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Effects of *Xylopia aethiopica* ethanolic fruit extract And Diclofenac Sodium on Nociception, Inflammation and Sciatic Neuroarchitecture During Oxaliplatin Therapy of Wistar Rat.

Onwuka K.C.[1*], Okereke M.I.[2], & Iheukwumere C.B.[3]
[1,2,3]Department of Physiology, Faculty of Basic Medical Sciences, Abia State University.
[*]Corresponding Author Email: onwuka.kelechi@abiastateuniversity.edu.ng

ABSTRACT
Oxaliplatin therapy presents a dose-limiting neuropathic pain that causes neurological/systemic inflammation. *Xylopia aethiopica* (Negro pepper), as a medicinal plant, possesses analgesic properties. This study investigated the effects of ethanolic extract from *Xylopia aethiopica* on pain and inflammation in oxaliplatin therapy of Wistar rats. The rats were grouped into 5 groups (n=10): Except for the normal control, others were treated with oxaliplatin (8mg/kg of body weight, b.w.) once weekly. Toxicity study of *Xylopia aethiopica* Ethanoic Fruit Extract (XAEFE) indicated a lethal dose of 7,483.31 mg/kg b.w. Except for the negative control, others were treated daily with diclofenac sodium (analgesic) at 10 mg/kg b.w. (positive control), XAEFE at 400 mg/kg b.w. and XAEFE at 800 mg/kg b.w. respectively. Duration of treatments was 4 weeks after which they were assessed for nociception, Interleukin 1 beta (IL-1β), Interleukin 6 (IL-6) , monocytes and sciatic nerve histology. Writhing responses were significantly reduced in groups treated with XAEFE ($P<0.05$). However, when compared against all the groups except for normal control, the commercial analgesic significantly reduced the writhes at $P<0.05$. At $P<0.05$, the analgesic and XAEFE, at high dose, reduced the serum levels of IL-1β, IL-6 and monocytes when compared to negative group, with XAEFE showing increased reduction of IL-1β level when compared to the analgesic. Histological findings showed that XAEFE caused a normal sciatic nerve histology against those treated with the analgesic and oxaliplatin respectively. This study showed that *Xylopia aethiopica* may be more *effective than the analgesic* in offering protection against systemic inflammation and neurodegeneration.

Keywords:
Pain, inflammation, *Xylopia aethiopica*, *D*iclofenac, sciatic nerve

INTRODUCTION

Chemotherapy, as one of the main approaches to cancer treatment. However several antineoplastic drugs poses several adverse effects like chemotherapy-induced peripheral neuropathy) CIPN) which is usually characterized with severe pain, numbness, and sensory motor dysfunction, significantly affecting their quality of life (Park *et al*., 2012; Andre *et al*., 2018). All of these experiences may not be fatal but they eventually cause low quality of life of patients (Kanat, *et al*., 2017; Kinga, 2020).

Oxaliplatin-induced neuropathy is regarded as one of the commonest dose-limiting toxic effects of platinum-based antineoplastic drugs contributing to more than 60% of the neuropathy seen in patients receiving anticancer therapy. (Kinga, 2020, Zajaczkowska *et al., 2019*). It is commonly utilized for gastrointestinal tumors or, more specifically, colorectal cancer (CRC), and its neuropathy is classified into two categories.

The first is acute neuropathy (e.g., distal paresthesia, dysesthesias, and minor muscle spasm of the hands, feet, and perioral region), which is accompanied with cold allodynia in roughly 90% of patients and typically resolves within a week (Grothey, 2003). Chronic neuropathy is caused by the accumulation of oxaliplatin over the course of protracted treatment and affects around 24% of the world's population. (National Institute of Neurological Disorders and Stroke, 2022). The neuropathy induced by oxaliplatin therapy is, among other sub mechanism, a result of increased release of pro-inflammatory mediators such as interleukin- 1beta and tumor necrosis factor- alpha; (IL-1B and TNF-α) and mobilization of activated macrophages. These pain mediators eventually lead to mechanism that induce oxidative stress, alter ion channels and increased pain sensitivity (Oronsky *et al.,2017***;** Fumagalli *et al*., 2021; Antonio *et al*., 2022; Onwuka, 2025).

