Arch. Bas. App. Med. 3 (2015) 71 - 78

ARCHIVES OF BASIC & APPLIED MEDICINE

Research Article

Launaea taraxacifolia Aqueous Extract Attenuates Cisplatin-Induced Neurotoxicity by Decreasing Oxidative Stress and Neuronal Cell Death in Rats

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Received: April 2014

Abstract

Cisplatin chemotherapy is associated with neurotoxicity, and oxidative stress might play an important role in the pathogenesis. *Launaea taraxacifolia* aqueous extract (LTAE) may be a preventive agent via its known antioxidant properties. The study was aimed at investigating the chemoprotective effects of LTAE against cisplatin-induced oxidative stress and alteration of microanatomy of rat brain. Thirty rats were divided equally into six groups: control; cisplatin (10 mg/kg i.p.); LTAE at 100, 400 mg/kg; LTAE (100 mg/kg) plus cisplatin; LTAE (400 mg/kg) plus cisplatin. LTAE was administered p.o. for 21 days while cisplatin was given as a single dose on day 21 of experiment. Rats were euthanized on the 25th day of treatment. Brain tissue was examined with regard to biochemical and microanatomical parameters. Cisplatin caused a significant ($p<0.05$) reduction of glutathione (GSH) by 50% when compared with the control group and elevation of lipid peroxidation (LPO), activities of superoxide dismutase (SOD) and catalase (CAT) by 135%, 125% and 107% respectively. Co-treatment of LTAE 400 mg/kg with cisplatin elevated GSH by 105%, but significantly reduced LPO, SOD and CAT by 57%, 46% and 49% respectively.

Microscopically, cisplatin caused anatomical alterations in the cerebral cortex, cerebellum, dentate gyrus and cornu ammonis 3 (CA3). Co-treatment of LTAE 100 mg/kg and 400 mg/kg with cisplatin ameliorated both biochemical and histological alterations with the higher dose being more effective. In conclusion, *Launaea taraxacifolia aqueous extract* demonstrated chemoprotective effects against cisplatin-induced oxidative stress, neuronal death and alteration of microanatomy of rat brain, and these may be attributed to its antioxidant capabilities.

Keywords: Cisplatin, *Launaea taraxacifolia*, oxidative stress, neuroprotective, CA3, dentate gyrus, cerebellum

INTRODUCTION

Cancer chemotherapy has unwanted and sometimes severe side effects; hence efforts to reduce such side effects should be pursued to encourage chemotherapy with less side effects. One of such drugs is *Cisplatin* (a platinum-based agent) which is one the most widely used and most effective cytotoxic agents in the treatment of a variety of malignant tumours, including lung, colorectal, ovarian, breast, head and neck, bladder and testicular cancers in both children and adults (Gulec *et al.*, 2013). Cisplatin (cis-dichlorodiamine) was approved for the treatment of both ovarian and testicular cancer in 1978 (Higby *et al.*, 1974) and is also administered for many other types of solid tumors (McWhinney *et al.*, 2009). Cisplatin is the most commonly used chemotherapy drug in the USA (Seiwert *et al.*, 2007), however, the benefit of cisplatin is compromised by severe side effects including neurotoxicity, myelotoxicity, nephrotoxicity, ototoxicity and hematological toxicity (Boyle *et al.*, 1999; McWhinney *et al.*, (2009).

Although cisplatin induced neurotoxicity is reported to occur in a cumulative and dose-dependent (Amptoulach and Tsavaris, 2011), there have also been reports that single dose cisplatin administration elicited toxicities in different organs of laboratory animals (Ramadan *et al.*, 2001; Kim *et al.*, 2005; El-Sayed *et al.*, 2008; Hadi and Al-Thamir, 2013; Nasr, 2013). Cisplatin-mediated neurotoxicity is a significant limitation to effective anti-cancer treatment because it may lead to dose reduction or even treatment withdrawal (Nowis *et al., 2007).* Platinum-based agents have poor penetration through the blood-brain barrier (McKeage *et al.*, 2001). Cellular damage by cisplatin is thought to be caused by the formation of DNA adducts, by covalently linking DNA with protein complexes. Binding to DNA causes significant distortion of the helical structure and results in the inhibition of DNA replication and transcription (Botttone *et al.*, 2012). Cisplatin may also act on the mitochondria as it has been shown by evidence that mitochondrial dysfunction can be induced, probably through binding of cisplatin to mitochondrial DNA (Carozzi *et al.*, 2009). Mitochondrial dysfunction thus increases oxidative stress which plays an important role in the pathogenesis of cisplatin neurotoxicity (Hino *et al.*, 2005; Altun *et al.*, 2010). Indeed several antioxidant treatments have been used successfully in order to prevent cisplatin-mediated neurotoxicity. This oxidative role was demonstrated by Turan *et al.*, (2013) and Gulec *et al.*, (2013) who showed that cisplatin significantly increased the levels of oxidant parameters such as lipid peroxidation (thio-barbituric acid reactive substance (TBARS), myeloperoxidase (MPO) and 8-hydroxyguanine (8-OH-GUA) in brain tissue and suppressed the effects of antioxidants such as total glutathione (GSH) and superoxide dismutase (SOD). Glutathione (GSH) is involved in detoxification and protection of tissue from oxidant injury and might prevent accumulation of platinum compounds in the dorsal root ganglia (Beijers *et al.*, 2012).

