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Ameliorative potentials of Kolaviron and *Brophyllum pinnatum* extract on IBA-1, GFAP, cytochrome p450 and xanthine oxidase in $AlCl_3$-induced neurotoxicity in rats

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Abstract

This study aimed at investigating the comparative effect of kolaviron and ethanolic leaf extract of *Brophyllum pinnatum* on Aluminium Chloride induced Neurotoxicity in male Wistar rats. Thirty-five (35) Wistar rats weighing 150-250g were randomly divided into 7 groups of 5 rats each. Group 1 as the control group, group 2 (Aluminium chloride) was given $AlCl_3$ orally at a dose of 100mg/kg btw. Group 3 (kolaviron (kv) only) was given 200mg/kg bwt of Kv. Group 4 (*Brophyllum pinnatum* only) was given 600mg/kg bwt of ethanolic extract of *B. pinetum* (Bp). Group 5 ($AlCl_3$ + Bp). Group 6 ($AlCl_3$ + Kv), and Group 7 ($AlCl_3$ + Bp + Kv). All groups took normal rat chow and water *ad libitum* for 28 days. The results showed a significant ($p<0.05$) increase in the serum level of CYP450 in $AlCl_3$ (1.30±0.12) when compared with the control (0.15±0.03), $AlCl_3$+Bp (0.55±0.03), $AlCl_3$+Kv (1.00±0.23) and $AlCl_3$+Kv+Bp (1.00±0.01). The serum level of xanthine oxidase in $AlCl_3$ was 1.65±0.09, showing a significant ($p<0.05$) increase in Xanthine oxidase compared with the control (0.15±0.03), and other experimental groups. A significant ($p<0.05$) increase in GFAP levels was recorded in $AlCl_3$ (24.8±2.5) compared with control and other groups. Also, significant increase in IBA-1 level was recorded in the $AlCl_3$ (24.8±2.5) compared with control and other experimental groups. In conclusion, administration of *Brophyllum pinnatum* and kolaviron ameliorated the neurotoxicity induced by $AlCl_3$, probably via their anti-oxidative, anti-inflammatory and anti-apoptotic potentials.

Keywords: *B. pinnatum; Kolaviron;* $AlCl_3$; IBA-1; GFAP; Cytochrome P450; Xanthine oxidase

1. Introduction

Neurotoxicity is a condition where harmful substances disrupt the structure or function of the nervous system, it has become an increasing global concern, (Muralidharan and Swetha, 2023; Fang *et al*., 2022; Heneka *et al*., 2022). In recent years, the rise in exposure to industrial chemicals, environmental pollutants, and certain pharmaceuticals has heightened the risk of damage to the brain and nerves. Among these toxic agents like aluminium chloride ($AlCl_3$ has drawn special attention for its harmful impact on the brain (Anyanwu *et al*., 2024; Jadhav and Kulkarni, 2023; Exley, 2023; Niu,2023). Continuous exposure to $AlCl_3$ leads to its gradual accumulation in neural tissues, promoting oxidative stress, inflammation, and mitochondrial dysfunction, all of which contribute to the onset and progression of neurodegenerative disorders such as Alzheimer's disease (Kaur & Gill, 2006; Kumar *et* al., 2020; Was et al., 2022; Cardenas-Iniguez et al., 2022).

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This study seeks to explore the comparative neuroprotective roles of kolaviron and the ethanolic leaf extract of *Brophyllum pinnatum* (*Bryophyllum pinatum*) in mitigating $AlCl_3$-induced brain injury. Kolaviron, a bioactive biflavonoid complex extracted from Garcinia kola (bitter kola), and *Bryophyllum pinatum*, widely known as the "Miracle Leaf," are both valued in African traditional medicine for their antioxidant, anti-inflammatory, and healing properties (Iwu, 2014; Ojewole, 2005). These plants have long been used in the management of several ailments, yet their potential in combating aluminum-induced brain toxicity remains underexplored (Ujong, 2025; Justin *et al*., 2025; Kayinu *et al*., 2024; Althagafi, 2024).

