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ANTINOCICEPTIVE PROPERTIES OF LEAF AQUEOUS EXTRACT OF CROSSOPTERYX FEBRIFUGA (AFZEL. EX G. DON) BENTH

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ABSTRACT

Nociceptive pain is a sensational discomfort that is usually associated with injury or illness found affecting the body either internally or externally. *Crossopteryx febrifuga* is one of the medicinal plants which are locally used in the management of pain especially in the North Central Region of Nigeria. Many conventional drugs which are being applied in managing pain aside being not affordable and readily accessible by the majority of people at rural areas have one side effect or the other. Therefore, this research was conducted to evaluate the potentiality of aqueous extract of *C. febrifuga* in alleviating pain in Wistar rats. The study was carried out using acetic acid induced writhing and Edson hot plate methods. On acetic acid induced pain, the aqueous extract at 50 and 100 mg/kg inhibited pain significantly by reducing the number of writhing by average of 3.9 per minute while at 200 mg/kg, the extract reduced pain by reducing the number of writhing by average of 4.2 per minute**.** Similarly, the extract at all doses administered in hot plate induced method inhibited pain by increasing the time the rats took to jump off the hot plate. The data obtained from the analgesic study of *C. febrifuga* aqueous extract suggests that it has anti-nociceptive property as evident in both models. This, therefore revealed that the plant leaf aqueous extract possessed both the peripherally and centrally mediated analgesic properties. For this reason, the plant leaf could be a potential antinociceptive agent if subjected to clinical trial and proved promising.

Keywords: Antinocicepyive**,** *Crossopteryx febrifuga*, Evaluation, Pain, Writhing

INTRODUCTION

Many medicinal plants have been utilized in the management of pain since time immemorial. Some of the plants have been scientifically or clinically proven while others are yet not. *Crossopteryx febrifuga* is one of the plants used traditionally in the management of pain especially in the North Central States of Nigeria.

Nociceptive pain is a symptom associated with injuries both internal and external as well as diseases in the body. From the pathophysiology, some pains are centrally mediated while others are peripherally mediated. Therefore, from the studies of pain, it is known to modulate centrally through some mechanisms which include opiate, dopaminergic, descending noradrenergic and serotonergic systems (Pasero *et al*., 1999; Terman and Bonica, 2000). Similarly, Adeyemi *et al.* reported in 2004 that the analgesic drugs which are centrally acting in nature usually increase the level of pain in mice if subjected to stimuli such as heat and pressure. The analgesymeter antinociceptive evaluation by the application of analgesymeter is useful in elucidating centrally mediated antinociceptive responses whose priority is to target the changes that occurs at region of CNS above the spinal cord level (Vongtau *et al*., 2004).

Some synthetic drugs are known to alleviate pain and inflammation. Some medicinal plants have been evaluated for analgesic and anti-inflammatory properties. *C. febrifuga* is one of the plants. Salawu *et al*. (2008) opined in a study that there is likelihood of analgesic effect of *C. febrifuga* extract being mediated through central mechanisms involving opiate, dopaminergic, descending noradrenergic and serotonergic systems. It could also be via peripheral mechanisms involved in the inhibition of prostaglandins, leucotrienes, and other endogenous substances that are key players in inflammation and pain. He in addition observed that the significant increase in pain threshold produced by the methanol extract of *C. febrifuga* in the analgesymeter investigation suggested involvement of central pain pathways (Salawu *et al*., 2008).

Many conventional drugs which are being applied in managing pain aside being not affordable and less accessible have one side effect or the other. Therefore, this research was conducted to evaluate the potentiality of aqueous extract of *C. febrifuga* in alleviating pain in Wistar rats.

MATERIALS AND METHODS

Plant collection

Mature and healthy *Crossopteryx febrifuga* leaves were collected at Zango, Lokoja Local Government Area, Kogi State, Nigeria in an ethnomedicinal survey in October, 2020. The plant sample was identified, authenticated and its voucher number UBHdt/217 was assigned in the Herbarium Unit of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria.

Preparation of plant leaves into extract

The leaves were air dried under shade for two weeks and powdered. About 200 g of the powdered sample was loaded into thimble which was thereafter placed in a Soxhlet apparatus. Extraction of the powdered sample was done for 48 hours with a litre of methanol (98%) at a temperature not rising beyond the boiling point (64.7 ^{0}C) of methanol in the round bottom flask. The resulting solution was concentrated in vacuum to dryness thereby giving dried sample of methanol extract of 20 g. The dried extract was finally stored in a refrigerator at 5 ^{o}C for preservation sake until it was required for use.