While the cerebral cortex is involved in various functions ranging from cognition to vision, auditory, visual

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and others, the cerebellum is involved in co-ordination of willed muscular functions, whereas the hippocampus is involved in memory storage as well as some limbic functions. All or any of these components of the central nervous system may be affected by toxicity of administered drugs.

Launaea taraxacifolia Wild, of the Asteraceae family (Bitter lettuce, Wild lettuce) is known as *Yanrin* in the south-west Nigeria where it is a common vegetable. *L. taraxacifolia* contain antioxidants and has locally been used as a remedy for various ailments such as skin and eye diseases (conjunctivitis), yaws, measles and diabetes (Adebisi, 2004). The antioxidant property of *L. taraxacifolia* due to its flavonoids has been documented (Gbadamosi *et al.,* 2012; Oduse *et al.,* 2012), while flavonoids, phenol and ascorbic acid has been reported in the water and methanol extracts of its leaves (Arawande *et al.,* 2013). Literature did not show any data concerning the role of *Launaea taraxacifolia* water extract (LTAE) on cisplatin-induced oxidative damage in the brain of rats. This study was designed to test the hypothesis that LTAE may have a protective role on cisplatin-induced neuropathy in rats via its antioxidant property by studying the biochemical and microanatomical alterations it might elicit.

MATERIALS AND METHODS

Preparation of Plant Material: Fresh leaves of *Launaea taraxacifolia* harvested from the Botanical Gardens, Ibadan, Nigeria were authenticated by Professor A.E. Ayodele of the Department of Botany, University of Ibadan where herbarium specimen with voucher specimen number UIH-22370 was deposited. The qualitative tests for the detection of secondary metabolites; alkaloids, tannins, flavonoids, saponins and phenolic compounds, in plant were carried out on *Launaea taraxacifolia* using standard procedures (Trease and Evans, 1989). The leaves (2,000 g) were air dried for 4 days), powdered and soaked in 8 litres of distilled water for extraction and heated at a sustained temperature was kept at 60 ºC for 24 hours after which they were filtered using filter papers. The resultant filtrate was concentrated using a rotary evaporator to give a residue which was termed *Launaea taraxacifolia* aqueous extract (LTAE). The dosage of the dried extract to be administered was then calculated from the stock solution prepared by diluting 1 g of extract with 10 mL of distilled water.

Chemicals: *Cisplatin* was procured from Korea United Pharm. Inc. (Naojang, Chungnam, Korea). All other reagents were of analytical grade and were obtained from the British Drug Houses (Poole, Dorset, UK).

Animal Protocol: Experiments were performed on adult male Wistar rats weighing 200 - 210 g, obtained from the Experimental Animal Unit of Faculty of Veterinary Medicine, University of Ibadan, Nigeria, and were housed in well-ventilated plastic cages, provided with rat pellets and water *ad libitum*. The animals were maintained under standard conditions of temperature and humidity with alternating 12 h light/dark cycles. The experimental protocols were carried out according to the guidelines set by the University of Ibadan Ethical Committee, which conformed to the acceptable guidelines on the ethical use of animals in research (Public Health Service, 1996).

Experimental design

Thirty healthy adult male Wistar rats were randomly divided into six groups (N=5):

I. Control: Received water (5 mL/kg body weight) orally.
II. Cisplatin (CIS): Received a single dose of CIS intraperitoneally at 10 mg/kg b.wt on day 21 of the experiment.
III. LTAE low: Received 100 mg/kg of LTAE orally for 21 days.
IV. LTAE high: Received 400 mg/kg of LTAE orally for 21 days.
V. LTAE 100 mg + CIS: Received 100 mg/kg b.wt of LTAE orally for 21 days plus 10 mg/kg of cisplatin intraperitoneally on day 21 of the experiment.
VI. LTAE 400 mg + CIS: Received 400 mg/kg of LTAE orally for 21 days plus 10 mg/kg of cisplatin intraperitoneally on day 21 of the experiment.

The dose and route of administration of the single dose of cisplatin was based on the methods of Hadi and Al-Thamir (2013) and Fahmy *et al.,* (2013). All the animals were euthanized on day 25 of the experiment.