To understand how these natural compounds influence the brain under toxic stress, the study evaluates a set of critical biomarkers: IBA-1 (a marker of microglial activation and inflammation), GFAP (an indicator of astrocyte reactivity), Cytochrome P450 (an enzyme responsible for detoxifying harmful compounds), and Xanthine Oxidase (a major source of free radical production and oxidative damage). Alterations in the levels or activity of these markers provide insight into how $AlCl_3$ disrupts normal brain processes and how plant-based compounds can modulate or reverse such effects (Wang et al., 2021; Zhou et al., 2020; Chen et al., 2019; Kumar et al., 2022).

By comparing the responses of these biomarkers to treatment with kolaviron and *Brophyllum pinnatum* extract, the research aims to determine which of the two agents offers greater neuroprotection and how they each contribute to restoring biochemical stability in the brain. The findings are expected to broaden our understanding of plant-derived neuroprotective mechanisms and highlight the value of indigenous medicinal plants as safer, accessible, and affordable alternatives to synthetic drugs (Ijomone et al., 2013; Olaleye et al., 2010; Nwankwo et al., 2000; Abarikwu *et al*., 2016).

Ultimately, this work underscores the importance of natural therapies in addressing brain health challenges linked to environmental toxins. It hopes to provide a scientific foundation for using locally available plants such as Garcinia kola and Kalanchoe pinnata as potential preventive or therapeutic options for neurodegenerative diseases, especially in regions where modern medical interventions are either limited or costly (Akinmoladun et al., 2007).

2. Materials and methods

Chemical reagents used were ethanol (98–99%, BDH Chemicals Ltd. Poole, England), chloroform, methylated spirit, and 10% formalin. **Equipment** utilized included a haematocrit centrifuge, microscope, weighing balance, homogeniser, blender (Allyson model FY-999), stirrer, pipette, and sample bottles (EDTA and plain)

2.1. Methodology

2.1.1. Plant Collection and Extraction

Fresh leaves of *Bryophyllum pinatum* were purchased from Ugep, Cross River State, and authenticated by a botanist at the University of Calabar. The leaves were washed and air-dried, pulverised, and soaked in ethanol (98–99%) for 24 hours and then filtered with whatman no. 1 filter paper. The filtrate was air-dried to obtain a paste with a 5.3% yield, which was refrigerated at 4 °C for subsequent use. The ethical approval was gotten from University of Cross River State (UNICROSS) with voucher number FBMS/UNICROSS/25/013.

2.1.2. Experimental Animals and Grouping

Forty (40) adult Wistar rats (60–170 g) were obtained from the Department of Medical Physiology, UNICROSS, and acclimatized for two weeks under controlled environmental conditions (12 h light/dark cycle, 27 °C). The animals were randomly divided into seven groups (n = 6).

Control group was fed with normal rat chow and drinking water, group 2 ($AlCl_3$ only) had 100 mg/kg of aluminium chloride orally. Group 3 (Kolaviron only) received 200 mg/kg of kolaviron orally, while group 4 (Extract only) took ethanolic extract of *B. pinnatum* 600 mg/kg orally. Group 5 was $AlCl_3$ + extract group, while group 6 was $AlCl_3$ + Kolaviron and group 7 was $AlCl_3$ + Kolaviron + extract group. All groups received normal rodent chow and drinking water *ad libitum* for 28 days.

2.1.3. Determination of IBA-1

Brain tissues was collected from the animals and preserved (in formalin)**.** Then, sections were made and stained using immunohistochemistry (IHC) to detect and visualize IBA-1. This allows us to see where and how much of the protein was present. Alternatively, ELISA may be used to quantify the exact amount of IBA-1 in brain homogenates.

2.1.4. Determination of GFAP

Immunohistochemical staining using anti-GFAP antibodies reveals how astrocytes respond to $AlCl_3$ exposure and treatment. Under the microscope, the intensity and spread of GFAP staining showed how much astrocyte activation had occurred. An ELISA test can also be used to measure GFAP levels quantitatively.

2.1.5. Determination of cytochrome P450

The activity of Cytochrome P450 was measured using an enzyme assay, where the brain tissue was homogenised and tested for specific enzyme reactions. The rate of these reactions was tracked using a spectrophotometer, which detected colour changes indicating enzyme activity.

