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Research Article

Comparative effect of Kolaviron and *Bryophyllum pinnatum* extract on apoptotic biomarker in aluminium chloride-induced neurotoxicity in rats

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Abstract

This study compared the neuroprotective potentials of kolaviron and ethanolic leaf extract of *Bryophyllum pinnatum* on apopotic biomarkers (ERK, TNF-α and BDNF) in $AlCl_3$-induced neurotoxicity. Forty-two male Wistar rats (n = 6 per group) were allocated to seven groups: Normal control; $AlCl_3$ only (100 mg/kg $AlCl_3$); Kolaviron only (Kv, 200 mg/kg); Crassulaceae only (Cr, 600 mg/kg); $AlCl_3$ + Kv; $AlCl_3$ + Cr; and $AlCl_3$ + Kv + Cr. Treatments were administered orally for 28 days. Results shows that ERK (%) was 100.0 ± 4.3 (Control), 320.1 ± 2.1 ($AlCl_3$), 90.2 ± 4.5 (Kv), 95.7 ± 5.1 (Cr), 150.2 ± 10.3 ($AlCl_3$+Kv), 185.7 ± 9.8 ($AlCl_3$+Cr) and 172.4 ± 8.7 ($AlCl_3$+Kv+Cr). Serum TNF-α (pg/mL) was 22.00 ± 11.43 (Control), 254.0 ± 5.41 ($AlCl_3$), 26.00 ± 10.68 (Kv), 22.05 ± 11.92 (Cr), 112.90 ± 2.02 ($AlCl_3$+Kv), 180.20 ± 48.96 ($AlCl_3$+Cr) and 27.35 ± 4.19 ($AlCl_3$+Kv+Cr). The results of BDNF (ng/mL) in control group was 2.50 ± 0.30 and 1.5 ± 0.20 in $AlCl_3$ group. The results showed significant ($p<0.05$) increased in ERK and TNF-α in $AlCl_3$ group with a corresponding deceased in BDNF in $AlCl_3$ group when compared with control. But, interventions with Kolaviron and *Crassulaceae* decreased ERK and TNF-α with a concurrent increased in BDNF level. Kolaviron more strongly suppressed TNF-α and ERK hyperactivation, whereas *Crassulaceae* more effectively restored BDNF. The combined treatment produced more amelioration, substantially lowering ERK and TNF-α and improving BDNF toward control levels, attenuating the damaging effect of $AlCl_3$ on the brain cells.

Keywords: Neurodegeneration, Kolaviron; *Bryophyllum pinnatum*; Aluminium chloride; ERK; TNF-α; BDNF.

INTRODUCTION

Neurodegenerative disorders are characterized by progressive neuronal dysfunction driven by oxidative stress, inflammation and reduced trophic support[1]. Aluminium chloride ($AlCl_3$) is widely used experimentally to induce neurotoxicity that mimics aspects of neurodegeneration (oxidative damage, elevated pro-inflammatory cytokines, reduced BDNF)[2,3,4]. Natural phytochemicals with antioxidant and anti-inflammatory properties such as kolaviron (a biflavonoid complex from Garcinia kola seeds) and ethanolic extracts of Crassulaceae (Bryophyllum pinnatum) have reported to have neuroprotective effects and may modulate ERK, TNF-α and BDNF pathways[5,6,7]. This study compares the two agents and their combination in an $AlCl_3$ model to determine relative and additive neuroprotective efficacy.

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, are major public health concerns that pose a growing threat to aging populations around the world. These disorders are characterized by a progressive loss of structure or function of neurons, ultimately leading to cognitive decline, memory impairment, motor dysfunction, and behavioural changes[2]. One of the hallmark features of many neurodegenerative diseases is the accumulation of abnormal proteins in the brain, which leads to oxidative stress, neuroinflammation, and neuronal death[8]. As these diseases remain largely incurable and affect millions globally, there is an urgent need to explore new therapeutic options.

Experimental research commonly utilizes animal models such as mice or Wistar rats to replicate features of neurodegenerative diseases. Among these, aluminium chloride ($AlCl_3$) is widely used to induce neurotoxicity in Wistar rats because of its ability to mimic key pathological changes associated with neurodegeneration. $AlCl_3$ exposure has been shown to

trigger the production of reactive oxygen species(R.O.S), elevate pro-inflammatory cytokines (such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), etc), and reduce the levels of neurotrophic factors(such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3),etc, thereby leading to widespread neural damage and functional impairments[9].