Xylopia aethiopica, also known as African pepper, It is a popular aromatic spice commonly used in traditional dishes like peppersoup (Nwidu *et al*., 2016). This spice has been of particular interest due to its anti-inflammatory and antioxidant effects, as it is commonly used in traditional medicine. It has shown promise in various studies for its potential anti-inflammatory, antioxidant, analgesic and neuroprotective properties (Nwidu *et al*., 2016) it is commonly used in form of the dried fruit decoction to treat bronchitis, asthma, arthritis and rheumatism in Ghana, Nigeria and Cameroon (Obiri, 2013). Earlier findings have established its anti-inflammatory activity in both acute and chronic inflammation in murine subjects (Obiri, 2014). The seeds are used for several purposes including as a post-partum tonic, to improve healing and stimulate milk production (Morankinyo, *et al.*, 2025) and as traditional remedy for cough, rheumatism, dysentery and malaria (Fetse, *et al*., 2016). However, there is paucity of information of the effect of *Xylopia aethiopica*, fruit seeds on nociception and inflammation in oxaliplatin therapy especially when compared with a common analgesic, diclofenac sodium, which is also a Non-steroidal Anti-inflammatory Drug (NSAID) and requires continous use in cases of inflammatory pain.

The study investigated the effects of *Xylopia aethiopica* on nociception and inflammation and sciatic neuroarchitecture in oxaliplatin therapy of Wistar rats.

MATERIALS AND METHODS

Purchase of Animal and Plant Material Extraction

for the study, 68 male wistar rats weighing between 120 - 150 grams were utilized in the study; 50 of the rats were used for the neuropathy investigation, and 18 of the rats were used for the extract's lethal dose (LD50) evaluation. Before the studies started, the animals were kept in aluminum cages and given two weeks to acclimate. Before, the studies began, the experimental rats were deprived for 12 hours from food and given free access to clean water and Chikkun finisher's mash (Chikkun Feed, Nigeria). International criteria for the care and management of laboratory animals were followed in all animal experiments (Orieke et al., 2019). The study was carried out at

Fresh *Xylopia aethiopica* fruits were obtained from Orie-Ugba market in Umuahia north Local Government Area of Abia State and were authenticated at the Department of plant science and bio technology, faculty of biological sciences, abia state university, Uturu. (voucher No: ABSU/FBS/49). They were left to dry under sunlight after which they were pounded into smaller particles using mortar and pestle and pulverized into powder using a locally made motor blender. Using the cold maceration method, crude extract was made from the powdered material. After macerating 300g of the powdered material in 2 liters of ethanol for 48 hours, it was doubly filtered using a Whatman filter paper and a clean handkerchief. After that, the filtrate was dried out in a lab oven at a low temperature of 40 oC to produce a dark brown, oily extract that weighed 17.20 g and had an extract yield percentage of 5.73. Before being used, the extract was kept at a low temperature in the refrigerator.

After acute toxicity study, a dose of 400mg/kg and 800mg/kg were selected for biomedical evaluation as low and high doses in the experiment. These, respectively, represent an approximation of $1/20^{th}$ and $1/10^{th}$ of the lethal dose and falls within the safe and acceptable range for experimental studies. They were given daily for 28 days.

Acute Toxicity Studies

The new Lorke's approach, which Orieke et al. (2019) used, was modified for the acute toxicity assessment of both crude extracts. Two test phases were employed. Nine wistar rats, divided into three groups (A, B, and C) of three rats each, were given 10, 100, and 1000 mg/kg of the extract in the first stage. After that, the animals were watched for symptoms of toxicity and any deaths within a day. After there were no reported deaths, the study moved on to the second phase, which also used nine rats divided into three groups (A–C). The groups were given single oral treatment dosages of 1600, 2900, and 5000 mg/kg, respectively. The animals were then monitored for toxicity indications and fatalities for another 24 hours and 7 days. Lorke's method was used to compute the lethal dose value of the extract based on the number of deaths documented across the groups :

Lethal dose;

$$LD50 = \sqrt{(D0\ x\ D100)}$$

Where:

D_0: Highest dose that gave no mortality.

D_{100}: Lowest dose that produced mortality

Quantitative Phytochemical Study

Preliminary Phytochemical experiments were conducted using the methods of Trease and Evans (1989), Harborne (1973), and Sofowora (1993), as cited in Deka and Kalita (2012).

Purchase, Concentration and Administration of Oxaliplatin and Diclofenac Sodium.

