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ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES OF ETHANOLIC EXTRACT OF THE STEM BARK OF *KIGELIA AFRICANA* IN WISTAR ALBINO MICE AND RATS

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ABSTRACT

Kigelia africana (Lam) Benth has various ethno-medicinal uses in different parts of Africa. In the present study, defatted ethanolic extract of the stem bark of *Kigelia africana* was evaluated for analgesic effects in rats using an analgesy-meter and in mice using the tail immersion and acetic acid-induced writhing tests. The anti-inflammatory property of the extract was assessed in rats using the carrageenan-induced paw edema model. Graded doses (25, 50 and 100 mg/kg) of *Kigelia africana* extract were administered intra-peritoneally 30 minutes prior to the induction of mechanical, thermal or chemically-induced pain in the rats and mice. *Kigelia africana* exhibited a dose-related and significant anti-nociceptive effect against acetic acid induced abdominal constrictions in mice. At a dose of 50 mg/kg the percentage of pain inhibition was 49.20% ($p<0.01$) while at 100 mg/kg, there was a 71.12% inhibition ($p<0.01$). The results of the tail immersion test in mice and from the analgesy- meter test in rats, also demonstrated that *Kigelia africana* exhibited significant analgesic properties. In addition, the extract produced significant anti-inflammatory effect in the rats. These results confirm and justify the traditional use of *Kigelia africana* stem bark for its analgesic and anti-inflammatory properties. They also suggest that the analgesic activity of the extract is mediated via inhibition of central and peripheral mechanisms. Inhibition of carrageenan-induced inflammation by the extract may be mediated in part by a non-selective cyclooxygenase inhibitory mechanism.

Keywords*:* *Kigelia africana*, Analgesic, Anti-inflammatory, Rats, Mice, Carrageenan.

INTRODUCTION

Traditional herbal remedies have a long and popular usage in treatment of pain related ailments (Adzu and Abdul, 2007). The drugs which are currently used in the management of pain and inflammatory conditions include the opioids and the non-steroidal anti-inflammatory drugs (NSAIDs) (Yaksh and Wallace, 2011). These groups of drugs have serious adverse effects. While the opioids and opiate-like drugs have addictive tendencies, and cause varying degrees of side effects ranging from sedation, constipation and urinary retention, to severe respiratory depression; use of the NSAIDs result in gastrointestinal bleeding, ulceration, increase in the incidence of edema, hypertension and cardiovascular thrombotic events (Furst *et al.,* 2009). The search for newer, less toxic, analgesic drugs is therefore necessary. NSAIDs are used very commonly by the populace for various reasons and are obtained as non-prescription medications. Given the widespread use and abuse of these drugs and the adverse effects

that attend their use, there is need to continue to screen plants for newer analgesics and to conduct scientific evaluations to substantiate their efficacy and safety (WHO, 2000).

Plants represent a large reservoir of novel compounds that can be developed for use as analgesics, being the source of important drugs such as Aspirin and Morphine among others (Elisabetsky *et al*., 1995). *Kigelia africana* (Lam) belongs to the family Bignoniaceae. The plant is commonly known in English as sausage tree, and in indigenous Nigerian languages as 'Pandoro' or 'Iyan' (Yoruba), 'Hantsar giiwa' (Hausa), 'Alamborogoda', 'uturubien'(Igbo), (Nigerian Natural Medicine Development Agency, NNMDA, 2006). It is known in Swahili as 'Mbungati', and in Afrikaan as 'Worsboom' (Grace and Davis, 2002). The plant is widely distributed throughout the African tropics. It is also currently found in China, South East Asia, Australia, Hawaii, South and Central America (Grace and Davis, 2002).

The Ethno-medicinal properties of this plant have been extensively reviewed (Olatunji and Atolani, 2009). *Kigelia africana* is traditionally used in African folk medicine for the treatment of various clinical conditions which include: malaria, dysentery, constipation, cough and kidney disorders. The fruit and oil ointment from the plant are used in the treatment of rheumatism, malignant tumors such as breast cancer (Odugbemi et al., 2008; NNMDA, 2006). The bark and fruits of the plant is used in Central Africa for the treatment of constipation, haemorrhoids, rheumatism and infections of the genito-urinary tract. The powdered fruit is sprinkled on wound and sores as topical dressings for their antibacterial and antifungal properties (Watt and Breyer-Brandwijk, 1962; Pooley, 1993; Grace and Davis, 2002).

