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Jack Fruit: An Estimation of *Hunteria Umbellata* Fruit Extract against Formalin Induced Nociception

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

The purpose of the study is to ascertain the impact of ethanolic fruit extract from Hunteria umbellata on formalin-induced nociception in Wistar rats. Six sets of thirty Wistar rats, weighing 110.7 to 169.4 g each, were employed for the investigation. Group 1 functioned as the control group and was given nothing except unlimited amounts of rat food and water. Formalin was administered just to Group 2, which served as the FOG. Group 3 rats were given the standard drug group (SDG). Group 4 rats received 50 mg of Hunteria umbellata fruit extract per kilogramme of body weight. Group 5 rats received 100 mg of Hunteria umbellata fruit extract per kilogramme of body weight. Group 6 rats received 150 mg of Hunteria umbellata fruit extract per kilogramme of body weight. The experimental rats were given 50L of a 2% formaldehyde solution subcutaneously

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into their left hind paws an hour after extract and medication administration in order to cause pain. The duration of paw licking was immediately used to identify the spontaneous nociceptive behaviour. Following a 14-day period of treatment, samples were taken and tested for signs of pain. The significance level was set at p 0.05 after post hoc LSD and SPSS analysis of the data. The outcome showed that, in contrast to the formalin only group, the extract (LDEG, MDEG, HDEG) significantly enhanced (p0.05) the reaction time of nociceptive behaviours (FOG). In contrast to the control group, serum nociceptive molecules considerably (p 0.05) increased in the formalin only group (FOG). In conclusion, the extract proved useful for treating nociception by traditional medical professionals (herbalists).

Keywords: Hunteria umbellata; jack fruit; nociception; formaldehyde; pain.

1. INTRODUCTION

Non-steroidal anti-inflammatory medicines (NSAIDs) are the most often prescribed medications for treating pain and inflammation in clinical settings [1, 2].

Due to their poor potency and side effects, analgesic medications like opiates and NSAIDs are not thought to be helpful in every situation. The negative effects of opiates and NSAIDs could include opiate overdose, gastrointestinal problems, and liver failure [3]. Finding better options is therefore necessary. Due to the presence of a varied and complex diversity of compounds from which it is possible to develop new analgesic drugs, medicinal plants can function as a viable alternative source [4].

Huntera umbellate, which is primarily found in Sub-Saharan Africa, is a helpful and beneficial medicinal plant having a wide range of domestic and ethnomedicinal uses. The plant is referred to informally by the Edo, Igbo, and Yoruba people of Nigeria as "Osu", "Npokiri," "Abeere," and "Erin," respectively. It is known that H. umbellate has a wide range of traditional medical use in the area. In African traditional medicine (ATM), the plant's dry seeds are highly prized for treating a variety of human ailments. African traditional herbalists use various parts of the plant to treat veterinary and human conditions locally, including pain, gastric ulcers, liver conditions, obesity, diabetes mellitus, fever, leprosy sores, menstrual irregularities, infertility, yawning, intestinal worms, abdominal colic, and discomfort, to name a few [5].

Traditional midwives, for example, place a high importance on the cold water decoction prepared from the plant's fresh leaves in the induction and augmentation of labour, while the water decoction created from the mature and ripe fruits' seeds is used to cure infections, stomach ulcers, diabetes, and obesity. However, recent research has supported the traditional use of the fresh leaves as an oxytocic medication. Its oxytocic activity is also demonstrated to be mediated via muscarinic acetycholinergic mechanism. Hunteria zeylanica stem bark alkaloids have also been reported to have antipyretic properties. Additionally, it has been discovered that an aqueous extract of the fruit pulp of H. umbellate can effectively control fever without affecting its antibacterial activities [6].

Additionally, Hunteria umbellata has been demonstrated to be highly effective against bacteria including Escherichia coli, Proteus spp., and Staphylococcus aureus6. Recent studies have shown that the aqueous seed extract of H. umbellata has oral hypoglycaemic activity of 50–200 mg/kg in a variety of hyperglycemic models, which was mediated by inhibition of intestinal glucose uptake, inhibition of adrenergic mechanism, increased peripheral glucose uptake, and improvements in insulin resistance [7].