Oxaliplatin (VSI Oxaliplatin Lyophilized powder manufactured by Naprod Life Sciences Pvt. Ltd, India. NAFDAC Registration Number (NRN): B4-3208. Anatomical Therapeutic Chemical (ATC) code: L01XA03) was used. It was bought in powder form from an Enugu pharmacy. In contrast to unstable saline solutions, a stock solution of 1 mg/ml in 5% dextrose solution will be created for injection administration for storage reasons for 30 days (Mehta et al., 2015). In this investigation, rats were given a dosage of 8 mg/kg of

body weight (b.w.). The modified approach of Ito et al. (2019) was employed because it implied both systemic inflammation and peripheral neuropathy. Over the course of four weeks, oxaliplatin was given once a week on Days 1, 8, 15, and 22.

Diclofenac sodium powder was purchased in tablet forms (Diclofenac 50mg, manufactured by Auscel Laboratories Limited (Nigeria), NRN=A11-1288, ATC-code: M01AB05. The tablets are crushed. 50mg of the drug was dissolved in 50 ml of distilled water to obtain a stock solution of 1mg/ml (3.14 mM). They were stirred in a magnetic stirrer and left. from this stock, 10mg (10mg/ml of stock solution) was used for administration in positive control. This method was adopted from Ismail *et al* (2024) and David, *et al* (2017).

Experimental design for the study

Fifty (50) rats assigned to 5 groups of 10 rats each were treated according to the order below:

Table 1: Group Administrations

Group	Group Name	Dministration(s) given to groups
1	Normal control	Normal saline (10 mil/kg of body weight of rat; mg/kg b.w
2	Negative control	Oxaliplatin (8 mg/kg b.w)
3	Positive control	Oxaliplatin (8 mg/kg b.w) + Diclofenac sodium (10 mg/kg b.w)
4	**Low Dose**	Oxaliplatin (8 mg/kg b.w) + *Xylopia aethiopica* extract (400 mg/kg b.w
5	**High Dose**	Oxaliplatin (8 mg/kg b.w) + *Xylopia aethiopica* extract (800 mg/kg b.w)

Oxaliplatin was administered intraperitoneally, whereas the extract was given orally. All treatments lasted 28 days. An electronic balance (DJ-A1000, China) was used to measure body weight at the beginning and completion of the treatment. At the end of the experiment, the animals were tested for writhing nociception, euthanized, and tissues were taken for histological research and the examination of inflammatory and oxidative stress markers. Histological tests were conducted on the sciatic nerve and pro-inflammatory biomarkers (IL-1β). Tumor necrosis factor (TNF-α) and monocytes were tested utilizing essay kits and laboratory methods.

Evaluation of Responses of Treated Animals To acetic acid-induced pain Stimulus

The method used by Ijioma et al., (2014) was adopted. Twenty five of the treated rats assigned to their groups as previously mentioned were used for tis test. Each rat received an intraperitoneal (I.P) injection of 0.6% acetic acid at a dosage of 10 mL/kg body weight. Each rat's writhes (stretching of the rear limbs and bending of the trunk) were recorded for 30 minutes. Percentage inhibition was calculated using the following expression:

$$\%\ inhibition = ([Wc - Wt]x100)/Wc$$

Where:

Wc = Writhes in control

Wt = Writhes in test

Analysis of Results

The Statistical Package for Social Sciences (SPSS, Version 20.0, IBM SPSS Inc, Chicago, IL) was used for data analysis. One-way Analysis of Variance (ANOVA) was used, and data were evaluated using the Duncan Multiple Range Test, supplemented with the Student's t test for post-hoc comparisons of the means of the various doses and fractions. P-values less than 0.05 were statistically regarded as significant differences between the test and control groups, as well as between test groups in terms of measured value.

RESULTS AND DISCUSSION

Results of phytochemical analysis of *Xylopia aethiopica* extract

Table 2 provides quantitative and qualitative results of the phytochemical analysis of *Xylopia aethiopica* extract. It showed that the extract has a high concentration of flavonoids, phenols, alkaloids, and saponins with highest concentrations of flavonoids followed by saponins and phenols respectively. The study also showed that the extract levels of cardiac glycosides are the lowest, followed by steroids and Tannins.

Table 2: Results of quantitative phytochemical analysis of *Xylopia aethiopica* extract

Phytochemicals	Quantitative results (mg/100 g)	Qualitative results
Alkaloids	27.42±0.29	++
Tannins	9.75±0.11	++
Flavonoids	32.24±1.93	+++
Phenols	21.57±0.48	++
Terpenoids	7.23±0.12	+
Saponins	23.55±0.37	+++

Cardiac glycosides	2.02±0.11	+
Steroids	4.69±0.09	+

Values are presented as mean ± standard deviation.