Recent scientific interest has shifted toward natural compounds with neuroprotective potential, especially those derived from medicinal plants. These compounds are often rich in antioxidants and anti-inflammatory agents that can counteract the harmful effects of neurotoxins like $AlCl_3$. Kolaviron is one such natural compound, a biflavonoid complex extracted from the seeds of *Garcinia kola*[10]. Also commonly known as Bitter Kola, has demonstrated significant antioxidant, anti-inflammatory, and neuroprotective properties in various experimental studies. Kolaviron works by scavenging free radicals, modulating pro-inflammatory pathways, and enhancing antioxidant enzyme activity, which collectively help in protecting neural tissues from damage[8].

Similarly, plants in the *Crassulaceae* family are widely recognized in traditional medicine for their healing properties. Ethanolic extracts of these plants are known to contain bioactive compounds such as flavonoids, phenolics, and terpenoids. These constituents have shown potential to reduce inflammation, protect against oxidative damage, and promote neuronal repair and regeneration. Although previous studies suggest beneficial effects of *Crassulaceae* extracts on the nervous system, more comparative studies are needed to validate these findings against other known phytochemicals like kolaviron[10].

To evaluate the effectiveness of these natural compounds, it is typical to evaluate and rely on specific biomarkers. Extracellular signal Regulated Kinase (ERK) provides insight into the integrity of brain circulation, which is essential for nutrient delivery and waste removal in neural tissues. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that reflects the degree of neuroinflammation, a key factor in the progression of neurodegeneration. Brain-derived neurotrophic factor (BDNF), on the other hand, plays a critical role in promoting neuronal growth, survival, and synaptic plasticity. Alterations in these markers can indicate the severity of neural damage and the neuroprotective efficacy of interventions

MATERIALS AND METHODS

The plant *Crassulaceae* (Bryophyllum pinnatum, Africa never die, Miracle leaf) was obtained from Neighbourhood gardens and market, Yala Local Government Area of Cross River State, on January 2025. It was identified and authenticated by the Department of Botany, University of Calabar. Its ethanolic leaf extract was prepared in University of Cross River State (UNICROSS), Okuku Campus. Ethical approval was obtained in (unicross), with vachour number FBMS/UNICROSS/25/013.

Preparation of *Bryophyllum pinnatum* leaf extract

Crassulaceae (Miracle leaf) was washed to remove all existing debris and pluck from the stem. Then dried and grinded to smoothness, we achieved 450grams of grinded leaf. It was soaked into ethanol solution (BDH) chemical Ltd poole England. Having alcoholic percentage of (98%-99%) and mixed consistently to ensure homogeneity. It was then left for 24hours to aid dissolution and extraction. After 24 hours the supernatant was suction filtered. First using whitman number one filter paper, then air-dried for 24 hours into paste form and stored airtight at normal room temperature.

Experimental animal

In this research, forty (42) Wistar rats weighing between 150-250g were obtained from the animal house of Physiology Department, Faculty of Basic Medical Sciences, University of Cross River State (UNICROSS) Okuku campus. The animals were housed in well ventilated cages. The beddings, feed and water was replaced twice every day(morning and evening), and kept under controlled environmental conditions (room temperature of about 27°C and 12-hour light/dark cycle).

The animals were allowed feed and water *ad libitum*. Groupings were done as follows: Group 1 (normal control) was fed on normal rat feed and water, group 2 ($AlCl_3$ only feed on aluminium chloride (100mg/kg body weight), group 3, (kolaviron (Kv group) took 200mg kg body weight of kolaviron (Kv), group 4 (Extract group) took *Crassulaceae* extract (600mg/kg body weight orally), group 5 was $AlCl_3$ + Kv took $AlCl_3$ (100mg/kg) + Kv (200mg/kg) and group 6 ($AlCl_3$ + Cr) was placed on $AlCl_3$ (100mg/kg) + Cr (600mg/kg) and group 7 $AlCl_3$ + Kv + Cr was on $AlCl_3$ (100mg/kg) + Kv (200mg/kg) + Cr (600mg/kg).

All animals had free access to drinking water and food intake for 28 days. At the end of treatment, animals were anesthetized and sacrificed. Blood was collected by cardiac puncture and centrifuged. Brains were rapidly excised; hippocampi were dissected on ice, homogenized in RIPA buffer with protease/phosphatase inhibitors for protein assays and ELISAs; portions fixed for histological assessments.