Without any scientific backing, herbalists in Nigeria use this plant to dull the perception of pain.

The current study was fashioned to assess the analgesic ability of the ethanol fruit extract of *H. umbellata* in Wistar rat.

2. MATERIALS & METHODS

2.1 Experimental Animals

A total of thirty (30) Wistar rats were randomly allocated into distinct groups. They ranged in weight from 110.7 to 169.4 grammes. The rats in each group were housed in separate cages at Chukwuemeka Odumegwu Ojukwu University's animal house, where they were exposed to

natural light and dark cycles and given two (2) weeks of acclimatization as well as unlimited access to normal rat food and water ad libitum. The National Institute of Health Guidelines for the Care and Use of Laboratory Animals were followed for each rat [8].

2.2 Extract Preparation

The Fresh fruits were obtained from the market, and were washed thoroughly using distilled water. The fruits were placed on a fenestrated mat to allow the water to drain and air dried for about 28 days. After drying, the fruits were weighed before and after grinding into powdered form and were stored in airtight containers, and kept in a clean, dry, damp free store at normal room temperature till they're ready to be used.

2.3 LD_{50} Determination

The median lethal dose (LD_{50}) of *Hunteria umbellata* fruit was carried out in the department of Physiology, Faculty of Basic Medical Science, Chukwuemeka Odumegwu Ojukwu University, Uli campus. This was determined using a method of Dietrich Lorke [9].

2.4 Experimental Animal Groupings

The animals were randomly divided into six (6) groups of five (5) animals each.

- Group 1 served as the control group and received only rat feed and water ad libitum.
- Group 2 served as the formalin only group (FOG) and received formalin only
- Group 3 rats were the standard drug group (SDG) and received 100mg/body weight of diclofenac 14 days
- Group 4 rats were the low dose extract group (LDEG) and received 50mg/body weight of *Hunteria umbellata* fruit extract 14 days.
- Group 5 rats were the medium dose extract group (MDEG) and received 100mg/body weight of *Hunteria umbellata* fruit extract for 14 days.
- Group 6 rats rats were the High dose extract group (HDEG) and received 150mg/body weight of *Hunteria umbellata* fruit extract for 14 days.

2.5 Formaldehyde Induced Pain Model and Nociceptive Behaviour

After one hour of the administration of extract and drug, 50µL of 2% formaldehyde solution was injected subcutaneously into the left hind paw of the experimental rats. The spontaneous nociceptive behaviour was immediately determined by measuring the duration of paw licking (9, 10). Rats were immediately placed in a transparent plastic cage and the paw licking time and frequency was recorded from initial 0 to 5 min (first-phase, neurogenic) and then 15 to 30 min (second-phase, inflammatory).

The percent (%) inhibition of the duration of licking was also calculated as follows:

Inhibition (%) = Duration of paw licking (control) - Duration of paw licking (test)] x 100/Duration of paw licking (control).

2.6 Sample Collection

At the end of the fourteen days treatment with *H. umbellata*, animals were anesthetized using chloroform in an enclosed container for two minutes. After 2 minutes, blood samples were collected from the animals using a capillary tube through ocular puncture. Blood obtained were put in a well-labelled EDTA container and were centrifuged at 1000RPM to obtain serum for two minutes.

2.7 Determination of Pain Molecules

Serum pain chemicals were analyzed by enzyme linked immunosorbent assay (ELISA).

2.8 Statistical Analysis of Results

Data obtained from this study was analyzed using Statistical Science for Social Sciences (SPSS) version 25. Data obtained for brain weight was analyzed using ANOVA followed by post hoc LSD. Data was considered significant at $p<0.05$.