Sample collection and histological preparation: On day 25 of the experiment, all animals in both control and experimental groups were euthanized by cervical dislocation. Each rat was decapitated at the cervico-medullary junction for uniformity and the skulls opened after which the brains were extracted. Adopting the method of Igado *et al.,* (2012), one half of the brain, the right hemisphere, was preserved for histology and fixed in 10% buffered formol saline for a week. whereas the other half preserved for biochemical tests was rapidly rinsed, mopped with filter paper, weighed and kept in freshly prepared cold phosphate buffered solution (PBS) and then kept in the freezer till processed. The cerebellum, cerebral cortex and hippocampus of each animal were dissected and then processed by routine paraffin embedment technique. Sections on glass slides were stained with Haematoxylin and Eosin (H&E), and examined under the light microscope (Olympus CH Japan) for histological studies.

Biochemical Assays: The left hemisphere of the brain samples were homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 1.15% potassium chloride, and the homogenate centrifuged at 10,000 g for 15 minutes at 4 °C. The supernatant was collected for the estimation of the various biochemical bioassays. Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Farombi *et al.,* (2000) and expressed as micromoles of MDA per milligram protein. Estimation of catalase (CAT) activity was done using hydrogen peroxide as substrate according to the method of Clairbone (1995). Superoxide dismutase (SOD) was assayed by the method described by Misra and Fridovich (1972). Protein concentration was determined by the method of Lowry *et al.,* (1951). Reduced glutathione (GSH) was determined at 412 nm using the method described by Jollow *et al.,* (1974).

Histology: The cerebellum from each group was obtained and homologous sampling was assured by obtaining transverse sections of the right cerebellum from each specimen from the lateral zone portions of the cerebella hemisphere (vermal, paravermal and flocullus portions were not utilized) for

uniformity. Coronal sections of the right half of each brain were made to obtain samples of the frontal cortex and hippocampal tissue. The tissues were sectioned at 5 µm thickness with a Rotary Microtome (Leica RM2125 RTS, Germany) and then stained with Haematoxylin and Eosin according to the method of Bancroft and Gamble, (2008). The slides were observed with light microscope (Olympus CH, Japan) and photomicrographs taken with Sony DSC-W 30 Cyber-shot (Japan).

Statistical analysis: All data were expressed as means ± standard deviation. Data were analyzed using one-way analysis of variance (ANOVA) using GraphPad Prism 4.0 version software, San Diego, CA, USA. Post hoc comparisons were performed after ANOVA using Dunnett's test. Statistical significance was set at $p<0.05$

RESULTS

Biochemical parameters: Table 1 summarizes the biochemical parameters assayed. It shows that LPO end products was found to be statistically higher ($p<0.05$) by 135.5% in the cisplatin group when compared with the control group. Similarly, cisplatin significantly elevated the activities of SOD and CAT (107% and 125% respectively) when compared with the control. The level of reduced glutathione (GSH) was significantly reduced by cisplatin with respect to the control by 50.2%. Also, in comparison with animals treated with cisplatin alone, the group that received the low dose LTAE as co-treatment with cisplatin, had values for LPO, CAT, and SOD that were statistically lower (56.2%, 49.8%, and 51% respectively, $p<0.05$). GSH was found to be statistically higher in the low dose LTAE group when compared with the cisplatin group (109%). Similarly, animals treated with the high dose LTAE as co-treatment with cisplatin had a reduction in the level of LPO and the activities of CAT and SOD which were significant when compared with the cisplatin group (56.7%, 49.4%, and 45.5% respectively, $p<0.05$).

Table 1:
Effects of *Launaea taraxacifolia* aqueous extract (LTAE) on the biochemical parameters of the brain of cisplatin-treated rats.

GROUP	GSH	LPO	CAT	SOD
Control	21.78	4.28	19.05	1.23
Cisplatin (CIS)	10.84*	10.08*	42.87*	2.55*
LTAE low	21.89	4.44	19.07	1.1
LTAE high	22.26	4.31	21.46	1.06
LTAE low + CIS	22.65**	4.42**	21.51**	1.25**
LTAE high + CIS	22.21**	4.36**	21.71**	1.39**

CIS, cisplatin 10 mg/kg; LTAE low, 100 mg/kg; LTAE high, 400 m/kg; LTAE low + CIS, LTAE high + CIS. GSH (unit/mg protein), LPO (µmol MDA/mg protein), CAT (u/mg protein), SOD (units/mg protein). Values are expressed as mean ± S.D of five animals. *: $P < 0.05$ versus Control; **:$P < 0.05$ versus CIS.

