages. The animals were fed with normal commercial pellet diet (AGRICARE, Kumasi) and allowed free access to water. The animals were maintained under optimum laboratory conditions. All procedures and techniques used in the studies were in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals⁵. All protocols used were approved by the Departmental Ethics Committee.

2.4 Effect of *Jatropha curcas* on acute skeletal pain: The analgesic effect of JAT was evaluated in acute skeletal pain models as described elsewhere⁶ with slight modification. Baseline knee compression thresholds of the ipsilateral knees were measured with an analgesimeter (IITC Life Science Inc. Model 2888, Woodland Hills, CA, USA). The maximum compression force applied at withdrawal of the limb or vocalisation twelve hours after injection of 100 µl of a mixture of 3% kaolin-carrageenan intra-articularly into the left knee joint was recorded as the compression threshold for the knee joint of the corresponding limb. The animals were then treated with JAT (30- 300 mg kg⁻¹ p.o.), morphine (1-10 mg kg⁻¹ i.p.) or vehicle and knee compression thresholds were taken again hourly for 3 hours.

2.5 Effect of *Jatropha curcas* on chronic skeletal pain: Analgesic effect of JAT on chronic skeletal pain was evaluated with the paw compression analgesimeter. The rats were treated with JAT (30-300 mg kg⁻¹ p.o.), morphine (1-10 mg kg⁻¹ i.p.) or vehicle fourteen days after intra-articular induction of knee inflammation with 100 µl of a mixture containing 3% kaolin-carrageenan⁷. Chronic skeletal pain was measured from both paws of the rats hourly for three hours.

2.6 Statistical analysis: All data are presented as mean ± S.E.M (n=5). The time-course curves were subjected to two-way (treatment × time) repeated measures analysis of variance (ANOVA) with Bonferroni's *post hoc* test. $P < 0.05$ was considered statistically significant.

3. Results

3.1 Effect of JAT on acute skeletal hyperalgesia: Acute skeletal hyperalgesia was present in all the rats administered with 3% kaolin-carrageenan. The hyperalgesia was inhibited by the three doses of JAT (30-300 mg kg⁻¹) ($P < 0.0001$; Fig. 1a). A reverse dose-dependent analgesic effect was observed (Fig. 1b) for JAT treatments. Morphine (1-10 mg kg⁻¹) used as control significantly ($P < 0.0001$; Fig. 1c) (Fig. 1d) reduced acute knee hyperalgesia.

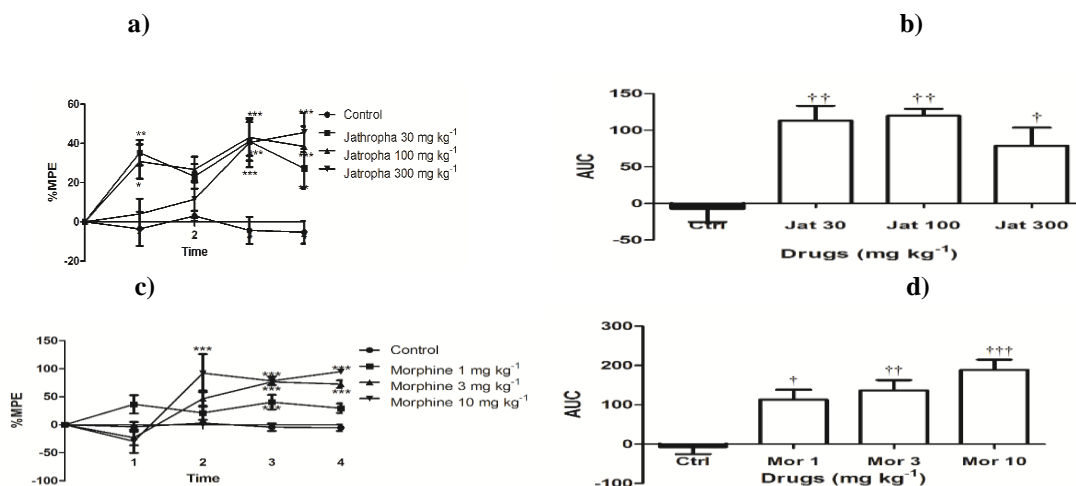


Figure 1 Effect of (a) JAT (30-300 mg kg⁻¹) and (b) morphine (1-10 mg kg⁻¹) on the time course curve of paw withdrawal latency in acute knee hyperalgesia and their respective area under the curves (AUC) (b and d). Data is presented as mean ± S.E.M.; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$ compared to vehicle-treated group (Ctrl) (Two-way ANOVA followed by Bonferroni's *post hoc* test). ††† $P < 0.001$, †† $P < 0.01$, † $P < 0.05$, compared to vehicle-treated group (One-way ANOVA followed by Tukey's *post hoc* test).