Analgesic and anti-inflammatory activities of orally administered ethanolic extracts of the stem bark of *Kigelia africana* in mice and guinea pigs have been reported (Owolabi and Omogbai, 2007). This study was conducted to evaluate the analgesic and anti-inflammatory activities and the acute toxicity of intraperitoneally administered ethanolic extract of the stem bark of *Kigelia Africana* with the aim of further elucidating the possible mechanisms of action, using different models of pain assessment.

MATERIALS AND METHODS

Collection and identification of plant material

Fresh stems of *Kigelia africana* plant were bought from Gegele Herbal Market in Ilorin, Kwara state, Nigeria. Taxonomic identification was done by Professor F.A. Oladele of the Department Plant Science, University of Ilorin. The stem bark of the plant was air dried at room temperature for 12 weeks before extraction.

Extraction of the plant material

Cold extraction of *Kigelia africana* stem bark was carried out by methods described by Sofowora (1982) and Harbone (1998). Five hundred (500) gramms of the powdered sample was extracted with 1litre of ethanol (BDH) for 72 hrs. The solution was filtered, concentrated and freeze-dried at Central Research Laboratory of Obafemi Awolowo University, Ile-Ife. The freeze-dried powdered extract was used for the acute toxicity test and the analgesic and anti-inflammatory assays.

Preparation of Drug solution and plant Extract

Tramadol hydrochloride (Grunentha, Germany); Diclofenac (Mepha, Switzerland); Celecoxib (Cynus Healthcare, India) and Meperidine (Pethidine hydrochloride) (M & H, India) used for the experiment were obtained from the Pharmacy Department of the University of Ilorin Teaching Hospital Ilorin., Nigeria; while Carrageenan (Sigma, UK) and Acetic acid (BDH) were purchased from the respective companies. 50 mg/ml of Tramadol hydrochloride and Meperidine were diluted in 10 ml of de-ionized water to give a concentration of 5 mg/ml. and 10 mg/ml respectively. Six hundred (600) mg of the freeze- dried *Kigelia africana* extract was dissolved in 20 ml of de-ionized water and filtered, to give a final concentration of 30 mg/ml. Route of extract and drug administration was intraperitoneal.

Animals

Wistar albino rats of both sexes, weighing between 150-250g were obtained from the National Veterinary Research Institute Jos, Nigeria. The acute toxicity tests and experiments using the analgesy-meter were carried out at National Institute of Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria. Wistar albino rats weighing (150-250g) and Swiss mice (16-25g) that were subsequently used were procured from Obafemi Awolowoo University Central animal house, Ile-Ife and used for the other experiments. In all cases, the animals were acclimatized for one week at the animal houses and kept under standard environmental conditions with free access to feed and water *ad libitum* before they were used for the experiments.

Acute Toxicity tests in Rats

The method originally described by Lorke, (1983) and the Organization for Economic Cooperation and Development (OECD, 2000) was used for the acute toxicity test. Twelve female rats that were nulliparous and non-pregnant were randomly distributed into four groups of 3 rats each (n=3). Graded doses (300, 500, 1000 and 2000 mg/kg) of the ethanolic extract of *Kigelia africana* stem bark were administered intraperitoneally as a single dose to rats in each group of animals. The rats were closely monitored individually for 30 minutes following drug administration, then periodically during the first 24 h and subsequently, daily for 14 days for signs of acute toxicity. The signs that were examined included the following: changes in the skin and fur coat, eyes, mucus membranes, central nervous system and behavioral patterns. The LD_{50} of the plant extract was then estimated using the Organization for Economic Cooperation and Development (OECD) guideline, 2000.