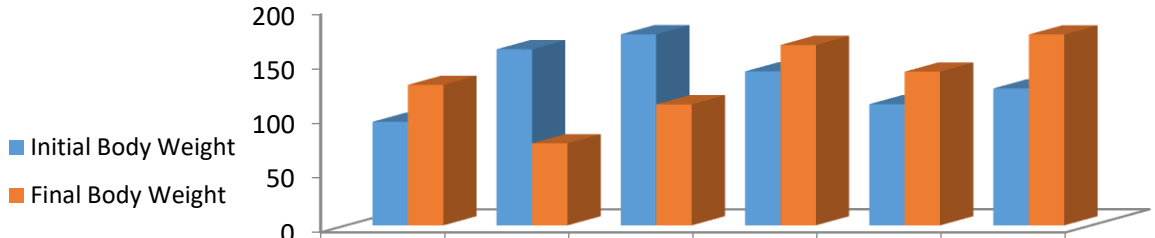
3. RESULTS AND DISCUSSION

Pain is a distressing sensory and affective experience that is connected to or defined in terms of tissue damage, whether it is present or potential. Pain is characterised as a subjective, unpleasant, physical, and psychological sensation that is felt when specific nerve fibres in the spinal cord are stimulated and travel along specific pathways to the brain [12].

The term "pain" refers to both nociceptive pain, which is frequently caused by tissue damage that activates nociceptive receptors, and non-nociceptive pain, which can result from injury to neural structures (neuropathic pain or neuralgia). While the latter is highly difficult to treat, there may or may not be signs of injury, causes chronic pain, and will linger long after the initial injury has healed the former is frequently acute, self-limiting after healing, and responds well to analgesics [13].

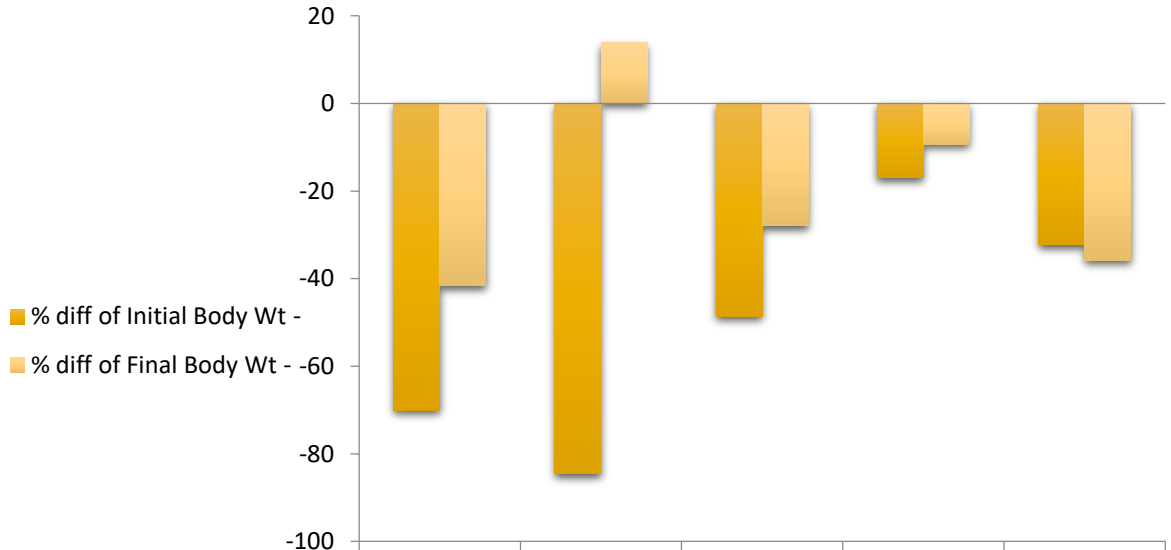
The current study used the formalin-induced pain method to examine the anti-nociceptive properties of the ethanol fruit extract of *H. umbellata*.

As an experimental model of analgesia, formalin-induced pain is beneficial for illuminating the mechanisms behind both pain and analgesia because it evaluates the body's reaction to a persistent nociceptive stimulation and, as a result, is similar to clinical pain [14].