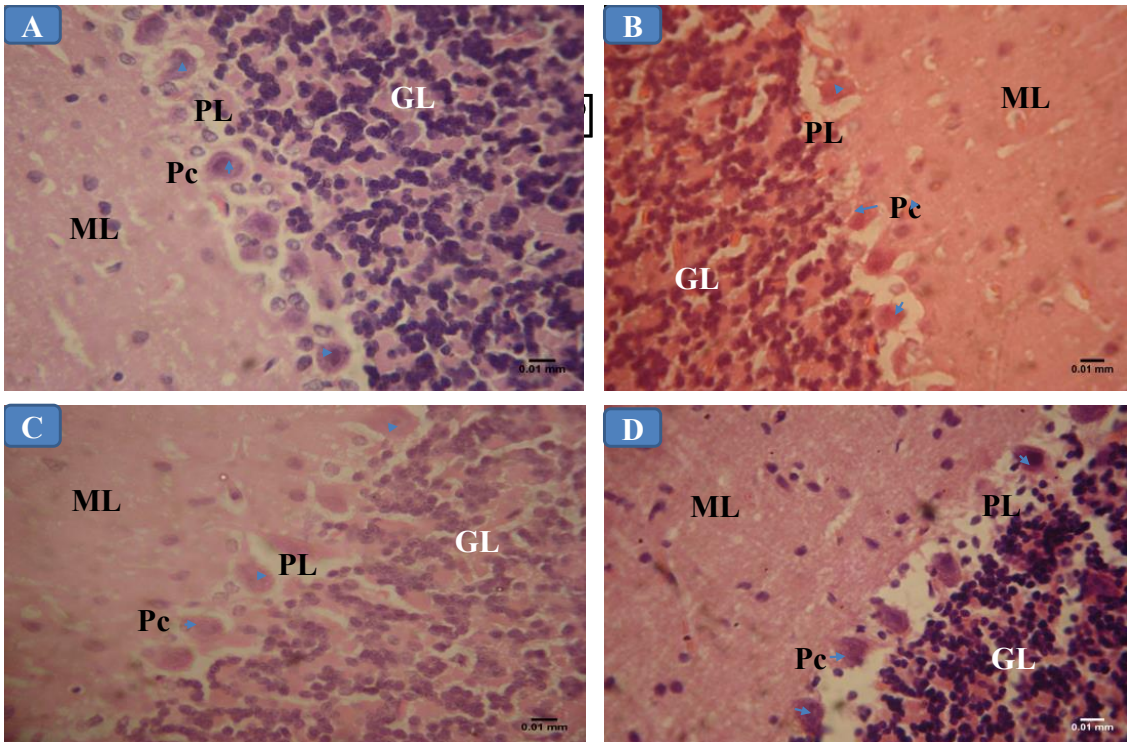

Plate 1:
Representative photomicrographs of cerebellum of rats.
A: Control, **B**: Cisplatin100 mg/kg, **C**: LTAE 100 mg/kg + Cisplatin, **D**: LTAE 400 mg/kg + Cisplatin. Normal layers: ML, molecular layer; PL, Purkinje layer; GL, granular layer are noted in all groups with nucleated and well-spaced Purkinje cells (Pc) in **A**. Purkinje cells are devoid of nuclei (karyolysis) in **B**, scanty nuclei in **C** but present in **D**. H & E stain. Scale bars indicate 0.01 mm.