Analgesic Activity Test

Healthy Wistar rats of 180 g to 200 g in weight were randomly obtained and maintained under standard environmental

conditions (free aeration, free access to food and water *ad libitum*) for acclimatization in 14 days before beginning the experiment in the animal house of the Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria. The following methods; acetic acid induced writhing and hot plate were employed in the study.

Acetic acid-induced writhing method

The method employed by Raquibul *et al*. (2010) was adopted with some modifications. Five groups each containing 5 rats obtained from random selection were used. In this experiment, three (3) groups of rats received (50, 100, 200 mg/kg) of extract accordingly. Normal control received normal saline (10 mg/kg). Positive control received pentazocine (20 mg/kg). Each group was treated 30 minutes before the administration of 0.6 % acetic acid. After an interval of 5 minutes, each rat was observed for writhing (abdominal contraction) for the next 10 minutes.

Hot plate method

The method employed by Raquibul *et al.* (2010) was adopted with some modifications. Five groups each containing 5 rats randomly selected were used. In this experiment, three (3) groups of rats received methanol extract of doses 50, 100, 200 mg/kg (ip) accordingly. Normal control received normal saline 10 mg/kg (ip). Positive control received morphine at 20 mg/kg (ip).

The Eddy's hot plate apparatus was powered on and after a while, the temperature reading was set at 55 ± 1 °C. Each rat was put on the hot plate and the period of reaction in seconds for jumping off the plate or flicking of hind paw at 0 second, 30 minutes, 60 minutes, 90 minutes and 120 minutes with cut off time of 15 secs was noted and recorded. Reaction time of rats following treatment were recorded and tabulated.

Statistical analysis

Reactions of the rats to acetic acid induced writhings and hot plate induced pain as well as their responses to treatment with crude drug and controls were recorded. The data obtained were expressed as mean ± SEM and analyzed using One Way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparison test with the aid of Graphpad prism6 software.

RESULTS AND DISCUSSION

Effect of *Crossopteryx febrifuga* Leaf Aqueous Extract on Pain

Effects of aqueous extract on acetic acid induced writhing

Investigation using acetic acid induced pain method, the extract at 50 and 100 mg/kg inhibited pain significantly by reducing the number of writhing by average of 3.9 per minute while at 200 mg/kg, the extract reduced pain by reducing the number of writhing by average of 4.2 per minute**.** Similarly, the standard drug, pentazocin at 10 mg/kg significantly inhibited pain by reducing number of writhing nearly by an average of 4 per minute (Figure 1)**.**

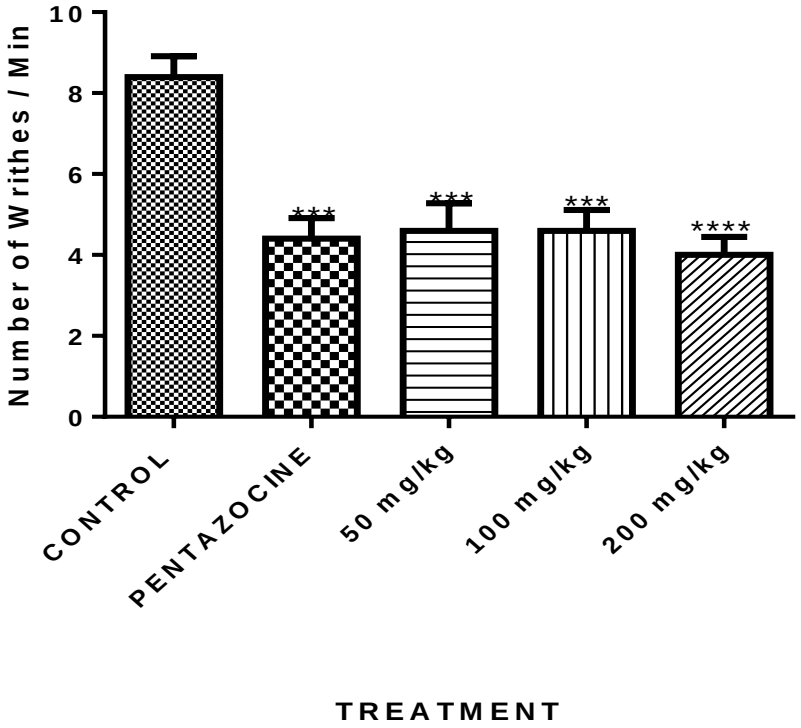

Figure 1: Effects of aqueous extract of *Crossopteryx febrifuga* on acetic acid induced writhing.