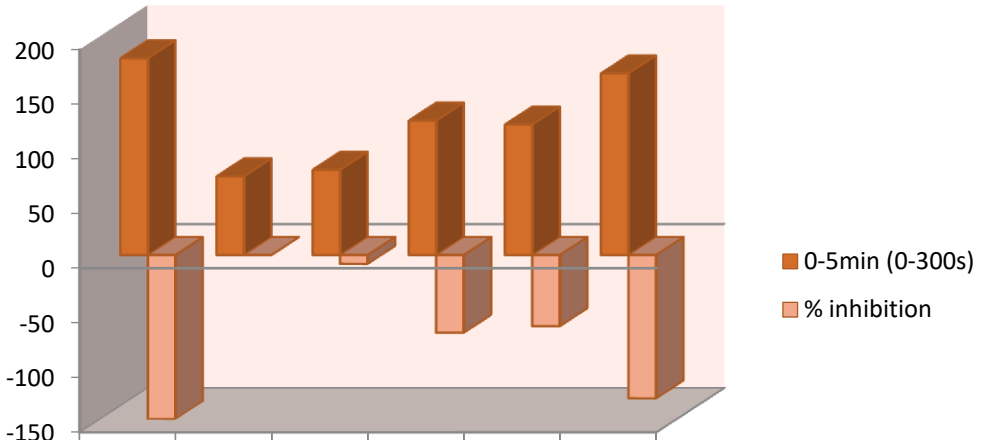
	Control	FOG	SDG	LDEG	MDEG	HDEG
Initial Body Weight	95.05	161.63	175.36	141.31	111.22	125.7
Final Body Weight	129	75.33	111.09	165.6	141.07	175.2

Fig. 1a. Body weight values of extract in study animals



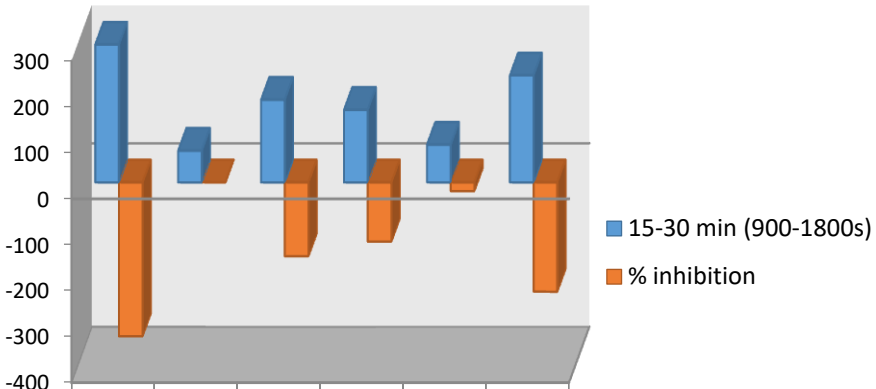
	FOG	SDG	LDEG	MDEG	HDEG
% diff of Initial Body Wt -	-70.04	-84.49	-48.67	-17.01	-32.25
% diff of Final Body Wt -	-41.6	13.88	-27.91	-9.36	-35.81

Fig. 1b. % Diff of initial and final body weight in study animals



	Control	FOG	SDG	LDEG	MDEG	HDEG
0-5min (0-300s)	180	72	78	123	119.4	166.2
% inhibition	-150	0	-8	-71	-65	-131

Fig. 2a. Pain behavioral values of study animals after 7 days of extract administration

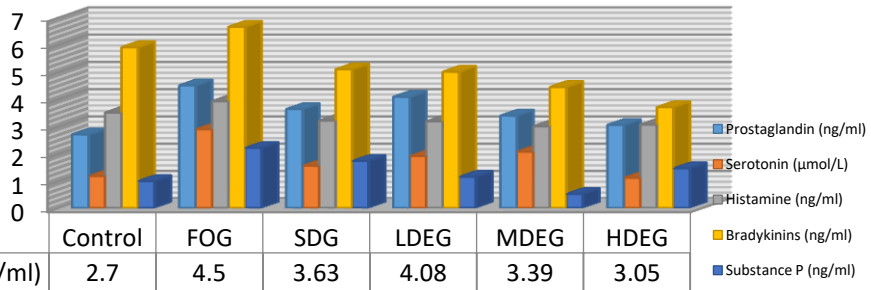


	Control	FOG	SDG	LDEG	MDEG	HDEG
15-30 min (900-1800s)	300	69	180	158	82	233
% inhibition	-335	0	-161	-129	-19	-238