Determination of Erk Activation

Erk (extracellular signal–regulated kinase) activation was selected as a primary molecular endpoint for evaluating intracellular pro-survival, plasticity, and stress-response signalling in the hippocampus of Wistar rats. The Erk pathway is a critical component of the mitogen-activated protein kinase (MAPK) cascade, which regulates processes such as neuronal growth, differentiation, and synaptic remodelling. Under conditions of neurotoxicity induced by aluminum chloride ($AlCl_3$), ERK signalling can become dysregulated, leading either to impaired neuronal survival or excessive apoptosis. Therefore, the ratio of phosphorylated ERK1/2 (p-ERK) to total ERK1/2 was employed as a reliable biomarker of ERK pathway activation, allowing assessment of how kolaviron and

Crassulaceae extracts modulate intracellular signalling pathways relevant to neuroprotection.

Tissue Collection and Protein Extraction

At the end of the experimental protocol, animals were anesthetized and sacrificed by cardiac puncture to minimize stress-related biochemical artifacts. Brains were carefully excised within minutes of sacrifice, and hippocampal tissues were dissected on an ice-cold surface to preserve protein phosphorylation states. Each sample was immediately transferred into ice-cold RIPA lysis buffer supplemented with protease and phosphatase inhibitors. The use of inhibitors was essential to prevent both proteolytic degradation of ERK and dephosphorylation of p-ERK, ensuring accuracy in subsequent analyses. The homogenized samples were centrifuged at 12,000 × g for 15 minutes at 4°C, after which the clear supernatant containing soluble proteins was collected. Protein concentration was determined using the Bradford or bicinchoninic acid (BCA) assay, providing precise quantification to standardize loading volumes for electrophoresis.

Western Blotting Analysis

Western blotting was employed as the gold-standard method for determining ERK activation. Equal amounts of protein (30–50 µg) from each sample were mixed with Laemmli buffer, boiled to denature tertiary structures, and loaded onto SDS–polyacrylamide gels for separation based on molecular weight. Proteins were then electrophoretically transferred onto PVDF membranes to facilitate immunodetection. To reduce non-specific binding, membranes were blocked with 5% non-fat milk in TBS-T buffer. Subsequently, membranes were incubated overnight at 4°C with primary antibodies specific for p-ERK1/2 (Thr202/Tyr204), total ERK1/2, and β-actin, which served as a stable loading control. Following several washes, membranes were incubated with horseradish peroxidase-conjugated secondary antibodies for one hour at room temperature. Protein bands were visualized using enhanced chemiluminescence (ECL) reagents, and images were captured with a gel documentation system. Band intensities were analysed by densitometry using ImageJ software, ensuring quantitative assessment of ERK activation.

Determination of TNF-Alpha

Tumor Necrosis Factor-alpha (TNF-α) is a pleiotropic proinflammatory cytokine that plays a crucial role in inflammation, immune responses, cell proliferation, differentiation, and apoptosis. Its dysregulation is implicated in various pathological conditions, including autoimmune diseases, infectious diseases, and neuroinflammation. Determining TNF-α levels in Wistar rats is a common practice in preclinical research to assess inflammatory states, disease progression, and therapeutic efficacy. The primary and most widely used method for quantifying TNF-α protein levels in Wistar rats is the Enzyme-Linked Immunosorbent Assay (ELISA).

Determination of BDNF

Brain-Derived Neurotrophic Factor (BDNF) is a crucial neurotrophin involved in neuronal survival, growth, differentiation, and synaptic plasticity. Its levels are indicative of brain health and are often studied in models of neurological and psychiatric disorders in Wistar rats. Similar to TNF-α, various methods are available for BDNF determination. The choice of method depends on the research question:

For quantitative protein levels in bulk samples (serum, plasma, homogenates), **ELISA** is the most common and robust. For distinguishing between proBDNF and mature BDNF, or for semi-quantitative protein assessment, Western Blot is valuablefor localization and semi-quantitative protein expression within tissues, IHC/IF is preferred. For gene expression analysis, qRT-PCR is used.

Data analysis

Data are expressed as mean ± SEM. One-way ANOVA followed with Tukey's post hoc test was used for multiple comparisons; normality was confirmed using Shapiro Wilk's test, while homogeneity of variance was done using Levene's test. $p<0.05$ was considered statistically significant.