2.1.6. Determination of xanthine oxidase

Xanthine oxidase (XO) activity was measured using a colorimetric enzyme assay, where xanthine is converted to uric acid in the presence of XO. The rate of this reaction was measured using a spectrophotometer, giving a clear indication of oxidative stress levels in the brain

2.2. Statistical Analysis

Data expressed as mean ± SEM. One-way ANOVA with Tukey's post hoc test was used for multiple comparisons; $p< 0.05$ considered significant.

3. Results

3.1. Cytochrome P-450 level in the different experimental groups

The result of the serum CY P-450 level (pg/mL) in the control, aluminium chloride ($AlCl_3$); Kolaviron; *Brophyllum pinnatum* (Bp), $AlCl_3$ + Kv; $AlCl_3$ + Bp and $AlCl_3$ + Kv + Bp were (0.15±0.03), (1.20±0.12), (0.25±0.02), (0.25±0.03), (0.55±0.03), (1.00±0.23), (0.30±0.00) respectively. The result presented shows a significant increased level $p<0.05$ in $AlCl_3$ when compared with the control value, which was significantly ($p<0.05$) reduced towards control value by administration of kolaviron and *Brophyllum pinnatum,* figure 1.

3.2. Serum xanthine oxidase level in the different experimental groups

The result of the serum Xanthine Oxidase level (mg/mL) in the control, aluminium chloride ($AlCl_3$); Kolaviron; *Brophyllum pinnatum* (Bp), $AlCl_3$ + Kv; $AlCl_3$ + Bp and $AlCl_3$ + Kv + Bp were (0.15±0.05), (1.65±0.09), (0.30±0.06), (0.30±0.06), (0.70±0.35), (0.90±0.01), (0.50±0.01) respectively. The result presented shows a significant increased level $p<0.05$ in $AlCl_3$ group when compared with the control, which was significantly ($p<0.05$) reduced towards control by intervention of kolaviron and Bp extract, figure 2.

3.3. GFAP level in the different experimental groups

The result of the serum GFAP level in the control, aluminium chloride ($AlCl_3$); Kolaviron; *Brophyllum pinnatum* (Bp), $AlCl_3$ + Kv; $AlCl_3$ + Bp and $AlCl_3$ + Kv + Bp were (5.3±0.8), (24.8±2.5), (7.1±0.9), (8.2±1.0), (8.2±1.1), (13.5±1.8), (11.2±1.4) respectively. The result obtained shows a significant increased level ($p<0.05$) between $AlCl_3$ only treated group when compared with the control, but was reduced towards normal following administration of kolaviron and *Brophyllum pinnatum*. Figure 3

3.4. IBA-1 level in the different experimental groups

The result of the serum IBA1 level in the control, aluminium chloride ($AlCl_3$); Kolaviron; *Brophyllum pinnatum* (Bp), $AlCl_3$ + Kv; $AlCl_3$ + Bp and $AlCl_3$ + Kv + Bp were (5.3±0.8), (24.8±2.5), (7.1±0.9), (8.2±1.0), (13.5±1.8), (13.5±1.8), (11.2±1.4) respectively. The result shows a significant ($p<0.05$) increase between $Alcl_3$ only treated group when compared with the normal control, which was reduced towards normal by intervention of kolaviron and *Brophyllum pinnatum*. Figure 4.