3.2 Effect of JAT on chronic skeletal hyperalgesia: Treatment of induced chronic skeletal hyperalgesia in the rats with JAT produced significant analgesic effects in both the ipsilateral (ipsi) and contralateral (contra) limbs (ipsi: $P < 0.0001$; Fig. 2a and contra: $P < 0.0001$; Fig. 2c). The extract produced step-wise analgesic effects in both the ipsilateral (Fig. 2b) and contralateral (Fig. 2d) limbs.

Similarly, Morphine (1-10 mg kg⁻¹) significantly (Fig. 3b and d) increased the latency to ipsilateral and contralateral paw withdrawal.

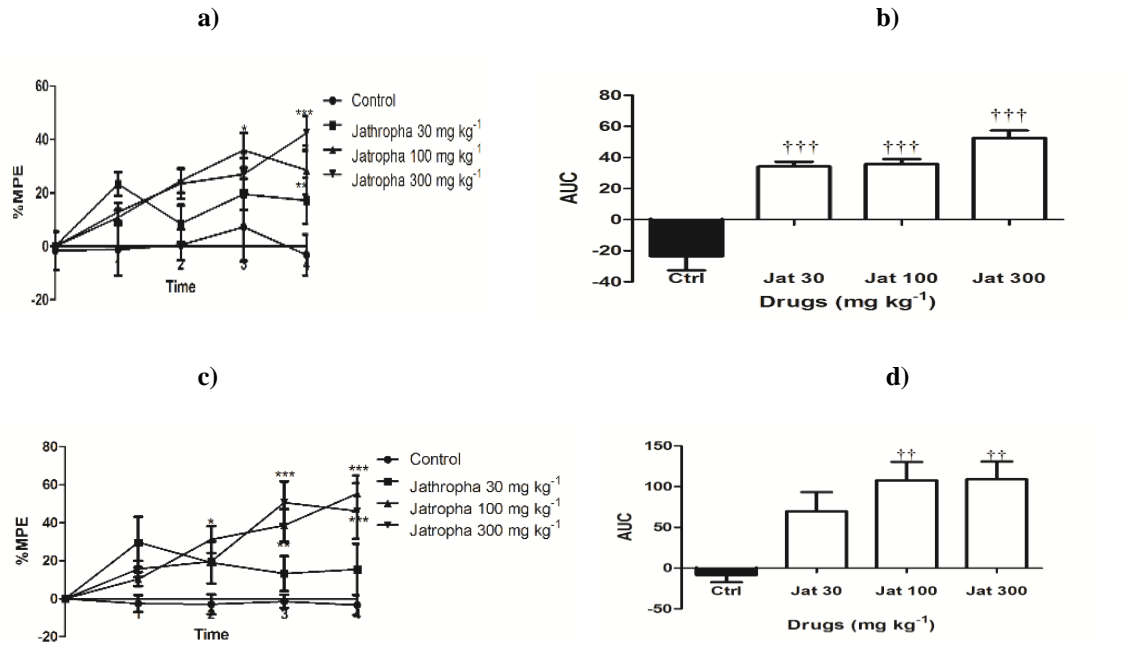
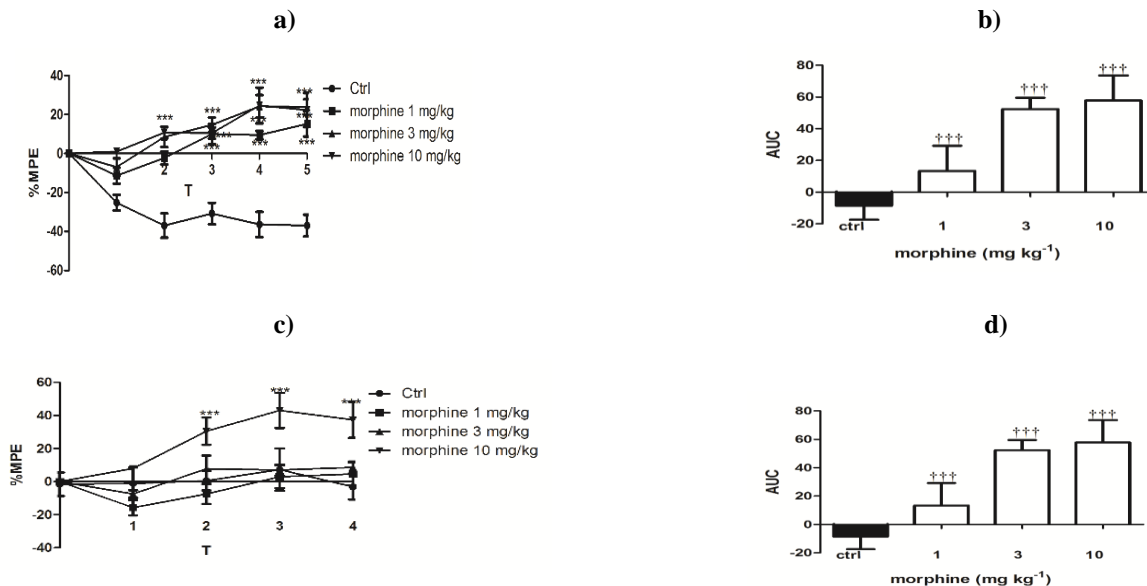