Effect of aqueous extract of *Crossopteryx febrifuga* on hot plate induced pain

The extract at all doses administered inhibited the hot plate induced pain as shown by increasing the time the rats took to jump off the hot plate (Figure 2). At 50 mg/kg, the extract increased the period by about an average of 0.8 second in comparison to normal control. At 100 and 200 mg/kg, the extract increased the time of reaction by an average of 1 second and 0.5 second respectively in comparison to normal control. The reference drug, morphine at 10 mg/kg increased the reaction time significantly ($P<0.05$) by 1.8 seconds in comparison to normal control.

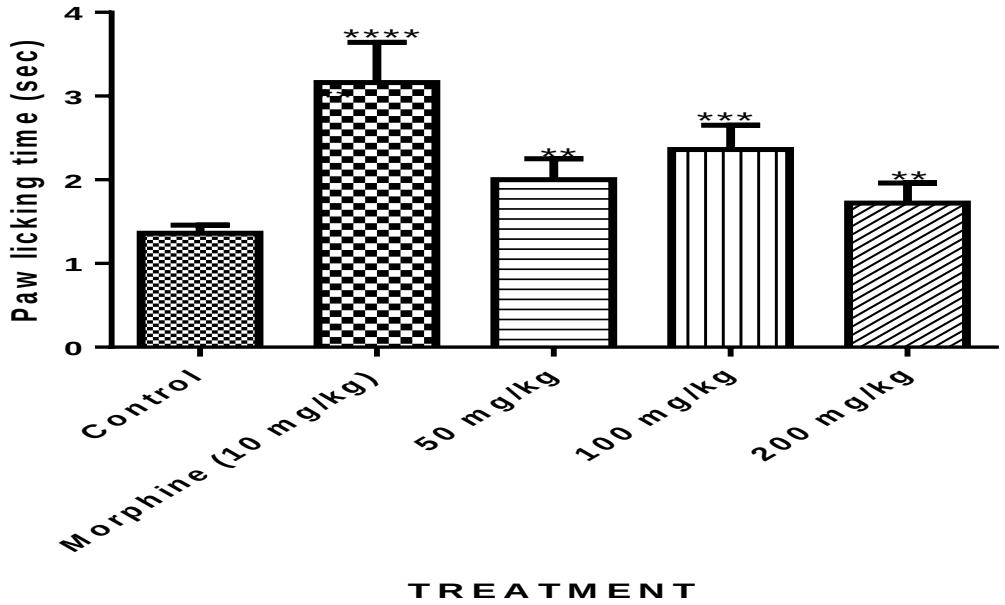

Figure 2: Effect of aqueous extract of *Crossopteryx febrifuga* on hot plate induced pain

Normally, acetic acid causes pain by liberating endogenous substances such as serotonin, histamine, prostaglandins (PGs), bradykinins and substance P, which stimulate nerve endings.

Significant pain reduction ($P<0.05$) was noted in acetic acid induced writhing and hot plate models which tested peripheral and central analgesic property respectively. This concurs with the work of Salawu *et al*. 2008 on the same *C. febrifuga* methanol extract from its bark which using similar models revealed a dose dependent significant decrease in pain. The antinociceptive effect is perhaps through peripheral mechanisms involving inhibition of prostaglandins, leucotrienes, and other endogenous substances that are key players in pain or central mechanisms involving dopaminergic, opiate, noradrenergic and serotonergic systems.

The data obtained from the analgesic study of *C. febrifuga* aqueous extract suggests that it has anti-nociceptive property as evident in both models. This, therefore revealed that the plant leaf methanol extract possessed both the peripherally and centrally mediated analgesic properties. The writhing caused by acetic acid is a critical tool for determining peripherally acting analgesic (Gene *et al*., 1998). Analgesymeter is a useful tool for illustrating centrally mediated anti-nociceptive activities as it is centered on the changes that occur at region above the spinal cord (Vongtau *et al*., 2004). The significant rise in threshold produced by *C. febrifuga* with the aid of analgesymeter indicates its role along the central pain pathways.

Pain is centrally mediated through some mechanisms known as dopaminergic, serotonergic, opiate and noradrenergic systems (Ternman and Bonica, 2000; Paesro, 1999). Since the pattern of action of the aqueous extract of *C. febrifuga* is somewhat similar to that of morphine and pentazocine which are well known central and peripheral analgesic respectively, the plant leaf aqueous extract probably has bioactive constituents that are responsible for the perceived biphasic pain alleviation. Also noted was dose dependent action of the plant leaf extract which invariably was in line with those reported by Sabina *et al* (2013) and Nikhil *et al*. (2020).

It is noteworthy that *C. febrifuga* aqueous extract demonstrated significant reduction in pain using both acetic acid and hot plate methods in animal model. This observation concurred with the claim of using the plant leaf and bark in treating general body ache by the traditional healers of the Northern Nigeria.

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