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ANTI-NOCICEPTIVE POTENTIALS OF METHANOLIC EXTRACT OF *ARTOCARPUS ALTILIS* (BREADFRUIT) ON CHEMICAL MODEL OF PAIN STUDY IN LABORATORY RODENTS

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ABSTRACT

This study evaluates the anti-nociceptive potentials of methanolic extract of artocarpus altilis (breadfruit) on chemical model of pain study in laboratory rodents. The study was done using 25 albino wistar rats of both sexes, weighing 200-250g, using acetic acid induced writhing test as a chemical model of nociception. The LD50 value was determined as 3600mg/kg using Karber's method. Standard doses were taken below the LD50 value as 100mg, 200mg and 300mg/kg of the plant extract. The rats were divided in five groups of five animals per group (both sexes). Group1 served as control group and were given 5ml of distilled water orally. Group 2, 3 and 4 were given methanolic extract of Artocarpus altilis in doses of 100mg, 200mg and 300mg/kg orally; and group 5 received 100mg/kg of aspirin orally, as a reference drug. Number of writhings in treated and control groups were compared. The result showed that methanolic extract of Artocarpus altilis seeds given orally caused significant ($p < 0.05$) analgesic effect on nociceptive response initiated by 0.6% acetic acid; although this analgesic effect was less than that produced by aspirin. Thus, it can be inferred that the methanolic extract of Artocarpus altilis possessed significant analgesic effect in rats.

KEYWORDS: Artocarpus altilis, acetic acid, aspirin, chemical model, writhing.

INTRODUCTION

Pain is an unpleasant sensation that can range from mild, localized discomfort to agony. It can also be considered a feeling of distress, suffering, or agony, caused by stimulation of specialized nerve endings. Its purpose is chiefly protective; it acts as a warning that tissues are being damaged and induces the sufferer to remove or withdraw from the source, to protect a damaged body part while it heals, and to avoid similar experiences in the future.[1,2]

Pain has both physical and emotional components. The physical part of pain results from nerve stimulation. Pain may be contained to a discrete area, as in an injury, or it can be more diffuse, as in disorders like fibromyalgia. Pain is mediated by specific nerve fibers that carry the pain impulses to the brain where their conscious appreciation may be modified by many factors. Pain is a feeling triggered in the nervous system.[3]

The International Association for the Study of Pain widely used definition states that: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[4] Pain is the most prominent number of a class of sensations known as bodily itches, tickles, orgasms, and so on.[5]

Pain motivates the individual to withdraw from damaging situations, Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage or disease.[6]

Pain is a major symptom in many medical conditions, and can significantly interfere with a person's quality of life and general functioning.[7] Psychological factors such as social support, hypnotic suggestion, excitement, or distraction can significantly modulate pain's intensity or unpleasantness.[8]

Breadfruit is a common name for fruits belonging to the genera Artocarpus[9] although it usually refers to Artocarpus altilis[10,11] Research on the efficacy of breadfruit extracts from various parts of the plants has shown promising results. Artocarpus extracts and metabolites from leaves stem, fruit and bark contain numerous beneficial biologically active compounds and

these compounds are used in the various biological activities including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, antiarthritic, tyrosinase inhibitory and cytotoxicity.[12]

Previous research on the chemical constituents of *Artocarpus altilis* has resulted in the isolation of several classes of compounds such as flavonoids[13] and triterpenoids.[14] A previous study indicated that some flavonoids from *artocarpus altilis* could inhibit 5-lipoxygenas of cultured mastocytoma cells.[15] The aqueous leaf extract *Artocarpus altilis* proved has an antihypertensive as it produces negative chronotropic and hypotensive effects through α-adrenoceptor and Ca^{2+} channel antagonism.[16] In our area, due to the availability and accessibility to plant products and herbs, the alternative therapies to orthodox treatments are always these plant products and herbs.[9,17] The present study tends to investigate the effect of methanol extract of *Artocarpus altilis* (breadfruit) on chemical model of pain study.

MATERIALS AND METHODOLOGY

The study was conducted in the Physiology Department, Faculty of Basic Medical Sciences, in the University of Port Harcourt.