Analgesic Activity

Pressure test using analgesy-meter

The method described by Randall and Selitto (1957) and modified by Kitchen (1984) was used for the evaluation of analgesic activity of the extract using analgesimeter. Thirty (30) albino rats of both sexes were randomly assigned into five groups of 6 animals each (n=6). Ten (10) ml/kg body weight of the vehicle (0.9% NaCl) in distilled water) was administered to the control group, while 25, 50, and 100 ml/kg body weight of *Kigelia africana* extract was administered to the 3 test groups respectively. Five (5) mg/kg of Tramadol HCl was administered to the reference (standard) drug group. Mechanical pain was induced on the tail of the rats by the use of analgesy-meter (model 7200, Ugo Basile, Italy) which exerted force at a constantly increasing rate. The rats were restrained while their tails were placed between the plinth and the plunger. The force was

continuously monitored by a pointer moving along a linear scale. Pain response was taken to be the point at which the rat struggles to set itself free or its tail slips off the plinth of the instrument. The weight causing pain before treatment (0) and then at 15, 30, 60, and 120 minutes after the extract and drug treatment to individual rat in all the groups was recorded. Percentage pain inhibition (increase in pain threshold) produced relative to the control group was calculated for each extract- or drug-treated group over the period of study using the formula:

$$\text{Pain inhibition (\%)} = \frac{Ft - Fo}{Fo} \times 100$$

Ft = Force at which the animal tries to free its tail after drug administration.
Fo = Force at which the animal tries to free its tail before drug administration.

Hot water tail immersion test

The method described by Janssen et al. (1963) and used by Olaleye et al. (2000) was used in this experiment. Thirty (30) mice were randomly assigned into six groups of five mice each (n=5). The mice in the groups were treated with 25, 50, and 100 mg/kg of *Kigelia africana* stem bark extract, Tramadol hydrochloride (5 mg/kg), Meperidine (10 mg/kg) or normal saline (10 ml/kg) respectively 30 minutes prior to commencement of the experiment. The lower 5 cm portion of the tail of each mouse in all the groups was immersed in a beaker of water maintained at 50 ^{0}C ± 1.0^0 C. The time taken for the mouse to (withdraw) flick its tail was recorded as the reaction time, with a cut-off time of immersion set at 10 sec. The percentage of pain inhibition was calculated as follows:

$$\text{Percentage Inhibition} = \frac{(\text{Test mean})_t - (\text{Control mean})_t}{(\text{Control mean})_t} \times 100$$

Where t = time

Acetic acid writhing response

This was based on the method described by Koster et al., (1959). Thirty (30) mice were randomly assigned into six groups of five mice each (n=5) and treated intraperitoneally with 25, 50, and 100 mg/kg of *Kigelia africana* extract. The reference group of mice was given Tramadol hydrochloride (5 mg/kg) or Meperidine (10 mg/kg while the control group was given normal saline (10 ml/kg), 30 minutes before the administration of 1.2% acetic acid. The number of abdominal constrictions and stretching (writhing) movements for each mouse in all the groups was counted for 10 minutes after the injection of acetic acid. The percentage pain inhibition was calculated as follows:

$$\text{\% inhibition} = \frac{(\text{Control mean})_t - (\text{Test mean})_t}{(\text{Control mean})_t} 100$$

Where t = time

Anti-Inflammatory Activity

Carrageenan-induced edema

Thirty (30) albino rats were randomly assigned to six treatment groups of five animals each (n=5). Edema was induced on the right hind paw of rats by a sub-plantar injection of 50µl of 1% Carrageenan solution (Winter et al 1962). The linear paw circumference was measured as described by Hess and Miloning (1972), Olajide et al., (2000) and Owoyele et al., (2005). The plant extract (25, 50, 100 mg/kg) or Diclofenac (2 mg/kg) or Celecoxib (100 mg/kg) was administered 30 minutes before the injection of 1% Carrageenan solution, while control rats received distilled water 5ml/kg intraperitoneally. The volume of the injected paw was measured before the administration of Carrageenan and at 3 hours after the induction of inflammation (Owoyele et al., 2005). Inflammation was expressed as an increase in paw volume due to Carrageenan injection and the percentage inhibition produced was calculated using the formula:

$$\text{Percentage inhibition} = \frac{(C_t - C_o)\ \text{control} - (C_t - C_o)\ \text{treated} \times 100}{(C_t - C_o)\ \text{control}}$$

Where

C_t = Paw circumference volume at time t

C_o =Paw circumference before sub-plantar injection of Carrageenan.

C_t - Co= Paw edema

Statistical analysis

The results were expressed as Mean ± Standard Error of Mean (SEM) and Percentages (%). Statistical analysis of the data was done using Student's t-test and one way analysis of variance (ANOVA), in Primer biostatistics software package. Values of $p<0.05$ were considered significant.