Figure 2 Effect of JAT (30-300 mg kg⁻¹ p.o.) on the time course curve of ipsilateral (a) and contralateral (c) paw withdrawal latency and the AUC (b and d respectively) in chronic knee hyperalgesia. Data is presented as mean ± S.E.M.; ****P* < 0.001; ** *P* < 0.01; **P* < 0.05 compared to vehicle-treated group (Two-way ANOVA followed by Bonferroni's *post hoc* test). †††*P* < 0.001 ††*P* < 0.05 compared to vehicle-treated group (One-way ANOVA followed by Tukey's *post hoc* test).



4. Discussion

Ethanollic root extract of *Jatropha curcas* exhibited anti-nociceptive properties in acute and chronic skeletal pain models in rats. The skeletal pain model in rats investigated arthritic types of pain experienced in man⁸. Ethanollic root extract of *Jatropha curcas* may therefore be used to manage such types of painful conditions. Morphine, the standard drug produced similar effects.

Carrageenan, an inflammatory agent, when injected into the rat knee causes plasma extravasation and oedema due to the release of neuropeptides and other inflammatory pain mediators into the joint cavity. The elicited injury leads to both

peripheral and central sensitization⁹⁻¹⁰. The acute skeletal hyperalgesia induced in the knee joint therefore resulted from neuronal activation of glutamate, substance P, nitric oxide and its metabolites. One notable mediator well studied in this model is prostaglandin E₂. Spinal PGE₂ basal levels are reported to be increased as early as 5 h after induction of knee joint inflammation with carrageenan-kaolin mixtures and this elevation persists for about 72 h after the injury¹⁰. Increased expression of Transient Receptor Potential Vanilloid-1 (TRPV1), Nav1.8 sodium channels, and the transcription factor c-fos have also been reported in acute skeletal hyperalgesia¹¹⁻¹². JAT produced acute skeletal anti-hyperalgesic properties possibly by inhibiting the further production and release of these inflammatory mediators in the joints and spinal cord. Additionally, JAT may produce its analgesic effects directly on the receptors.

The secondary hyperalgesia was mediated by changes within the central nervous system from an increased afferent barrage from the site of injury. Receptors involved in the maintenance of central sensitization in this model of secondary hyperalgesia are GABA, NMDA, non-NMDA and neurokinin-1 receptors¹³. Additionally, supraspinal activation of descending facilitatory pain pathway contributes to the chronic hyperalgesia¹⁴. This may suggest a central anti-hyperalgesic mechanism of JAT. Opioid agonists such as morphine relieve skeletal hyperalgesia by agonistic effect on opioid receptors located spinally and supraspinally in the rostral ventrolateral medulla and periaqueductal gray¹⁵.

5. Conclusion

Ethanollic root extract of *Jatropha curcas* relieves acute and chronic skeletal pain in rats.

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