Plant Materials

Artocarpusaltilis (breadfruit) were purchased from Port-Harcourt Central Fruit market. The fruits were identified and confirmed for use by a botanist in the University Of Port Harcourt herbarium. The fruits were then ground into powder form. The powdered *Artocarpusaltilis* was soaked with 100% methanol in a glass jar container and was left for a period of 72 hours. Thereafter, the mixture was decanted using filter paper and then evaporated using rotatory evaporator. The extract was evaporated to semi-solid form and then preserved in a refrigerator, from which appropriate quantity was collected to formulate the various administered doses.[18]

ANIMALS

Twenty-five (25) male albino Wistar rats weighting 200-250g were used for the study, under the approval of the ethics committee on care and handling of experimental animals in the University of Port Harcourt. The albino rats were supplied from the animal house of the Department of Human Physiology, University Of Port Harcourt. The animals were housed under standard conditions of temperature (23±2°C), humidity (55±15%) and 12 h light (7.00 am-7.00 pm). The animals were put into a wire meshed wooden and were allowed to acclimatize for 14days while fed with normal commercial rodent chew and allowed water *ad libitum*. After acclimatization, they were randomly grouped into five groups according of five animal each.

Treatment

The acetic acid induced writhing test in rats was employed.[19] The rats were fasted for 24 hours with free access to water. Group I which served as the control group (negative control) was given 5ml/kg of distilled water orally. Group II, III and IV received 100, 200 and 300mg/kg of methanol extract of *Artocarpus altilis* orally; and the Group V received 100mg/kg of Aspirin (Acetylsalicylic acid: reference drug) orally respectively.

Thirty minutes after the various administrations, the rats in all groups were given intraperitoneal injection with acetic acid (10ml per body weight). Five minutes after acetic acid injection, rats were placed in a Plexiglas (transparent glass chamber), and the number of abdominal contractions was counted for each rat for a period of 10 minutes. A writhe is defined as contraction of the abdominal muscles accompanied by elongation of the body and the hind limbs.[19] A significant reduction in the number of acetic acid induced abdominal constrictions of the treated rats compared to the untreated rats (control group of rats), was taken as an indication of analgesic effect.

RESULT AND DISCUSSION

Table 1: ANOVA Table showing the pain behaviour of writhing response of rats and analgesic activities of Aspirin and Metabolic extract of *Artocarpus altilis.*

GROUP	DOSE (Mg/kg)	No OF WRITHINGS (MEAN ± SEM)	ANALGESIC INHIBITION (%)
DISTILLED WATER	5ml	112 ± 11.48	–
Artocarpus altilis	100mg	83.0 ± 8.36*	26%
Artocarpus altilis	200mg	70.40 ±7.78 *	37%
Artocarpus altilis	300mg	43.00 ±3.86 **	62%
ASPIRIN	100mg	35.60 ±2.98 **	68%

Values are Mean ± SEM. *P<0.05 (Significant), **P<0.01(Highly significant), different from control group.

The control animals showed 112 writhing count per 10 minutes, but animals treated with aspirin caused significant reduction of writhing count, from 112 to 35.6 (P<0.01), which is highly significant. Animals treated with methanol extract of *Artocarpus altilis* in 100mg, 200mg and 300mg/kg reduced the writhing count from 112 to 83, 70.4 and 43 respectively.

The results suggested that methanol extract of Artocarpus altilis (300mg) and Aspirin had analgesic action and showed highly significant (P<0.01) reduction of pain in comparison with control group. The group that was administered with 300mg of methanol extract of Artocarpus altilis had higher analgesic inhibition or activity (62%) than those administered with 100mg and 200mg (26%, 37%).

% Analgesic inhibition or activity was calculated by using the formula=
% analgesic activity =

$$\frac{\text{Mean writhing count (control group – treated group)}}{\text{Mean writhing count of control group}} \times 100$$

TABLE 2: Turkey's comparisons test showing the comparison between the various groups and their significance.