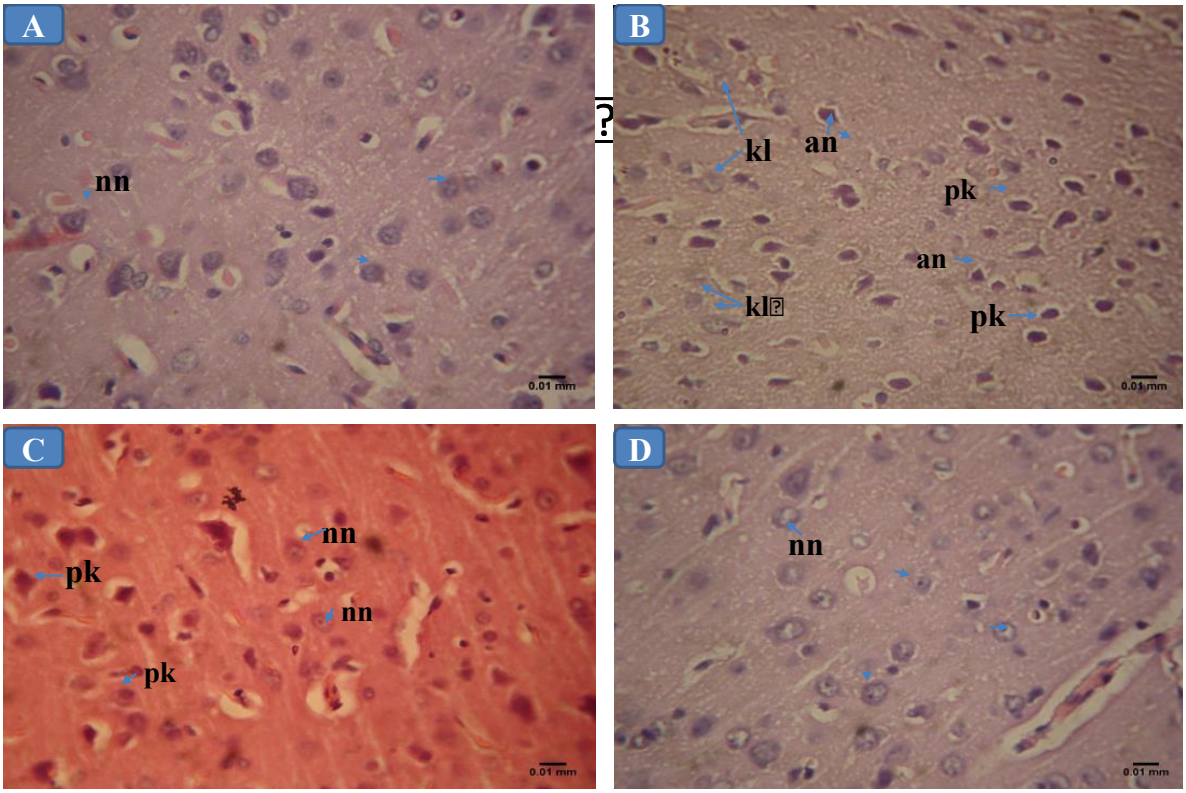

Plate 2:
Representative photomicrographs of cerebral cortex of rats.
A: Control, **B**: Cisplatin100 mg/kg, **C**: LTAE 100 mg/kg + Cisplatin, **D**: LTAE 400 mg/kg + Cisplatin. Normal cerebral neurons (*nn or arrowheads)* observed in **A**. Neurons exhibiting features of cell death, *pk* (pyknosis), *kl* (karyolysis), *an* (angulated neurons) are observed in **B**. These features are scanty in **C**, while they are absent in **D.** H & E stain. Scale bars indicate 0.01 mm.

When compared with the animals treated with cisplatin, GSH was found to be statistically higher in the high dose LTAE group (105%). It was observed that all parameters were restored to near control (Table 1) in animals treated with either the low or high doses of LTAE as co-treatment with cisplatin. Similarly, it can be observed that treatment with LTAE alone in either low or high dose had no significant effect on the LPO, CAT, SOD or GSH.

Histological parameters

Cerebellum: The cerebellum of the control rats showed the normal histological features of 3 layers, namely, molecular, Purkinje and granular layers as shown in Plate 1A. The effect of cisplatin is shown in Plate1B where the Purkinje cells of the cerebellum of the rats with alteration in their microanatomy like pyknosis, karyorherxis and karyolysis with respect to the control animals. Plate 1C demonstrates the effect of co-treatment of cisplatin with the lower dose of LTAE showing similar cellular alteration as it is in the cisplatin group. In Plate 1D, co-treatment of cisplatin with the higher dose of LTAE exhibited milder histological alteration when compared with the lower LTAE dose and the cisplatin group. The features observed in the cerebellum of rats that received only LTAE (100 mg/kg and 400 mg/kg) did not differ from those of control.

Cerebral cortex: As shown in Plate 2A, the cerebral cortex of the control rats showed the normal histological features of the different layers of the cortex. The neurons are large with round or ovoid nucleus exhibiting dispersed chromatin. The effect of cisplatin is shown in Plate 2B where the cortical neurons show features of pyknosis. Figure 2C demonstrates the effect of co-treatment of cisplatin with the LTAE at the lower dose showing similar cellular alteration as in the cisplatin group. In Plate 2D, co-treatment of cisplatin with the LTAE at the higher dose exhibited milder histological alteration when compared with the lower LTAE dose and the cisplatin group. The features observed in the cerebral cortex of rats that received only LTAE (100 mg/kg and 400 mg/kg) did not differ from those of control.

Dentate gyrus: The dentate gyrus of the hippocampal formation of the control rats showed the normal histological features of the molecular layer, granule cell layer and the polymorphic layer. Of interest was the granule cell layer consisting of several layers of granule cells with large nuclei exhibiting open chromatin as shown in Plate 3A. The effect of cisplatin is shown in Plate 3B where the granule neurons show evidences of toxicity as exhibited by pyknosis, karyolysis and karyorrhesis. Also noted are the neurons of the subgranular zone of the dentate gyrus showing cellular death. Plate 3C shows the effect of co-treatment of cisplatin with the LTAE at the lower dose showing similar cellular alteration as in the cisplatin group. In Plate 3D, co-treatment of cisplatin with the LTAE at the higher dose exhibited milder histological alteration when compared with the lower LTAE dose and the cisplatin group. The features observed in the dentate gyrus of rats that received only LTAE (100 mg/kg and 400 mg/kg) did not differ from those of control.