RESULTS

Erk immunoreactivity in the different experimental groups:

The result of the ERK level of both animals treated with aluminium chloride ($AlCl_3$), Kolaviron and ethanolic leaf extract of *Crassulaceae* (Cr) is (100.0±4.3), (320.1±2.1), (90.2±4.5), (95.7±5.1), (150.2±10.3), (185.7±9.8), (172.4±8.7) respectively. The result presented shows a significance difference level ($p<0.05$) increase in $AlCl_3$ treated group when compared with the normal control. Intervention with Kv and Cr reduces ERK level towards normal, Figure 1.

Serum tissue necrotic factor- alpha (TNF-A) in the different experimental groups:

The result of the serum TNF-A level of both animals treated with Aluminium chloride ($AlCl_3$), Kolaviron and ethanolic leaf extract of *Crassulaceae* (Cr) is (22.00 ±11.43), (254.0 ±5.41), (26.00 ±10.68), (22.05 ±11.92), (112.90 ±2.02), (180.20 ±48.96), (27.35 ±4.19) respectively. The result presented shows a significant different level $p<0.05$ between AlCl3 treated group when compared with the normal control value. The increased was reduced towards normal level followed treatment with Kv and Cr, figure 2.

Brain derived neurotrophic factor (BDNF) reactivity in the different experimental groups:

The result of the serum BDNF level of both animals treated with aluminium chloride ($AlCl_3$), Kolaviron and ethanolic leaf extract of *Crasulaceae* (Cr) is (2.5±0.3), (1.5±0.2), (2.8±0.4), (2.7±0.3), (2.2±0.3), (1.8±0.2), (2.1±0.3) respectively. The result presented shows a significant ($p<0.05$) decrease BDNF level in $AlCl_3$ group when compared with the normal control, thiswas

significantly increased due to intervention of Kv and Cr toward normal, figure 3.

Histological Study

Photomicrographs of sections of the hippocampus (CA3) of control group showed intact neurons, PLATE 1.

In the $AlCl_3$ only group, the neurons presented with prominent eosinophilic cytoplasm, swelling / vacuolated neuron and pyknotic nuclei, PLATE 2.

Photomicrographs of sections of the hippocampus (CA3) of Kv and Cr groups showed intact neurons, PLATES 3 and 4.

In the $AlCl_3$ + Kv and $AlCl_3$ + Cr groups, the neurons presented with prominent eosinophilic cytoplasm, and swelling / vacuolated neuron, but without pyknotic nuclei, PLATES 5 and 6.

While in the $AlCl_3$ + Kv + Cr group, some intact neurons were seen, the neurons also presented with prominent eosinophilic cytoplasm, but without swelling / vacuolated neuron, nor pyknotic nuclei, PLATE 7.

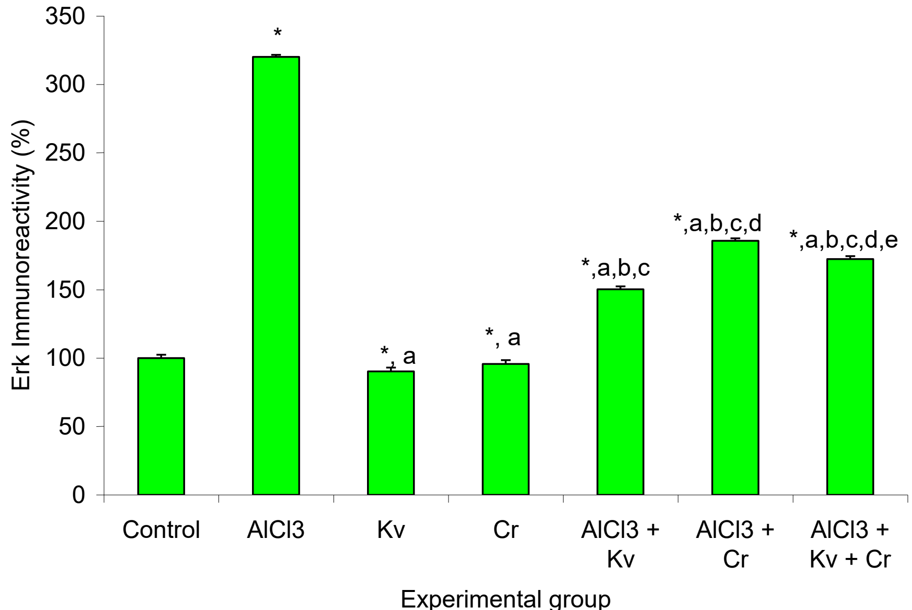


Figure 1: Erk immunoreactivity in the different experimental groups.