Results of acute toxicity evaluation of *Xylopia aethiopica* extract in rats

Within 24 hours and 7 days, graded dosages of the extract up to 5600 mg/kg caused no mortality in rats and no symptoms of severe toxicity such as tremors, convulsions, writhing reflexes, or agitations. However, 66.67% mortality was found in the third phase and group administered 7000 mg/kg body weight, but all rats in the 10,000 mg/kg treated group perished, resulting in 100% mortality. The application of Lorke's formula produced an LD50 value of 7,483.31 mg/kg b.w for the extract in rats. The results leading to the calculated LD50 are presented in Table 3.

Table 3: Acute toxicity (LD_{50}) evaluation of the extract in rats

Stage 1 of Acute toxicity (LD_{50}) evaluation of the extract in rats				
Group	**Dose (mg/kg)**	**No. of Deaths**	**Percentage of mortality**	Observation(s)
1a	10	0/3	0.00	No notable changes were observed
1b	100	0/3	0.00	No notable changes were observed
1c	1000	0/3	0.00	No notable changes were observed
Stage 2 of Acute toxicity (LD_{50}) evaluation of the extract in rats				
2a	1600	0/3	0.00	No notable changes were observed
2b	2900	0/3	0.00	No notable changes were observed
2c	5000	0/3	0.00	The free movement of rats were slowed. A rat showed regular refrain from others and food
Stage 3 of Acute toxicity (LD_{50}) evaluation of the extract in rats				
3a	5600	0/3	0.00	Animals started isolated themselves from each other. Occasional food refrain was observed
3b	7000	2/3	0.00	Food restraint became less frequent with weakened eyes and mild toxicity signs.
3c	10000	3/3	0.00	All animals die after the other with severe toxicity signs.

$LD_{50} = (5600 \times 10000)^{1/2}$

LD_{50} = 7,483.31 mg/kg body weight

Mild toxicity signs = calmness, restlessness, agitations and loss of motor coordination.

Severe toxicity signs = Tremor, convulsions, writhing reflexes, roughness of hairs and death.

Result of the effect *Xylopia aethiopica* on pain modulators.

The findings displayed in Table 4 showed that the high-dose XAEFE (800 mg/kg) significantly reduced IL-1β and IL-6 levels when compared to all treated groups including those of diclofenac at $P<0.05$. the diclofenac treated group also showed reduced the inflammatory biomarkers, at $P<0.05$, in comparison to the negative control. For the monocytes, there was no significance changes across the groups at $P<0.05$. Monocytes levels were significantly unchanged across treated group though there were elevated when compared to the normal control at $P<0.05$.

Table 4: Effect of *Xylopia aethiopica* Extract on Levels Of Pain Modulators in Oxaliplatin-Induced Peripheral Neuropathic Rats

Treatment groups	IL-1β (pg/ml)	IL-6 (pg/ml)	Monocytes (%)
Normal control	0.29 ± 0.04^{a}	26.88 ± 2.02^{a}	3.80 ± 0.45^{a}
Negative control (Oxaliplatin , 8 mg/kg)	1.46 ± 0.16^{d}	58.96 ± 3.71^{e}	4.80 ± 0.45^{b}
Diclofenac sodium (10 mg/kg) + Oxaliplatin (8 mg/kg)	1.07 ± 0.05^{c}	45.50 ± 1.41^{c}	$4.40\pm0.55^{a,b}$
Xylopia aethiopica extract (400 mg/kg) + Oxaliplatin (8 mg/kg)	$1.00\pm0.05^{b,c}$	50.72 ± 0.87^{d}	4.80 ± 0.45^{b}

Xylopia aethiopica extract (800 mg/kg) + Oxaliplatin (8 mg/kg)	0.93±0.03[b]	41.02±2.58[b]	4.60±0.55[b]

The data is shown as mean ± standard deviation (n = 10). Values with different superscripts indicate significant differences from the paired mean within the column.

Result on Evaluation effect of *Xylopia aethiopica* on Analgesic (Writhing) Response

Table 5 outlines the effects of *Xylopia aethiopica* extract on responses to pain stimulus in rats with Oxaliplatin-induced peripheral neuropathy. Notably, the analgesic, Diclofenac showed a strong pain inhibition (47.39 %) when compared to other treated groups at P<0.05. However, XAEFE showed increased pain inhibition activity when compared to the writhes of the negative control (71.67), even though there was no significant differences between the percentage pain inhibitions of its low (14.34%) and high doses (17.60%).