Tukey's Multiple Comparison Test	Mean Diff.	Q	Significant? P < 0.05?	Summary	95% CI of diff
GRP 1 vs GRP 2	29.00	3.834	No	Ns	-3.008 to 61.01
GRP 1 vs GRP 3	41.60	5.500	Yes	**	9.592 to 73.61
GRP 1 vs GRP 4	69.00	9.123	Yes	***	36.99 to 101.0
GRP 1 vs GRP 5	76.40	10.10	Yes	***	44.39 to 108.4
GRP 2 vs GRP 3	12.60	1.666	No	Ns	-19.41 to 44.61
GRP 2 vs GRP 4	40.00	5.289	Yes	*	7.992 to 72.01
GRP 2 vs GRP 5	47.40	6.267	Yes	**	15.39 to 79.41
GRP 3 vs GRP 4	27.40	3.623	No	Ns	-4.608 to 59.41
GRP 3 vs GRP 5	34.80	4.601	Yes	*	2.792 to 66.81
GRP 4 vs GRP 5	7.400	0.9784	No	Ns	-24.61 to 39.41

Comparing Group 1 (control group) versus Group 2 (100mg/kg of extract); the value of P (<0.05) was not significant and the confidence level was -3.008 – 61.01, thus; there was very little or no analgesic effect when the rats were treated with 100mg of the extract.

Comparing Group 1 (control group) versus Group 3 (200mg/kg 0f extract); the value of P (<0.05) was highly significant and the confidence level was 9.592 – 73.61, thus; there was an analgesic effect when the rats were treated with 200mg of the extract.

Comparing Group 1 (control group) versus Group 4 (300mg/kg of extract); the value of P (0.05) was extremely significant and the confidence level was 36.99 – 101.0, thus; there was a high analgesic effect when the rats were treated with 300mg of the extract.

Comparing Group 1 (control group) versus Group 5 (Aspirin); the value of P (<0.05) was extremely significant and the confidence level was 44.39 – 108.4, thus; there was also a high analgesic effect when the rats were treated with Aspirin.

Comparing Group 2 (100mg of extract) versus Group 3 (200mg of extract), Group 3 (200mg of extract) versus Group 4 (300mg of extract) and Group 4 (300mg of extract) versus Group 5 (Aspirin); the value of P (<0.05) for the three comparisons was not significant.

Comparing Group 2 (100mg of extract) versus Group 4 (300mg of extract) and Group 3 (200mg of extract) versus Group 5 (Aspirin); the value of P (<0.05) for both comparisons was significant.

Comparing Group 2 (100mg of extract) versus Group 5 (Aspirin); the value of P was highly significant.

The number of writhings is highest in Group 1 (Control group). It was less in Group 2, 3 and 4 and the least was in Group 5 (Aspirin group), indicating maximum analgesia offered by Aspirin (Acetylsalicyclic acid).

Also, in all the groups that were administered methanolic extract of *Artocarpus altilis* [Group 2, 3 and 4]; the number of writhings was highest in group 2 (100mg/kg of extract) and least in group 4 (300Mg/kg of extract).

DISCUSSION

The results of the present study demonstrated that methanol extract of *Artocarpus altilis* possessed analgesic activity evident, which is suggestive of the presence of peripherally mediated mechanisms. Methanol extract of *Artocarpus altilis* dose- dependently and significantly reduced the abdominal writhing. Acetic acid is believed to act indirectly by inducing the release of prostaglandins as well as lipoxygenase products into the peritoneum which stimulate the nociceptive neurons sensitive to the Non-steroidal anti-inflammatory drugs[20]; hence, the test is useful for the evaluation of mild analgesic non-steroidal anti-inflammatory compounds.

Therefore, the result of the acetic acid-induced writhing strongly suggests that the mechanism of this action may be linked partly to inhibition of lipoxygenase and or cyclooxygenece in the peripheral tissues, thereby reducing prostaglandin synthesis and interfering with the mechanism of transduction in primary afferent nociceptors. The Nociceptive property of the extract may be attributed to the presence of flavonoids and

phytosterol which are present in the plant.[12] However, the isolated flavonoid such as procumbentin and quercetin and sterols such as beta sitosterol may show more pronounced analgesic activity compared to the extract; in acetic acid-induced writhing.

CONCLUSION

In line with the findings of this study further studies are required to confirm that methanol extract of *Artocarpus altilis* at moderate non-lethal dose has a potent analgesic effect in acetic acid-induced writhing. This shows that the extract has marked beneficial effects against peripheral pain models. This protective action may be attributed to the presence of flavonoids and sterols.

RECOMMENDATION

Further investigations are ongoing in our Laboratory to elucidate the mechanism of action and elaborative investigations into its phytochemical composition to ascertain which active constituents are responsible for analgesic activity of *Artocarpus altilis*. These reports may serve as a foot step in the research of potent analgesic drug.

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