Values are expressed as mean +SEM, n = 5.
* = $p<0.05$ vs control ; 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

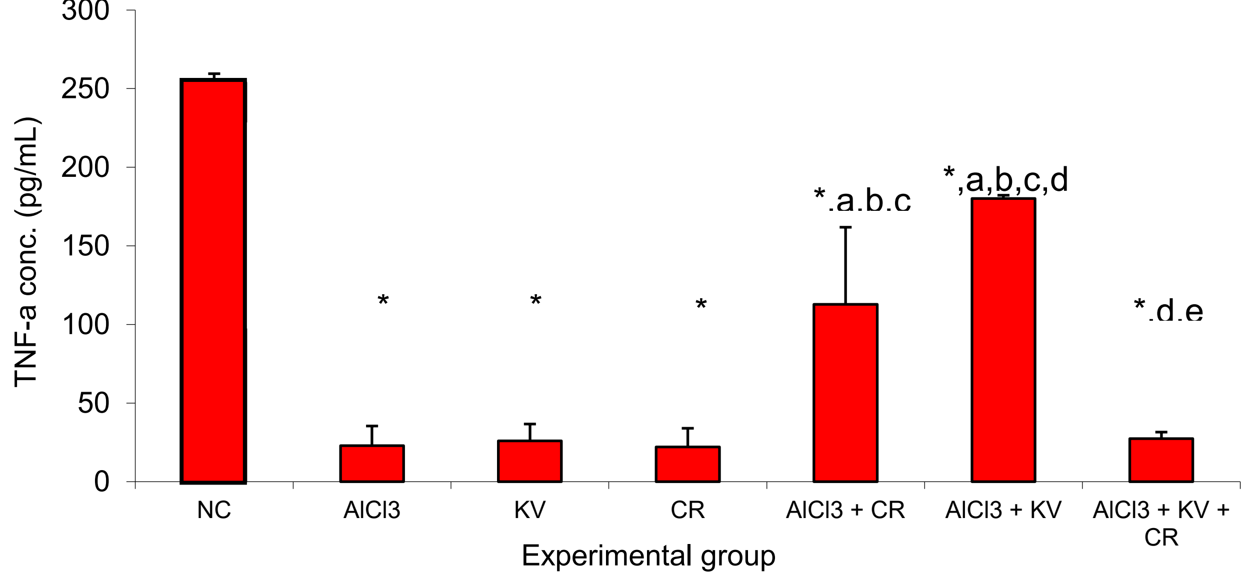


Figure 2: Tissue necrotic factor-alpha concentration in the different experimental groups.