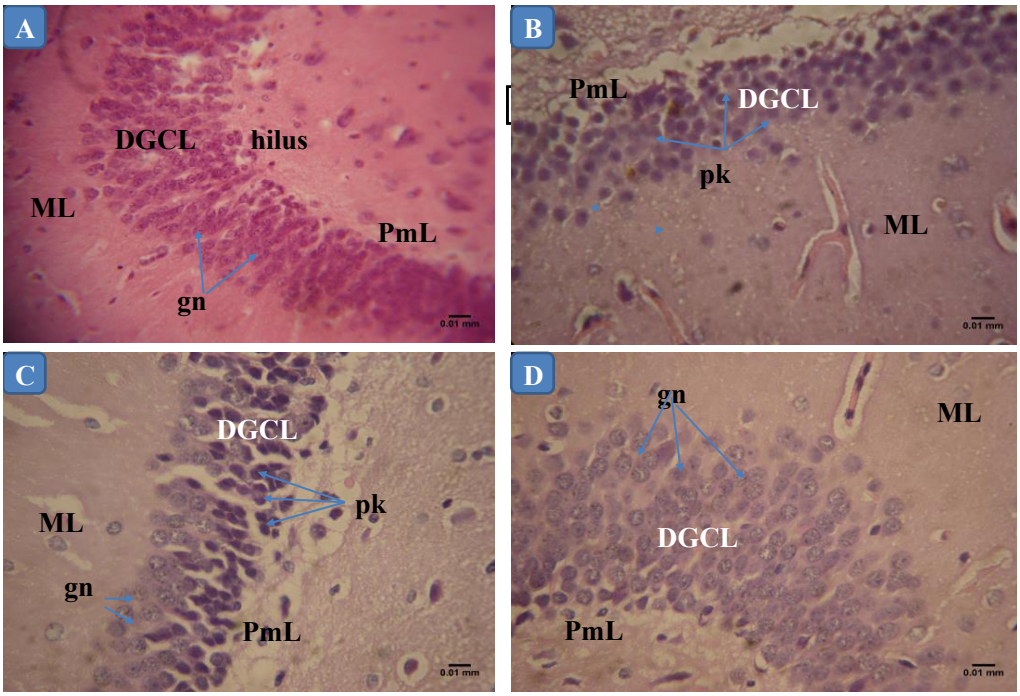

Plate 3:
Representative photomicrographs of dentate gyrus of hippocampal formation of rats.
A: Control, **B**: Cisplatin100 mg/kg, **C**: LTAE 100 mg/kg + Cisplatin, **D**: LTAE 400 mg/kg + Cisplatin. Normal layers: ML, molecular layer; DGCL, Dentate granule cell layer; PmL, polymorphic layer; are noted in all groups. Normal granule neurons (*gn)* observed in **A**. Neurons exhibiting features of cell death, *pk* (pyknosis) are widespread in **B**. The granule neurons nearer the hilus were pyknotic in **C**, while granule neurons were relatively well preserved in **D.** H & E stain. Scale bars indicate 0.01 mm.