Table 5: Effect Of *Xylopia aethiopica* Extract On Analgesic (Writhing) Response

Treatment groups	Writhes in 30 minutes	Percentage inhibition of pain stimulus when compared with normal control	Percentage inhibition of pain stimulus when compared with Negative control
Normal control	53.33±3.51[b]	-34.12±5.87[c]	25.51±4.91[c]
Negative control (Oxaliplatin , 8 mg/kg)	71.67±3.06[d]	-29.33±7.81[a]	0.00±0.00[a]
Diclofenac sodium (10 mg/kg) + Oxaliplatin (8 mg/kg)	37.67±4.16[a]	15.07±6.03[d]	47.39±5.81[d]
Xylopia aethiopica extract (400 mg/kg) + Oxaliplatin (8 mg/kg)	61.33±3.22[c]	-10.69±6.78[b]	14.34±4.49[b]
Xylopia aethiopica extract (800 mg/kg) + Oxaliplatin (8 mg/kg)	59.00±3.61[b,c]	-6.11±2.19[b,c]	17.60±5.03[b,c]

The data is shown as mean ± standard deviation (n = 10). Values with different superscripts indicate significant differences from the paired mean within the column.

Result of histopathology of sciatic nerve

Histological analysis suggested that oxaliplatin caused a Fibrous thickening of perineurium (degenerative change) which was normalized by high dose of XAEFE comparatively similar to te normal control. The low dose of extract caused Mild perineurial thickening as the diclofenac group displayed normal fascicular arrangement with thin perineurium similar to those of the diclofenac treatment.

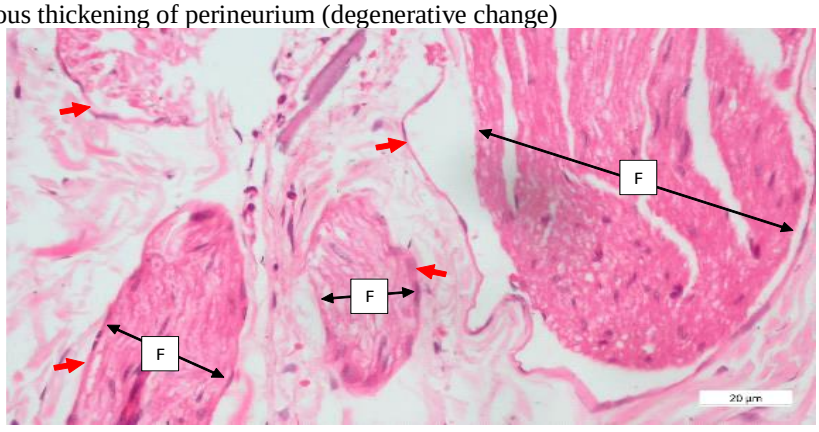

Figure 1: histology of the sciatic nerve in group 1: Sections of the sciatic nerve in this group showed normal nerve fascicles grouped in bundles (F) surrounded by thin perineurium (red arrow). H&E x400

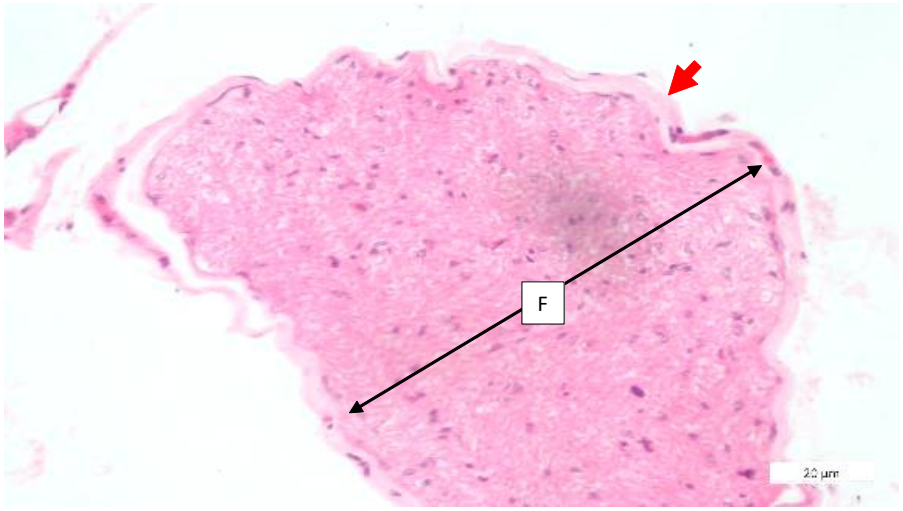

Figure 2: histology of the sciatic nerve in group 2. Sections of the sciatic nerve in this group showed normal nerve fascicles grouped in bundles (F) surrounded by **thickened perineurium** (red arrow). Note: Fibrous thickening of the perineurium is a degenerative change. H&E x400

