Heliyon 8 (2022) e11066

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Roasted cashew (*Anacardium occidentale* L.) nut-enhanced diet forestalls cisplatin-initiated brain harm in rats

Seun F. Akomolafe [a,*], Abiola M. Asowata-Ayodele [b]

[a] Department of Biochemistry, Ekiti State University, P.M.B. 5363, Ado Ekiti, Nigeria
[b] Department of Biological Sciences, University of Medical Sciences, Ondo, Ondo State, Nigeria

ARTICLE INFO

Keywords:
Cisplatin
Neurotoxicity
Oxidative stress
Cholinesterase
Monoaminergic enzyme

ABSTRACT

The incessant dose constraining symptom of the chemotherapeutic agent, cisplatin is neurotoxicity. This examination tried to explore the neuroprotective impact of roasted cashew nut-enhanced diet against brain deficits related with treatment with cisplatin. Rats were separated in to six groups: Control, CIS (cisplatin [7 mg/kg body weight, *i.p*]), CIS +10% CN (cisplatin plus 10% roasted cashew nut), CIS +20% CN (cisplatin plus 20% roasted cashew nut), 10% CN (10% roasted cashew nut) and 20% CN (20% roasted cashew nut) for 28 days. Key enzymes associated with brain function, including cholinesterases (AChE and BChE), monoaminergic enzyme (MAO), arginase, and adenosine deaminase (ADA), were investigated after the treatment. The following oxidative stress indicators were also measured in the rat brain: glutathione-S-transferase (GST), glutathione peroxidase (GPx), total antioxidant capacity (TAC), total thiol (T-SH), non-protein thiol (NPSH), thiobarbituric acid reactive substances (TBARS), reactive oxygen species (ROS), nitric oxide (NO), superoxide dismutase (SOD). Our outcomes demonstrated that roasted cashew nut enhanced diet showed inhibitory impact on activities of AChE, BChE, ADA, MAO and arginase in cisplatin-induced rats. The roasted cashew nut supplemented diet also boosted redox equilibrium and displayed protection against cispaltin-induced oxidative damage to rats' brains by an increase in SOD, CAT, GST and GPx activities, TAC, T-SH, NPSH and NO levels as well as a considerable drop in ROS and RBARS levels. Roasted cashew nut enhanced diet additionally forestalled neuronal degeneration in rat brain. Thus, roasted cashew nuts could be used as a nutraceutical or functional food to treat cisplatin-induced neurotoxicity.

Practical applications: The results show that increasing roasted cashew nut consumption can significantly improve antioxidant status, reduce lipid peroxidation, and suppress cholinesterase, adenosine deaminase, monoamine oxidase, and arginase activities in the brain under cisplatin-induced circumstances.

1. Introduction

One of the food groups that is promising as a dietary intervention for brain damage is the cashew (*Anacardium occidentale* L.), a type of tree nut. These are important wellsprings of improvements for people who have been treated or prevented by outdated innovations (Salas-Salvado et al., 2011). The nut of the cashew fruit is well-known, owing to its aroma and flavor, and is thus commonly consumed in roasted form, as well as used in juice and alcohol production. It has also been reported to have some medicinal properties (Mexis and Kontominas 2009; Papanastasopoulos and Stebbing, 2013; Mattison et al., 2018). In a previous study, we talked about how a diet high in cashew (*Anacardium occidentale* L.) nuts affected the sperm parameters, steroidogenic enzymes, and hormonal imbalances in male rats with cisplatin-induced reproductive impairment (Akomolafe et al., 2022).

Chemobrain, a term for the adverse effect of chemotherapy-induced brain deterioration, is frequently described by cancer patients who have tumors outside the CNS. Ahles and Saykin (2007) found that psychological deficits persist long after survival and have a negative impact on personal satisfaction (O'Farrell et al., 2013; Selamat et al., 2014; Zhou et al., 2016). The majority of breast cancer patients who had chemotherapy also experienced neurological damage (Wefel and Schagen, 2012). Reduced attention, executive functioning, handling speed, and memory were detected through formal neuropsychological testing (Ahles and Saykin, 2007). Advanced neuroimaging techniques indicate fundamental anomalies in white and gray matter, as well as obvious localized

* Corresponding author.
E-mail address: purposefulseun@yahoo.co.uk (S.F. Akomolafe).

https://doi.org/10.1016/j.heliyon.2022.e11066
Received 26 November 2021; Received in revised form 16 March 2022; Accepted 7 October 2022

changes in cerebrum function and gradually worldwide network discontinuities, in patients with chemotherapy-induced brain atrophy (Lepage et al., 2014; Janelsins et al., 2014; Simo et al., 2015).