RESULTS

Acute toxicity test

The intraperitoneal median lethal dose (LD_{50}) of the extract in mice was estimated to be 3000mg/kg and is within safe limits.

Analgesic activity

The analgesic activity of the plant extract determined by analgesy-meter showed intraperitoneal injection of 25mg, and 100mg/kg of *Kigelia africana* extract 30 minutes before application of tail pressure on rats, produced significant increase in the threshold of pain by 277.6% ($p<0.001$) and 290.9% ($p<0.001$) respectively (Table I). Tramadol hydrochloride 5mg/kg also produced an increase in pain threshold of 349.7% ($p<0.001$) in this same time period. At 2h post –treatment, significant increase ($p<0.01$) in pain inhibition was produced by Tramadol hydrochloride 5mg/Kg and *Kigelia africana* 100mg/kg when compared with the control (Table I). The result of hot water tail immersion test (Pain latency) also showed that *Kigelia africana* extract increased the pain latency duration. The extract, at 50 mg/kg and 100mg/kg increased the percentage pain inhibition threshold by 46.15% and 71.67% respectively (Table II). There was significant difference ($p<0.05$) between the percentage increase in pain threshold produced by 100mg/kg *Kigelia africana* (137.70%) and 5 mg/kg Tramadol hydrochloride (315.38%). *Kigelia africana* exhibited a dose-related anti-nociceptive activity against acetic acid-induced abdominal constrictions in mice. At a dose of 50 mg/kg, the percentage inhibition was 49.20% ($p<0.01$); while 100 mg/kg of the extract produced 71.12% inhibition ($P<0.01$).

Table I: Effect of *Kigelia africana* on the response of rats to pressure from the analgesimeter.

Treatment	***Dose***	***Tail Response to Pressure and Percentage Pain Inhibition***			
		15 mins	**30 mins**	**60 mins**	**120 mins**
Control (normal saline)	10ml/kg	6.98 ± 1.42*	5.27 ± 0.97**	5.45 ± 0.95	8.9 ± 1.62**
Tramadol HCl	5mg/kg	23.2 ± 2.68* (232.4%)	23.7 ± 0.93** (349.7%)	23.2 ± 1.8* (325.7%)	21.64 ± 3.36** (142.7%)
Kigelia	25mg/kg	21.6 ± 2.71** (209.5%)	19.9 ± 1.9** (277.6%)	14.9 ± 2.47** (173.4%)	11.8 ± 1.61 (32.5%)
Kigelia	50mg/kg	14.25±0.71 (104.2%)	13.8 ± 1.09 (161.9%)	16.1 ± 2.13** (195.4%)	11.3 ± 1.6 (26.9%)
Kigelia	100mg/kg	23.5 ± 1.50* (236.7%)	20.6 ±1.69** (290.9%)	17.2 ± 1.86** (252.3%)	**19.8 ± 1.5 (122.4%)

Values are mean ± SEM (n = 5) *p<0.001 vs. control (n = 5), **p<0.01 vs. Tramadol HCl (n=5)

There was no significant difference between inhibition produced at 100mg/kg *Kigelia africana* and 5mg/kg Tramadol HCl control (Table III). The extract at the dose of 100 mg/kg produced a significantly higher pain inhibition when compared with 10 mg/kg Meperidine (35.29%).

Anti-inflammatory Activity:

Kigelia africana extract exhibited anti-inflammatory effect against carrageenhhan-induced rat paw edema. At 25 and 100mg/kg, *Kigelia africana* significantly reduced paw size and caused inhibition of oedema by 69.23%($p<0.05$) and 51.28%($P<0.05$) respectively at 3h post treatment (Table IV). Diclofenac had an additive effect on Kigelia extract when they were co-administered. Celecoxib potentiated the anti-inflammatory effect of the extract as shown by the significant ($p<0.05$) reduction in paw size and an increase in the percentage inhibition of oedema.