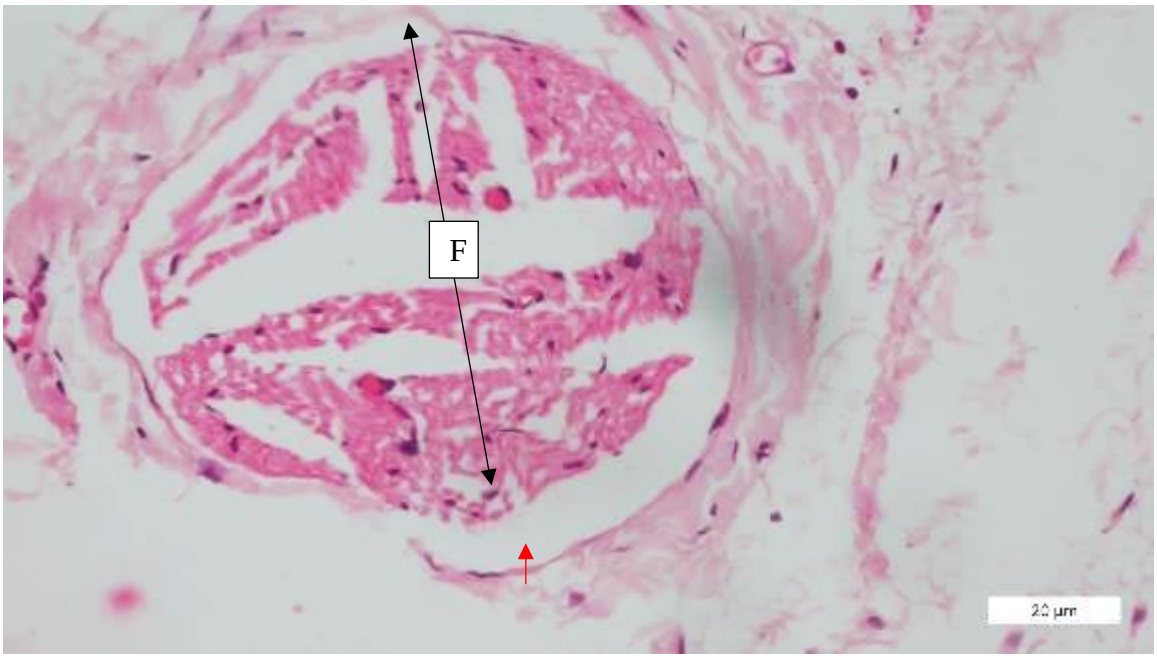

Figure 3: histology of the sciatic nerve in group 3. Sections of the sciatic nerve in this group showed normal nerve fascicles grouped in bundles (F) surrounded by thin perineurium (red arrow). H&E x400.