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

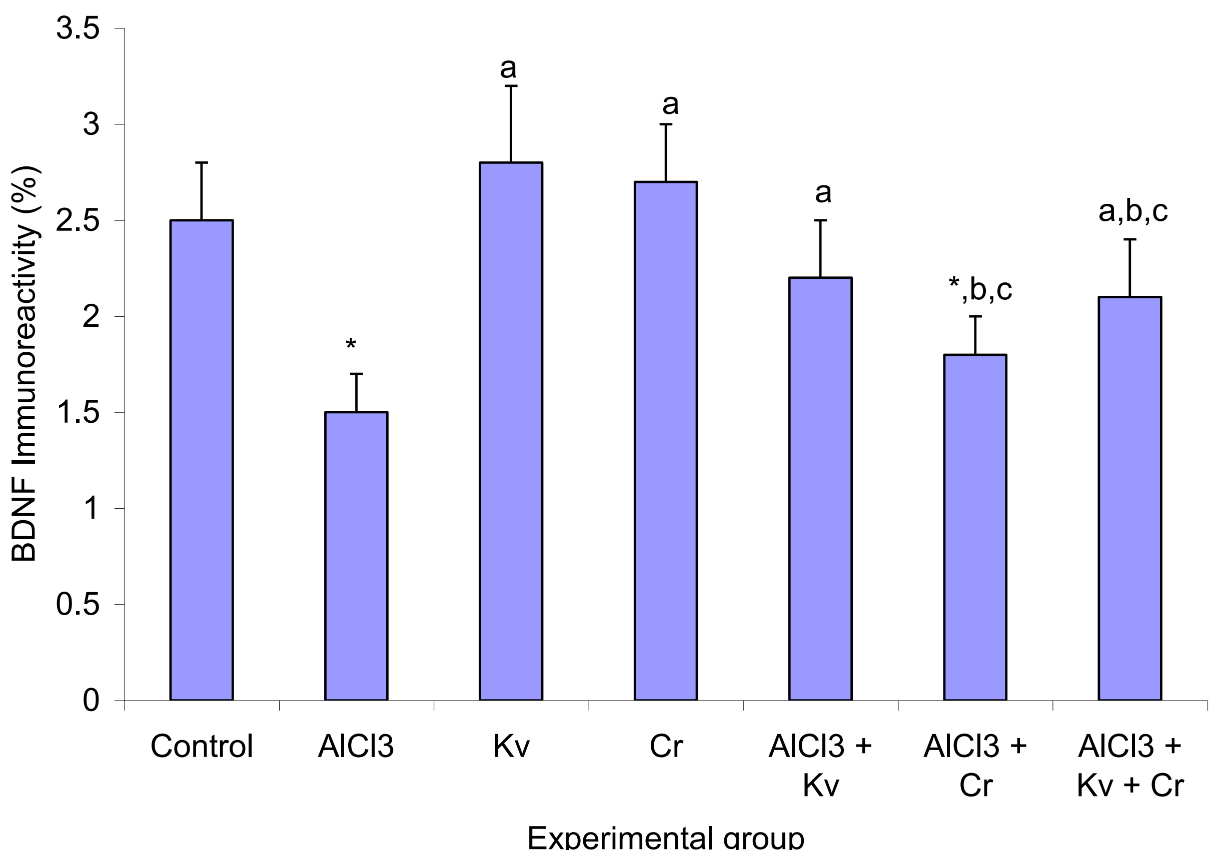


Figure 3: Brain derived neurotrophic factor (BDNF) immunoreactivity in the different experimental groups.

Values are expressed as mean +SEM, n = 5.
* = p<0.05 vs control ; a = p<0.05 vs AlCl3
b = p<0.05 vs Kv; c = p<0.05 vs Cr

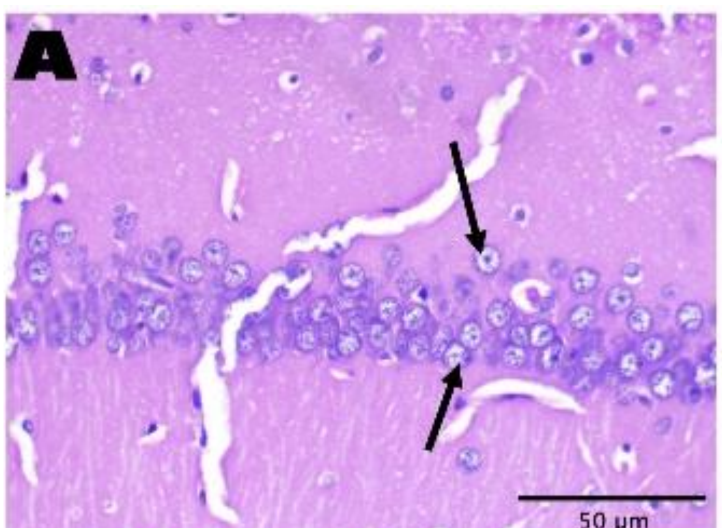


PLATE 1: Photomicrographs of sections of the hippocampus (CA3) of contol group.

→ = Intact neurons

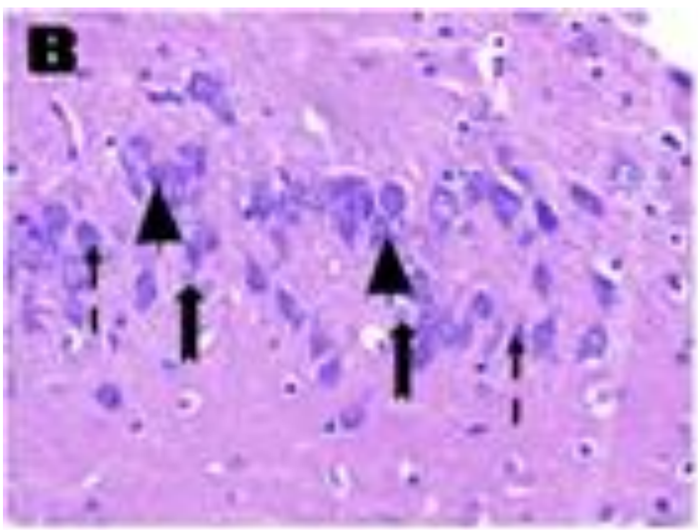
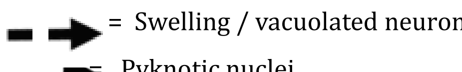


PLATE 2: Photomicrographs of sections of the hippocampus (CA3) of $AlCl_3$ only group.