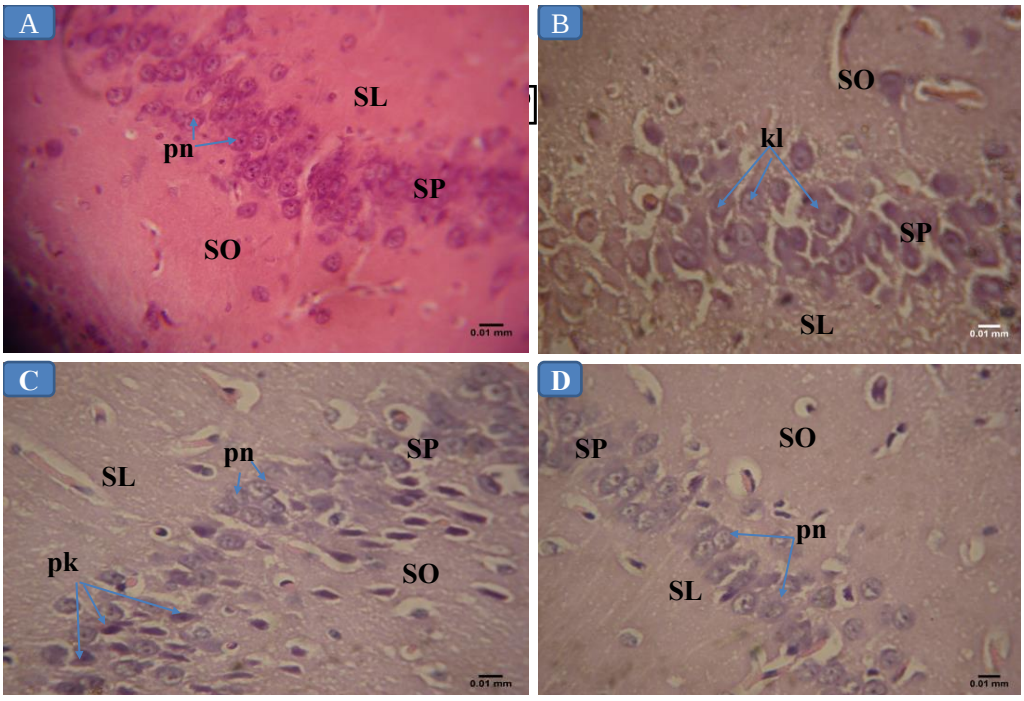

Plate 4:
Representative photomicrographs of Cornu Ammonis3 hippocampal subfield of rat brain.
A: Control, **B**: Cisplatin100 mg/kg, **C**: LTAE 100 mg/kg + Cisplatin, **D**: LTAE 400 mg/kg + Cisplatin. Normal layers: SO, stratum oriens; SP, stratum pyramidalis; SL, stratum lucidum, are observed in all groups. Normal pyramidal neurons (*pn)* observed in **A**. Neurons exhibiting features of cell death, *kl* (karyolysis) are observed in **B**. Few scattered pyknotic pyramidal neurons (*pk)* are observed in **C**, whereas pyramidal neurons are well preserved in **D.** H & E stain. Scale bars indicate 0.01 mm.

Cornu ammonis 3 (CA3): The CA3 of the hippocampal formation of the control rats showed the normal histological features of the stratum oriens, stratum pyramidalis, stratum lucidum, stratum radiatum and stratum lacunosum-moleculare, all of which show normal cytoarchiteure as shown in Plate 4A. Of special note are the large pyramidal neurons with nuclei exhibiting open chromatin as shown. The effect of cisplatin is shown in Plate 4B where the pyramidal neurons show evidences of toxicity as exhibited by pyknosis, karyolysis and karyorrhesis. Plate 4C shows the effect of co-

treatment of cisplatin with the LTAE at the lower dose showing similar cellular alteration as in the cisplatin group. In Plate 4D, co-treatment of cisplatin with the LTAE at the higher dose exhibited milder histological alteration when compared with the lower LTAE dose and the cisplatin group. The features observed in the CA3 of the hippocampus of rats that received only LTAE (100 mg/kg and 400 mg/kg) did not differ from those of control

DISCUSSION

We investigated a possible protective effect of *Launaea taraxacifolia* aqueous extract (LTAE) against cisplatin-induced neurotoxicity in rat brain by biochemical and histological methods. The oxidative stress-inducing capacity of cisplatin was demonstrated in this work as shown by the significant elevation of markers of oxidative stress which supports the earlier findings of Pan *et al.,* (2009) and Turan *et al.,* (2013) that cisplatin generates free radicals. An elevation of the tissue level of malondialdehyde suggests an increase in free radicals which may lead to oxidative stress when it overwhelms the body's natural antioxidant defense. Cisplatin treatment was reported to cause cellular damage characterized by a significant increase in tissue MDA level compared to normal control (Ilbey *et al.,* 2009). In this study, cisplatin also caused the elevation of the activities of the antioxidant enzymes SOD and CAT. This behavior of CAT and SOD may be viewed as an adaptive response of the enzymes to the production of free radicals indicated by the increased LPO, thus protecting the brain tissue from peroxidative damage that might occur in this situation (Ebokaiwe *et al.,* 2012).

The decreased GSH level indicates over-utilization of GSH during oxidative stress in the brain of cisplatin-treated rats. GSH is known to play important roles in a number of critical cellular processes by providing a major line of defense for the protection of cells from oxidative stress. It can scavenge free radicals, reduce peroxides and be conjugated with electrophilic compounds. It thus provides cells with multiple defenses against both reactive oxygen species (ROS) and their toxic by-products. Chirino *et al.,* (2009) had reported that on cisplatin entry into cells, adduct formation between cisplatin and GSH may occur which may lead to further reduction in the level of GSH.