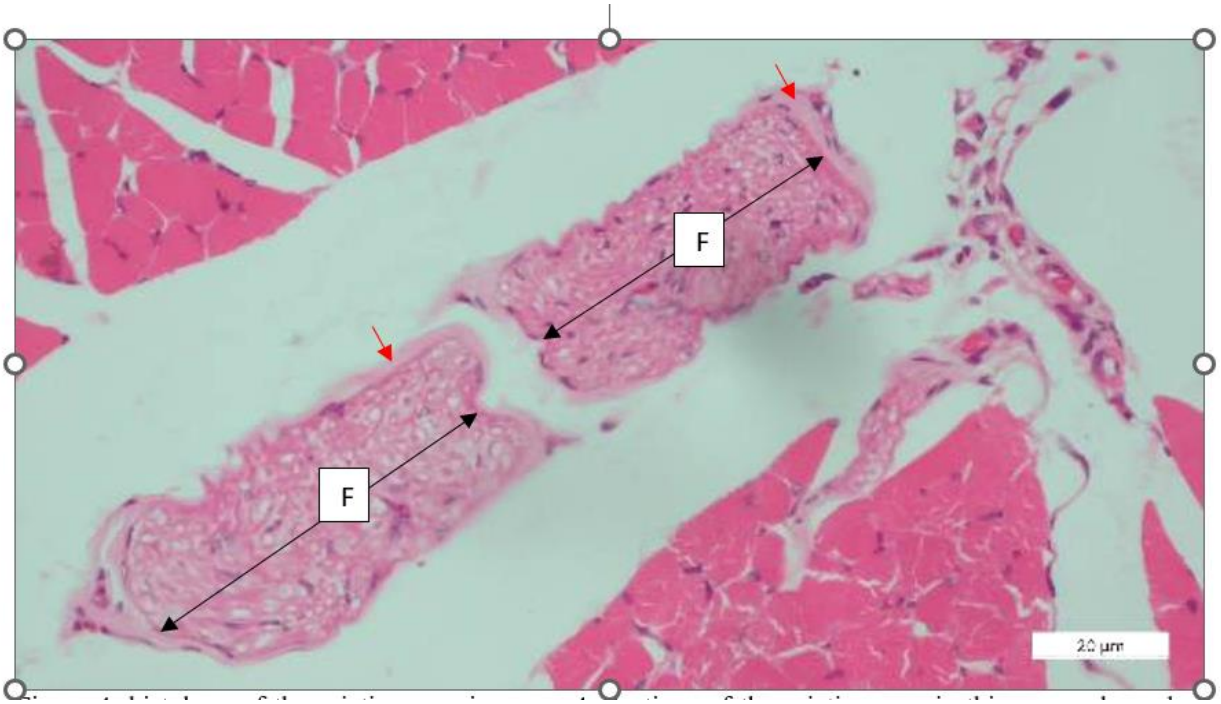

Figure 4: histology of the sciatic nerve in group 4. Sections of the sciatic nerve in this group showed normal nerve fascicles grouped in bundles (F) surrounded by relatively thick perineurium (red arrow). H&E x400

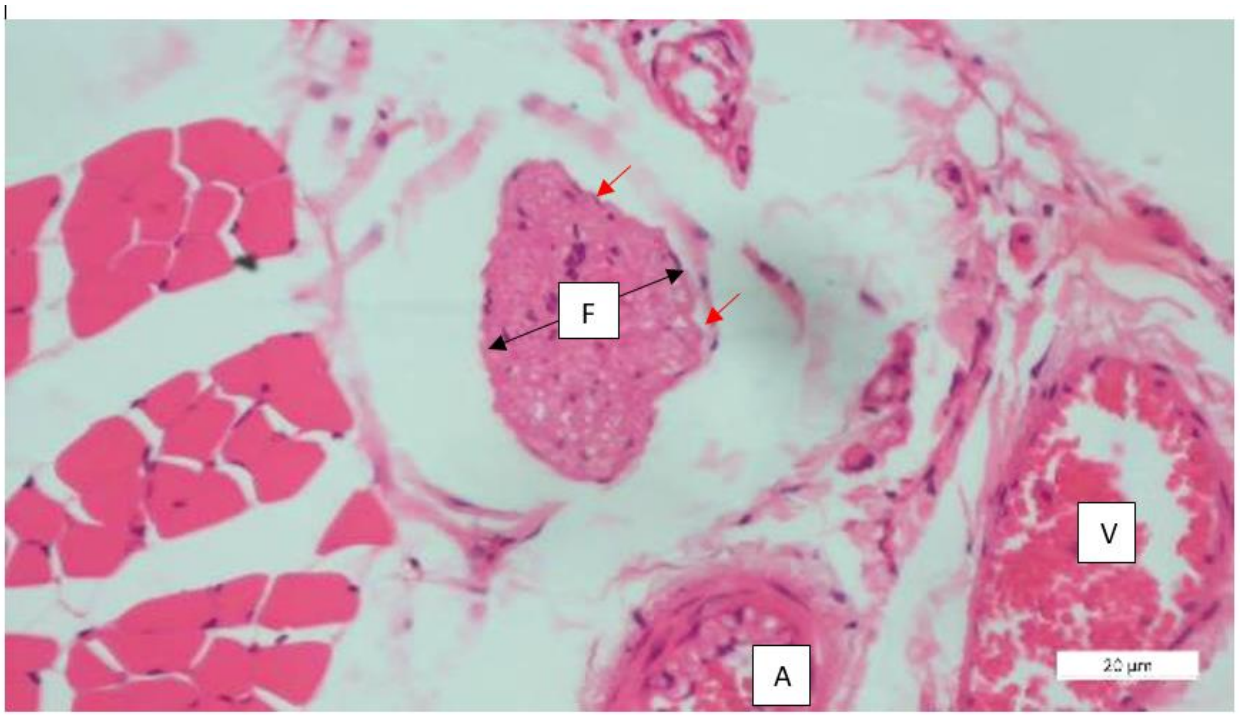

Figure 5: histology of the sciatic nerve in group 5. Sections of the sciatic nerve in this group showed normal nerve fascicles grouped in bundles (F) surrounded by thin perineurium (red arrow). Blood vessels: vein (V); artery (A). H&E x400