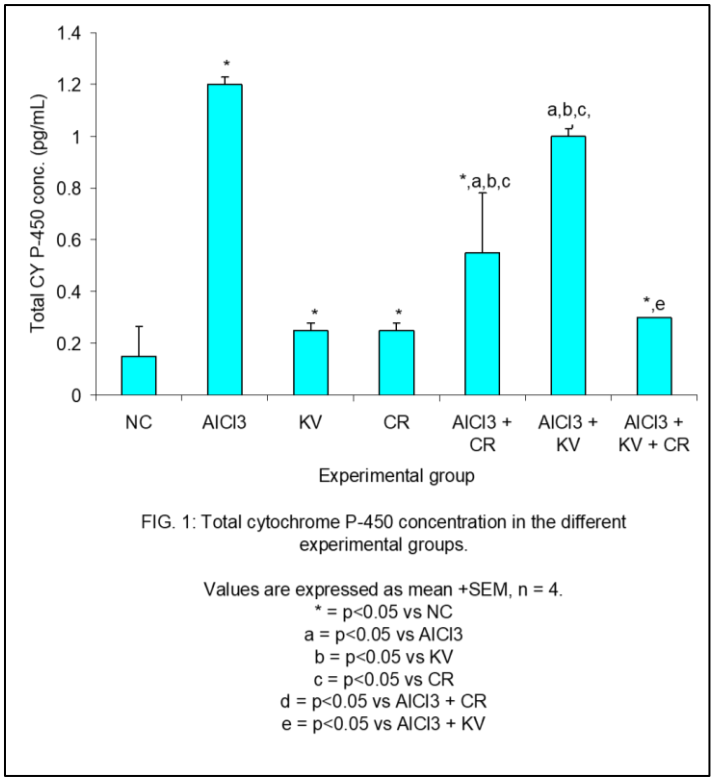


FIG. 1: Total cytochrome P-450 concentration in the different experimental groups.

Values are expressed as mean +SEM, n = 4.
* = p<0.05 vs NC
a = p<0.05 vs AlCl3
b = p<0.05 vs KV
c = p<0.05 vs CR
d = p<0.05 vs AlCl3 + CR
e = p<0.05 vs AlCl3 + KV

Figure 1 Total cytochrome p=450 concentration in the different experimental group

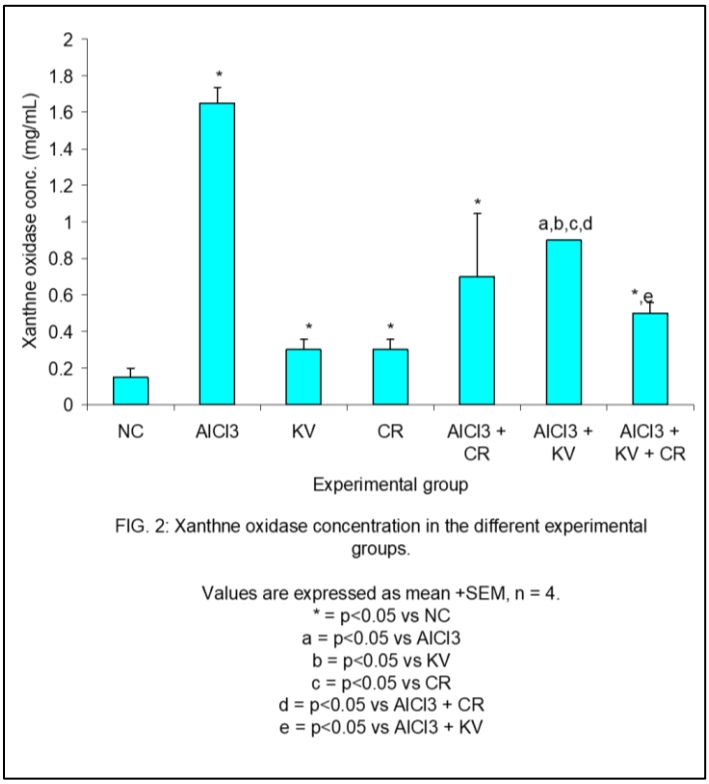
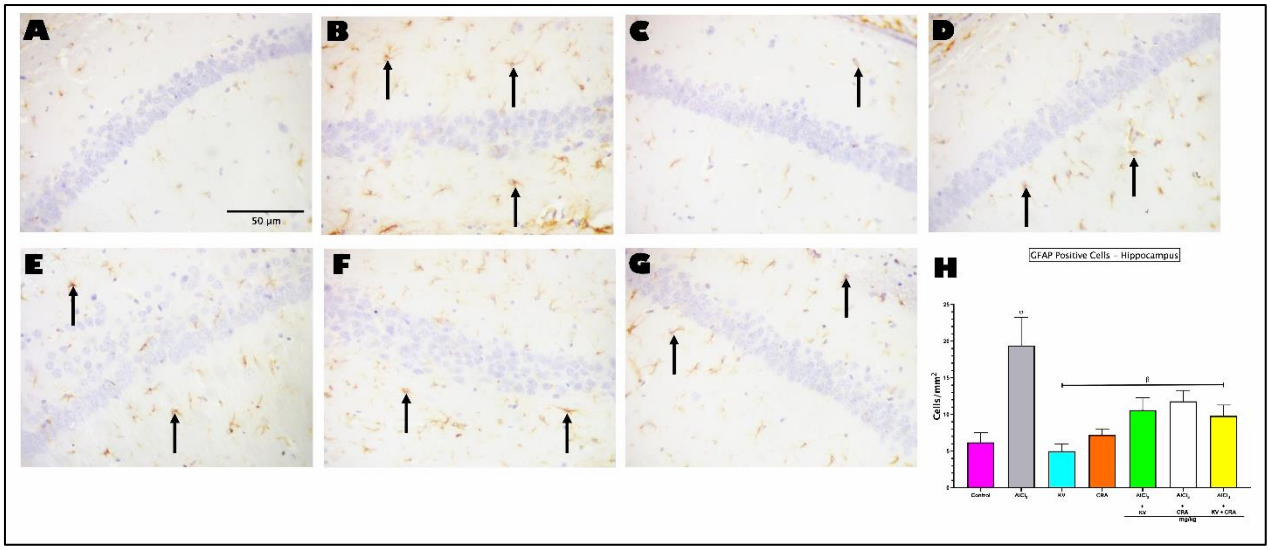