Table II: Analgesic activity of the ethanolic extract of *Kigelia africana* (Hot water tail immersion method)

Treatment	Dose	Latency time (Sec)	Percentage Protection (%)
Normal saline control	10ml/kg	2.60± 0.22*	0
Kigelia africana	25mg/kg	2.30±0.18	0
Kigelia africana	50mg/kg	3.80±0.59	46.15
Kigelia africana	100mg/kg	6.18 ± 1.40*	137.70
Tramadol hydrochloride	5mg/kg	10.80±2.50**	315.38
Meperidine	10mg/kg	5.80±0.72**	123.08

Mean ± SEM (n=5), *P>0.05 vs control (n=5) , ,**P<0.05vsTramadol HCl, **P<0.01 vs Mepridine (n=5)

Table III: Analgesic activity of the ethanolic extract of *Kigelia africana*: Acetic acid induced-Writhing method.

Treatment	Dose	Number of writhing (Mean±SEM)	Percentage Protection (%)
Normal saline control	10ml/kg	37.40±1.22	0
Kigelia africana	25mg/kg	28.80±1.61*	23.00
Kigelia africana	50mg/kg	19.00±4.88*	49.20
Kigelia africana	100mg/kg	10.80±6.07**	71.12
Tramadol hydrochloride	5mg/kg	10.80±5.51**	71.12
Meperidine	10mg/kg	24.2±2.88**	35.29

Mean ± SEM (n=5) *P<0.01vs control, **P<0.01 vs Control, **P<0.01 vs Tramadol HCl.

Table IV: Anti-inflammatory effect of *Kigelia africana on Carrageenan-induced* edema.

Groups	Dose (mg/kg) i.p	Initial paw size (cm)	Paw edema (cm)	Percentage inhibition (%)
			3 h	3h
Control (Distilled water)	5ml/kg	2.40±0.03	0.78±0.16*	0
Kigelia Africana	25	2.60±0.10	0.24±0.03*	69.23
Kigelia Africana	50	2.26±0.10	0.44±0.05*	43.59
Kigelia Africana	100	2.20±0.10	0.38±0.07**	51.28
Diclofenac	2.0	2.24±0.07	0.30±0.13**	61.54
Celecoxib	100	2.24±0.09	0.30±0.13**	61.54
Diclofenac 2 mg/kg + *Kigelia Africana* 100mg/kg		2.18±0.10	0.32±0.6**	8.97
Celecoxib 100 mg/kg + *Kigelia africana* 100mg/kg		2.34±0.10	0.16±0.13	79.49

Mean ± SEM (n=5), .* P <0.05vs control, **P>0.05vsDiclofenac and Celecoxib control

DISCUSSION

The anti-nociceptive activity of the ethanolic extract of the stem bark of *Kigelia africana* was evaluated in laboratory animals following mechanical (pressure), chemical and thermal methods of nociception. These are established methods used to evaluate analgesia. Whereas the tail immersion assay and the pressure method are most sensitive to centrally acting analgesics (Adeyemi et al 2004), the acetic acid writhing method is related to sensitization of nociceptive receptors to Prostaglandins, and represents an assessment of peripherally mediated pain. Thermally induced nociceptive tests are more sensitive to mu (μ)-opioid agonists and non-thermal tests to opioid kappa (κ)-agonists (Abbott 1988 and Furst et al., 1988).

Pain induced by the analgesy-meter provides a model for the study of non-inflammatory pain. Pre-treatment of rats with the varying doses of *Kigelia africana* extract 30 minutes before the application of pressure, inhibited pain induced mechanically by the analgesimeter. Tramadol is a centrally acting synthetic analog of codeine whose analgesic effect derives from at least two complementary mechanisms: binding to μ-opioid receptors and inhibition of the re-uptake of norepinephrine and serotonin (Yaksh and Wallace, 2011). The opioid activity of the drug is due in part, to a low affinity binding of the parent compound to the μ-opioid receptor and a higher affinity

binding of the O-desmethylTramadol metabolite (Yaksh and Wallace, 2011). The analgesic activity of 100 mg/kg extract was comparable to the analgesic potency of tramadol 5 mg/kg.