Fig. 2b. Pain behavioral values of study animals after 14 days of extract administration

A biphasic nociceptive response is produced when rats' hind paws are subcutaneously injected with dilute formalin. Formalin directly affects sensory C-fibers, causing the first transient phase. The second prolonged phase is linked to the development of injury-induced spinal sensitisation, which is responsible for facilitating pain processing. Inflammatory pain also causes a central sensitisation of the dorsal horn neuron [1, 2]. Medicines with a central mechanism of action, such as opioids, block both stages of formalin-induced pain, whereas drugs with a peripheral mechanism of action, such as diclofenac, block only the late phase [1,2].

The current study's findings demonstrated that, when compared to the control and extract groups, the reaction time in the formalin-only treated rats (group 2) dramatically decreased. Reduced pain behaviour reaction times are a sign that an animal is experiencing extreme or increased pain [15].



	Control	FOG	SDG	LDEG	MDEG	HDEG
Prostaglandin (ng/ml)	2.7	4.5	3.63	4.08	3.39	3.05
Serotonin (µmol/L)	1.17	2.89	1.55	1.91	2.07	1.11
Histamine (ng/ml)	3.5	3.92	3.21	3.18	3	3.06
Bradykinins (ng/ml)	5.9	6.65	5.09	5	4.44	3.7
Substance P (ng/ml)	0.99	2.21	1.73	1.15	0.52	1.46

Fig. 3. Values of pain chemicals of extract in study animals

However, the extract greatly lengthens the time it takes for pain to react, inhibiting both the early and late phases of formalin-induced pain, indicating both its central and peripheral anti-nociceptive activities. Aside this, HU produced more inhibition of the early phase than the late phase and was more efficacious than the conventional medication, diclofenac, in this phase.

The current study's findings also showed that group 2 (FOG), as compared to the extract groups, had much higher levels of the pain compounds typically generated by wounded tissues.

Substance P participates in the early phase of the formalin test, whereas histamine, serotonin, and prostaglandins are implicated in the late phase, and bradykinin affects both phases [16-19].

Formalin-induced muscular contraction is a sensitive method to identify peripherally acting analgesics, and it is believed that such a reaction involves local peritoneal receptors.

By reversing or lowering the heightened pain molecules generated by formalin, significant protection was seen in the extract-treated groups of rats (LDEG, MDEG, and HDEG), and this compared favourably with the usual medication. Diclofenac is one of the medications that is most usually used to treat mild to moderate pain, including the pain associated with migraines and fever. In the management of moderate to severe pain, it is frequently used with other non-steroidal anti-inflammatory medications and opioid analgesics [19]. Although the exact mechanism by which diclofenac inhibits prostaglandin formation is complicated, its effect results in analgesia [20].

According to reports, HU contains secondary metabolites which include alkaloids, saponins, tannins, flavonoids, and glycosides [7]. In several natural products, analgesic and anti-inflammatory effects have been linked to alkaloids.

Prostaglandins, which are implicated in the late stage of acute inflammation and pain perception, are known to be targeted by flavonoids [21]. The involvement of tannins and saponins in anti-nociceptive and anti-inflammatory actions has also received little attention. In vitro histamine release inhibition by saponins has also been documented [2]. Thus, HU's analgesic effect may have been caused by the presence of these biologically active components [22-28].

4. CONCLUSIONS

The ethanol fruit extract of H. umbellata showed remarkable anti-nociceptive properties in the animal models employed in this study, demonstrating its effectiveness in the management of pain by conventional medical practitioners (herbalists).

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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