FIG. 2: Xanthne oxidase concentration in the different experimental groups.

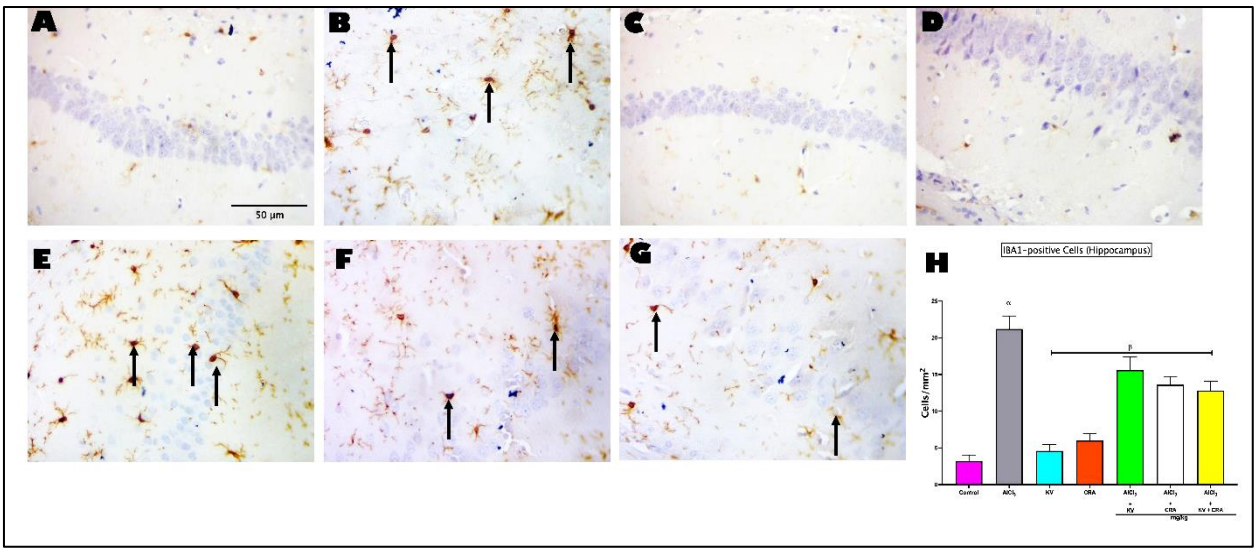
Values are expressed as mean +SEM, n = 4.
* = p<0.05 vs NC
a = p<0.05 vs AlCl3
b = p<0.05 vs KV
c = p<0.05 vs CR
d = p<0.05 vs AlCl3 + CR
e = p<0.05 vs AlCl3 + KV

Figure 2 Xanthine oxidase concentration in the different experimental groups.



Black arrows indicate GFAP positive astrocytes. H shows image J analysis of GFAP positive cell count in the hippocampus (CA3); Values are expressed as mean +SD, n = 5. Magnification x400.Scale bars 50 µm.Black arrow indicates IBA1-positive Microglia.