= Intact neurons

= Neurons with prominent eosinophilic cytoplasm



= Swelling / vacuolated neuron

= Pyknotic nuclei

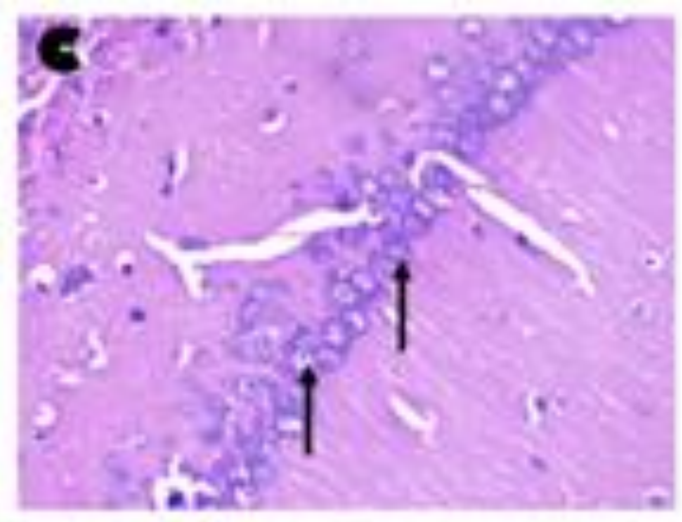


PLATE 3: Photomicrographs of sections of the hippocampus (CA3) of Kolaviron only rats.

= Intact neurons

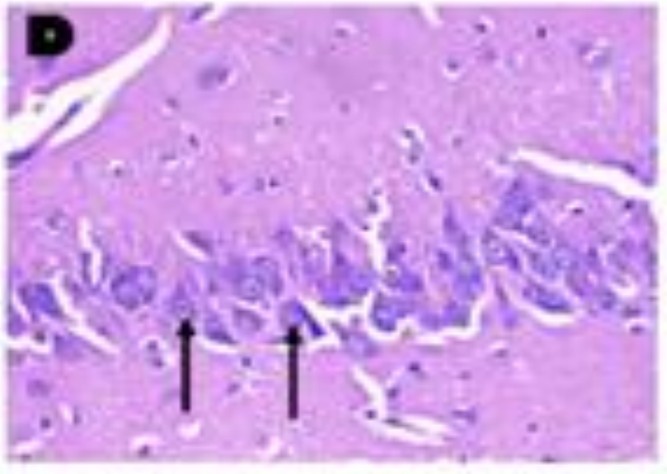


PLATE 4: Photomicrographs of sections of the hippocampus (CA3) of Crassulaceae only rats.

= Intact neurons

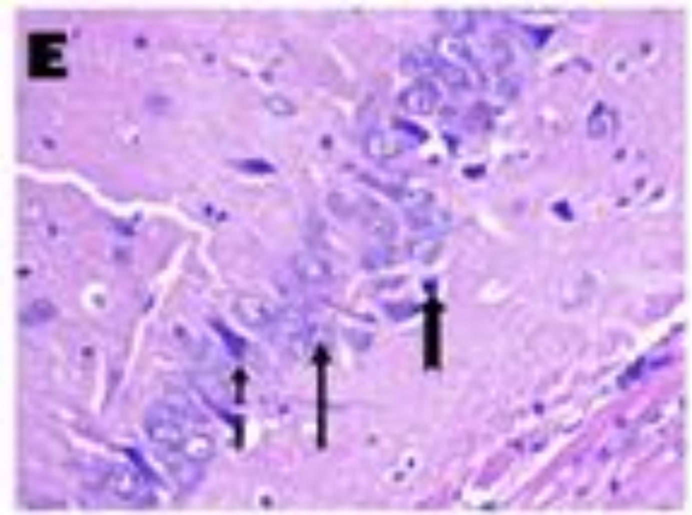


PLATE 5: Photomicrographs of sections of the hippocampus (CA3) of $AlCl_3$ + Kv rats.