This investigation the effects of *Xylopia aethiopica* ethanolic fruit extract (XAEFE) on nociception, inflammatory mediators, and sciatic nerve histology in oxaliplatin therapy, with diclofenac sodium (anti-inflammatory analgesics) serving as a standard comparator**.**

The strong flavonoid presence in the current study supports earlier pharmacological assertions that the plant's therapeutic actions are largely driven by antioxidant scavenging, cytokine suppression and cell membrane stabilization (Morakinyo, et al., 2025; Ehigiator & Adikwu, 2020).

The study showed that XAEFE has a LD_{50} value of 7,483.31 mg/kg indicated that the extract has a **wide margin of safety**. No mortality occurred up to 5,600 mg/kg, and only high doses (≥7,000 mg/kg) produced toxicity. This finding is consistent with the work of Ehigiator & Adikwu (2020), who also reported relative safety of *Xylopia aethiopica* extracts at therapeutic doses. This is a good outcome suitable for further physio-pharmacological examination or development

The elevated IL-1β and IL-6 caused by oxaliplatin administration was expected and consistent with established mechanisms of oxaliplatin induced neuropathy and inflammation (Oronsky, *et al.,* 2017; Yang, *et al.*, 2021; Fumagalli, *et al*., 2021) which indicated that cytokine over-expression is central to the chemotherapy induced neuropathy. This effect of oxaliplatin was observed in the work of Onwuka (2025) who stated inflammatory oxidative stress as a major pathogenesis of Oxaliplatin toxicity. Though diclofenac exhibited strong analgesic responses, XAEFE showed stronger anti-inflammatory activities as demonstrated in the histopathological findings. This difference may be due to the fact that, unlike diclofenac whose primary pathyway is inhibition of cycloxygenase (COX) pathway, *Xylopia aethiopica* may be involved with upstream modulation of cytokine suppression and oxidative stress pathways as observed by Obiri (2014) in murine inflammatory models and Román-Pintos et al. (2016) who emphasized the importance of antioxidant-mediated cytokine suppression in neuropathy attenuation. Moreover, *Xylopia aethiopica* extract displayed analgesic properties which was consistent with the findings of Ijioma et al. (2014) whose methodology was replicated. The effective reduction of IL-1β by the high of the seed in comparison to diclofenac is a critical findings because IL-1β is strongly implicated in neuropathic pain sensitization and neuroinflammatory cascades. The inflammatory action of the plant seed is strongly attributed to its rich flavanoid content while its analgesic effects may be attributed to its rich alkaloid content (Earnest & Goodies, 2014; Fetse, *et al.*, 2016; Morakinyo, *et al.,* 2025).

The unchanged levels of monocytes after invention treatment indicates that *Xylopia aethiopica* exhibits anti-inflammatory responses without immunosuppressive cell depletion. This is a desirable therapeutic outcome (Dinarello, 2011; Tanaka, *et al*., 2014; Hunter, *et* al., 2015) Oxaliplatin therapy causes perineurial thickening, which is consistent with prior observations of other studies. (Ling, *et al.*, 2007; Zajaczkowska, *et al.*, 2019). The normalization of perineurium thickness by the high dose of *Xylopia aethiopica* suggests structural neuroprotection potential which is beneficial for the preservation of nerve architecture. (Fumagalli, *et al.*, 2021). It is a good finding and advantage of *Xylopia aethiopica* over diclofenac most probably a function of its rich alkaloid content (Ehigiator and Adikwu, 2020; Morakinyo, *et al.*, 2025**).** It is particularly significant because neuropathic pain involves not only inflammatory signaling but also structural nerve alterations.

CONCLUSION

This study demonstrated that *Xylopia aethiopica* exerts significant anti-inflammatory, anti-nociceptive, and neuroprotective effects in oxaliplatin therapy. Although diclofenac remains superior for acute analgesia, the high dose of *Xylopia aethiopica* showed stronger cytokine suppression and preservation of nerve histoarchitecture, indicating promising therapeutic potential in the treatment of peripheral neuropathy caused by chemotherapy. These findings support further mechanistic and translational patent investigations for chronic toxicity profile, dose optimization, therapeutic uses/ combined therapy with NSAIDs. A further investigation into mechanistic pathways using induced inhibition is necessary to ascertain specificity of actions of the plant seed.

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