Figure 3 Photomicrograph showing immunohistochemical staining of GFAP positive cells in hippocampus of the different experimental groups (A-G).



Black arrows indicate GFAP positive astrocytes. H shows image J analysis of IBAS positive cell count in the hippocampus (CA3). Values are expressed as mean +SD, n = 5. Magnification x400.Scale bars 50 µm.Black arrow indicates IBA1-positive Microglia.

Figure 4 Photomicrograph showing immunohistochemical staining of IBA1 positive cells in hippocampus of the different experimental groups (A-G).

4. Discussion This study explored the modulatory roles of Kolaviron (KV) and ethanolic leaf extract of *Brophyllum pinnatum* (Cr) on aluminium chloride ($AlCl_3$)-induced neurotoxicity in Wistar rats

IBA-1 (Ionized Calcium-Binding Adaptor Molecule 1) is a protein mainly found in **microglial cells,** which are like the brain's clean-up/mop-up crew and first responders during injury or inflammation. When the brain is under stress or injured (as in the case of $AlCl_3$ toxicity), these microglia become activated and start expressing more IBA-1. High levels of IBA-1 suggested that the brain was reacting to an injury or threat, (Yamada *et al*., 2022; Hanamsagar *et* al.,2022; Wang *et al*., 2021; Kobayashi *et al*., 2020).

GFAP (Glial Fibrillary Acidic Protein) is found in astrocytes, this is a type of support cell in the brain. When the brain faces an injury or chemical stress, these astrocytes become more active and produce more GFAP. So, if GFAP levels are

high, it's usually a sign that the brain is inflamed or trying to repair itself, (Zhang *et* al.,2023; Zhou *et al.,* 2020; Moeton *et al*.,2014).

Cytochrome P450 enzymes are essential for detoxifying harmful compounds in the body. These enzymes are important for breaking down toxins and drugs in the body, including in the brain. When the brain is exposed to harmful substances like $AlCl_3$, it can affect how these enzymes function. An imbalance in CYP450 activity may either reduce the brain's ability to detoxify or cause excessive production of harmful by-products (Was *et al*., 2022; Cybel,2023).

Xanthine oxidase (XO) is an enzyme involved in purine metabolism—a normal part of cell energy use. However, when XO becomes too active, it can produce large amounts of reactive oxygen species (ROS), which can damage brain cells. High XO activity is a sign of oxidative stress, which plays a big role in $AlCl_3$-induced neurotoxicity (Stratoulias *et a.,* 2019; Battelli *et al*.,2016; Pacher *et al*., 2006).

Results from this study revealed that $AlCl_3$ exposure significantly elevated oxidative and neuroinflammatory markers CYP450, Xanthine Oxidase (XO), GFAP, and IBA-1—indicating neuronal damage, oxidative stress, and glial activation. These results align with earlier studies showing that aluminium disrupts neuronal redox balance and promotes neurodegenerative changes (Exley, 2014).

Treatment with Kolaviron and *Brophyllum pinnatum* extract effectively reversed these alterations, restoring biochemical parameters toward normal values. The reduction in CYP450 and XO levels suggests antioxidant modulation and improved detoxification capacity (Santos *et* al., 2023; Gupta *et al*., 2005; Batelli *et al*., 2016), while the lowered GFAP and IBA-1 levels indicate suppression of astrocyte and microglial activation (Yamada *et al*., 2022). The observed effects are consistent with reports that flavonoid-rich compounds possess potent free radical-scavenging and anti-inflammatory properties (Farombi *et al*., 2013; Takahashi *et al.,* 2013; Quazi *et al*., 2011; Adedara *et al*., 2016; Verkhratsky, 2016). In conclusion, aluminium chloride exposure induced significant oxidative stress and neuroinflammation, as evidenced by elevated CYP450, XO, GFAP, and IBA-1 levels in treated rats. Administration of Kolaviron and ethanolic leaf extract of *Brophyllum pinnatum* effectively mitigated these changes, highlighting their potent antioxidant and neuroprotective properties.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained from the Faculty of Basic Medical Sciences ethic committee with approval number: FBMS/UNICROSS/25/013

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