The study demonstrated that brain antioxidant defense systems, such as GSH that was depleted by cisplatin therapy, was restored to normal by treatment with LTAE. GSH, a tripeptide known to act as a non-enzymic antioxidant, may act by direct interaction of its thiol group with ROS, or it can serve as a co-substrate for biochemical conjugation of xenobiotics (Oyagbemi *et al.,* 2010). When compared with the animals treated with cisplatin, GSH was found to be statistically higher in the high dose LTAE compared with cisplatin group, this is important as GSH has been reported to protect against cisplatin-induced neurotoxicity in rats (Harmers *et al.,* 1993). This increased GSH should help in modulating cisplatin toxicity in the affected groups. The ability of LTAE to reduce the lipid peroxidative effect of cisplatin and so return the activities of SOD and CAT to near control levels are an indication of the potency of the extract to ameliorate the oxidative damage done to the brain tissue by cisplatin. This supports the report of Gbadamosi *et al.,* (2012) who reported the flavonoid contents of the leaves of *Launaea taraxacifolia* and the presence of phenols and ascorbic acid, both potent antioxidants in the leaves (Arawande *et al.,* 2013). There is no doubt that this antioxidant effect neutralized the oxidative damage adduced to the cisplatin. While SOD serves as the first enzyme in antioxidant defense that converts superoxide radicals to form H_2O_2 and consequently preventing the deleterious effects of the oxygen radicals, catalase is known to protect the cell against oxidative stress from exogenous or endogenous H_2O_2 at lower concentration (Masaki *et al.,* 1998). This neuroprotection exhibited by LTAE against cisplatin-induced oxidative stress agrees with previous findings by Al Moundhri *et al.,* (2012) who used curcumin; Boyle *et al.,* (1999) who worked with glutamate, and Turan *et al.,* (2013) who experimented with thiamine pyrophosphate.

Our histological observations agreed with the reports of Al Moundhri *et al.,* (2012) and Arrieta *et al.,* (2011) that cisplatin-induced neurotoxicity is associated with histological damage. This supported our findings of cisplatin's alteration of the histology of the densely packed layers of granule neurons of the dentate gyrus of the hippocampal formation and the pyramidal neurons of the CA3 zone of the hippocampus proper when compared with the neurons of the control rats. Of importance are the cells of hilar and subgranular zone (SGZ) of the granule cell layer of the dentate gyrus exhibiting cellular death. The normal role of neurogenesis may be affected due to the neuronal death shown in the SGZ of the granule cell layer of the dentate gyrus. Bottone *et al.,* (2012) had reported that cisplatin induces cell death *in vivo* and *in vitro* in cerebellum and hippocampus of rats. Our finding is thus agreeable with their observation in this rat model. By implication, cellular death in the granule neurons may disrupt the smooth flow of neural information from the entorhinal cortex to the granular layer and further propagation of mossy fibres to the CA3 and CA1 subzones of the hippocampus. With evidence of death of pyramidal neurons of CA3, the subsequent projection of impulses from CA3 via the Schaffer's fibres to CA1 may be affected further altering the flow of neural information. In essence, this suggests that memory and other hippocampal functions might potentially be affected in such rats (Owoeye et al., 2014).

Similarly, the Purkinje cells of the cerebellum of the rats exhibited alterations in their microanatomy like pyknosis, karyorherxis and karyolysis with respect to the control animals. So also was the alteration of the microanatomy of the cerebral cortical neurons of the cisplatin-treated rats when compared with the control rats. By implication, the cerebellar injury may cause gait, movement and posture disturbances while the cerebral cortical injury might result in loss of cognitive functions which may have overall effect on the behavior of the animals (Snell, 2006). Although Scuteri *et al.,* (2009) and Bottone *et al.,* (2012) reported that the mechanism of cisplatin-induced neurotoxicity is by induction of apoptosis in neuronal cells, Kim *et al.,* (2010) presumes that irreversible cell damage might result mainly from oxidative stress. The histological findings of the neural parts studied showed evidence similar to cellular events associated with cell death as some of the neurons exhibited nuclei that are shrunken and intensely basophilic (pyknosis), an indication of cessation of DNA transcription. The nuclei of some neurons exhibited fragmentation into several small pieces (karyorrhexis), whereas in some other neurons, there is complete dissolution of their nuclei - karyolysis (Stevens and Lowe, 2000). Although platinum drugs are reported to have poor penetration of the blood–brain barrier (Gregg *et al.,* 1992), sufficient

levels of cisplatin have been shown to cause toxicity in the brain (Gulec *et al.*, 2013), which our study has demonstrated. Co-treatment of cisplatin with the lower dose of LTAE showed partial histomorphological protection with the neurons still showing some features of cell death when compared with the cisplatin only group. However, in the group that received the higher dose of LTAE as co-treatment with cisplatin, there was significant improvement in the histological alteration. This suggests that LTAE could offer neuroprotection against cisplatin-induced neurotoxicity most likely through its antioxidant property.

In conclusion, *Launaea taraxacifolia aqueous extract* demonstrated chemoprotective effects against cisplatin-induced oxidative stress, neuronal death and alteration of microanatomy of rat brain, and these may be attributed to its antioxidant capabilities.

ACKNOWLEDGEMENT

The authors thank Mrs O. R. Folarin of the Department of Veterinary Anatomy, University of Ibadan, for technical assistance in slide preparation and Dr. A. P. Ebokaiwe of Biochemistry Department, University of Ibadan, for assistance in biochemical analysis.

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