= Intact neurons

= Neurons with prominent eosinophilic cytoplasm

= Swelling / vacuolated neuron

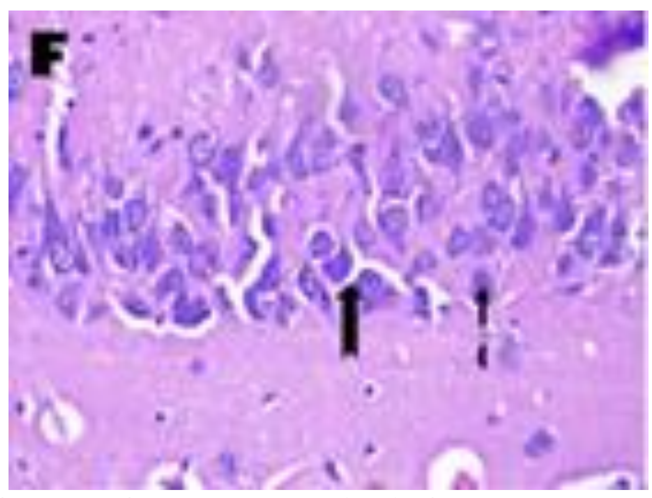


PLATE 6: Photomicrographs of sections of the hippocampus (CA3) of $AlCl_3$ + Cr rats.

= Neurons with prominent eosinophilic cytoplasm

= Swelling / vacuolated neuron

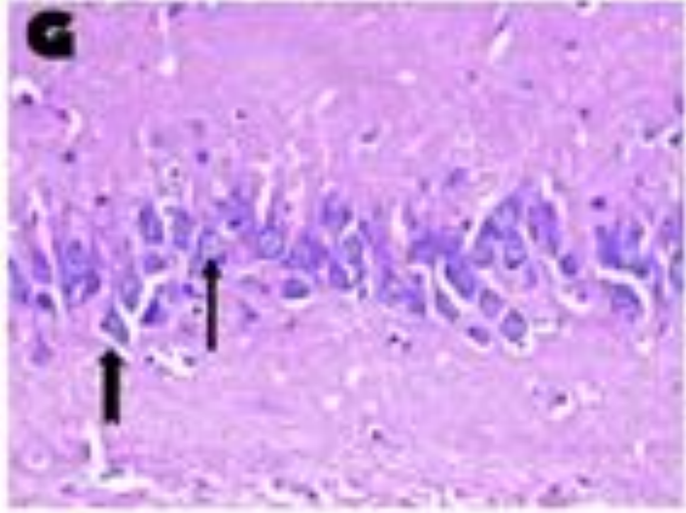


PLATE 7: Photomicrographs of sections of the hippocampus (CA3) of $AlCl_3$ + Kv + Cr rats.

= Intact neurons

= Neurons with prominent eosinophilic cytoplasm

DISCUSSION

The present study has clearly shown that Kolaviron and ethanolic leaf extract of Crassulaceae (*Bryophyllum pinnatum*) exert protective and restorative effects against aluminium chloride-induced neurotoxicity. Aluminium chloride alone disrupted neuronal homeostasis by upregulating ERK and TNF-α while downregulating BDNF, thereby recreating a pattern typical of neurodegenerative progression. Treatment with either Kolaviron or Crassulaceae partially reversed these alterations, while their combination produced an even stronger effect.

Kolaviron demonstrated superior efficacy in modulating pro-inflammatory responses and stabilising abnormal ERK activation, while Crassulaceae excelled in enhancing neurotrophic support as evidenced by improved BDNF expression. This differential efficacy underscores the unique biochemical composition of each extract and points toward the therapeutic potential of combined phytotherapy. Together, they provide a complementary neuroprotective strategy capable of addressing multiple mechanistic pathways simultaneously.

The implications of these results extend beyond preclinical models. By showing that natural compounds can produce measurable benefits in both serum and brain tissue biomarkers, this study supports their development as cost-effective and accessible interventions for neurodegenerative disorders. Future research should build upon these findings by exploring molecular mechanisms in greater depth, assessing long-term safety, and testing translatability to human populations. Clinical trials, advanced molecular imaging, and genomic profiling would further clarify their potential to influence neurodegenerative disease progression[11,12].

In conclusion, Kolaviron and ethanolic leaf extract of Crassulaceae work synergistically and exert complementary neuroprotective effects in $AlCl_3$-induced neurotoxicity in Wistar rats.

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Author's contribution: All the authors contributed to this manuscript. Ujong GO conceived the idea, Beshel JA edited the draft copy of the manuscript written by Idam and Ejim. Rademene Orie assisted the bench work, while Favour assisted in editing the final draft of the manuscript.

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

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