Further evaluation of the efficacy of intraperitoneally administered extract of *Kigelia africana* on centrally-induced pain was carried out in mice using the hot-water tail-immersion assay. This is a commonly used method for assessing opioid- mediated effects on pain threshold (Janssen et al., 1963, Adeyemi et al., 2004). *Kigelia africana* at 100 mg/kg increased pain threshhold (71.67 % inhibition) in mice, when compared with the positive controls; Tramadol HCl (318.39% inhibition) and Meperidine 10 mg/kg produced a 123.08% pain inhibition under the same test condition. Meperidine predominantly acts as a μ-receptor agonist and exerts its pharmacologic actions on the central nervous system (CNS) and the neural elements in the bowels (Yaksh and Wallace 2011). Morphine's effect in tail-flick tests (which is a measure of centrally mediated analgesia) is in part mediated by descending brainstem and bulbar serotoninergic systems (Abbott and Young, 1988). The prominent analgesic effect exhibited by Tramadol in the tail immersion assay may be due to an effect on both opioid receptors and the serotoninergic pathways. A previous study (Owolabi and Omogbai, 2007) employed the reaction time on hot plate by mice to study the analgesic effect of *Kigelia africana* stem bark extract. The study reported that the extract did not increase the mice reaction time on hot plate and concluded that the extract might not possess a central pain inhibitory effect. This is at variance with results obtained in the present study. Intraperitoneal doses of the plant extract which produced inhibition of centrally induced pain, as shown in the tail immersion and analgesy-meter tests in this study were much lower than had been previously reported.

Dose-related anti-nociceptive properties against acetic acid induced abdominal constrictions in mice exhibited by *Kigelia africana* is consistent with those of previous studies by Owolabi and Omogbai (2007). The pain sensation in acetic acid-induced writhing has been shown to be elicited by the triggering of a local inflammatory response which results in the release of free arachidonic acid from tissue phospholipids via cyclooxygenase (COX), and prostaglandin biosynthesis and release (Koster et al, 1959; Zulfiker et al., 2010). Tramadol (5mg/kg) was equipotent to 100mg/kg of the extract at inhibiting the writhing. Thus, *Kigelia africana* (100mg/kg) in its crude form is twenty times less potent than Tramadol HCL. Inhibition of acetic acid-induced writhing by the extract is indicative of peripheral pain inhibiting properties.

Using carrageenan as a stimulus for inflammation, an acute inflammatory response on the hind paw of rats was produced after 3 hours. Injection of 1% carrageenan produces a biphasic response; an early inflammatory response that lasts for six hours and a second late response that peaks at 72 hours (Inmaculada et. al., 2004). Injection of carrageenan into the rat paw induces the liberation of bradykinin which results in the biosynthesis of prostaglandins (PGs) which are responsible for the formation of the inflammatory exudate (Inmaculada et al 2004). At all doses of *Kigelia africana* employed in this study, there was reduction of the paw oedema at three hours after carrageenan injection. This result is in agreement with previous studies (Owolabi and Omogbai, 2007). The anti-inflammatory effect of the extract was not

dose-dependent. A similar pattern was reported by previous investigators on the anti-inflammatory effect of the aqueous extract of leaves of *Plantago australis* (Palmeiro et al, 2001).

Inhibition of COX, the enzyme responsible for the biosynthesis of the PGs and some related autacoids is believed to be the main mechanism of action of the non-steroidal anti-inflammatory drug (NSAIDs). The cyclooxygenase isoform (COX-2) is induced during inflammation and tends to facilitate inflammatory responses. Both Diclofenac and Celecoxib are NSAIDs. While Diclofenac is a relatively non-selective COX inhibitor, Celecoxib exerts a more selective inhibition of the COX-2 isoform of the enzyme. A comparison of the effects of co-administration Diclofenac or Celecoxib with *Kigelia africana* extract showed that Celecoxib, a selective COX 2 inhibitor, significantly potentiated the anti-inflammatory effect extract when both were co-administered. This suggests that *Kigelia africana* may exert a non-selective inhibition on the COX enzyme system as part of the mechanism of its anti-inflammatory action.

CONCLUSION

The present study supports previous reports on the analgesic and anti-inflammatory effects of extract of *Kigelia africana* stem bark. The study further shows that the extract possesses both central and peripheral analgesic activities. In addition, the anti-inflammatory action of the extract might be mediated via a non-selective COX-enzyme inhibition. The analgesic and anti-inflammatory activities of the extract, combined with the low toxicity reported, makes *Kigelia africana* a suitable candidate for further investigation as an agent for the treatment of acute and chronic pain and inflammatory conditions.

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