Brain degeneration in cancer patients after platinum-based chemotherapy is regularly noticed (Vichaya et al., 2015). A number of cancers are treated using platinum-based combinations, such as cisplatin, including gynecologic, head and neck, testicular and lung cancers (Gan et al., 2011; Fung and Vaughn, 2011; Skoogh et al., 2012; Yang et al., 2013). Cisplatin infiltrates the cerebrum, inhibiting the proliferation of neural stem cells (Bost et al., 2012). A number of studies have shown that cisplatin therapy reduces brain capacity in teenage rats and adult mice (Giridharan et al., 2012; Manohar et al., 2014; Hinduja et al., 2015). As a result, a potential therapeutic approach to reduce neurotoxicity caused by synthetic chemotherapeutic drugs must be investigated. There is evidence that natural plant products have significant potential to prevent or alleviate toxicity caused by chemotherapeutic drugs (Zhang et al., 2018; Abdallah et al., 2019).

The development of neurodegenerative diseases is significantly influenced by the cholinergic system enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). At the synaptic cleft of cholinergic neurons, acetylcholine is hydrolyzed by the enzyme AChE (Lendvai and Vizi, 2008). Cholinergic neuron impairment has been linked to the etiology of Alzheimer's disease (AD), and cholinesterase inhibitors are a common therapeutic method for treating this condition (Lendvai and Vizi, 2008).

Adenosine or 2^{I}-deoxyadenosine is irreversibly deaminated to inosine by the ADA enzyme (Burnstock et al., 2011). While adenosine breakdown is crucial, ADA also plays a very important role in controlling adenosine's effects on several systems, including the CNS (Burnstock et al., 2011). In addition to being a natural antihypoxic and anticonvulsant, adenosine also regulates platelet aggregation, blood flow, lipolysis, glycogenolysis and neurotransmission (Mcilwain, 1983; Stone, 1989). It is a key site in the purinergic system for adenosine level regulation. In animals, adenosine serves a critical neuromodulatory duty in the brain (Burnstock, 2006; Burnstock et al., 2011). It protects the body against pathological circumstances by altering neurotransmitter and trophic factor release (Burnstock et al., 2011).

The mitochondrial proteins known as monoamine oxidases (MAOs) control and breakdown monoamine neurotransmitters associated with the brain and other tissues. They are found in the outer mitochondrial membrane (Walker et al., 1971). Their ability to catalyze the oxidative deamination of amines that are biogenic in nature, associated with the brain and other peripheral tissues, which controls their levels, is one of their primary roles. MAOs have been linked to psychiatric and neurological illnesses such as depression, Parkinson's disease (PD), and Alzheimer's disease (AD) in recent studies. It has been demonstrated that inhibiting MAOs offers pharmacological advantages, including the ability to preserve neurons and possess antidepressant and antianxiety characteristics, suggesting that it may enhance the concentration of neurochemicals associated with the CNS (Saura et al., 1994).

There are no drugs available to prevent or cure brain weakening caused by chemotherapy. In the search for a solution for chemotherapy-initiated brain deficiencies, prevention has gotten significantly less attention; notwithstanding, a developing wide array of studies recommend the expected advantage of improving the brain's endogenous protectors by enhancing with phytochemicals from fruits and vegetables. There is growing evidence that suggests dietary habits may be very important in defending the brain from chemotherapy-induced brain damage. Dietary supplementation with diverse foods has been shown to have a variety of protective effects against mental illness (Yehuda et al., 2005). Higher consumption of particular nutrients or explicit dietary examples is linked to a lower risk of cognitive impedance, which is thought to be due to an increase in supplement consumption (Commenges et al., 2000; Engelhart et al., 2002; Morris et al., 2005).

However, there have been few studies on the paraphernalia of cashew nuts on neurochemicals linked to brain function in cisplatin-treated rats. Therefore, the objective of this investigation is to see how cashew nut supplementation affected neurochemicals linked to brain function.

To induce neurotoxicity, rats were given cisplatin and a diet supplemented with roasted cashew nuts. The enzymes, cholinergic (acetylcholinesterase), monoaminergic (monoamine oxidase), and purinergic (adenosine deaminase) were tested. It was assumed that adding roasted cashew nuts to a diet would enhance brain-related neurochemicals and lessen oxidative damage in rats' cisplatin-treated brains.

2. Materials and methods

2.1. Source of chemicals

Sigma Chemical Co. provided the chemicals (St. Louis, MO, USA). The phenolic components in the powdered-roasted cashew nuts were analyzed using high performance liquid chromatography technology.

2.2. Ethical approval

The Science National Academy and the Health National Institute produced a manual for the handling and use of laboratory animals, which was adhered to. The Ekiti State University Ethics Committee approved the use of animals (permission number: ORD/AD/EAC/19/0057).

2.3. Sample preparation

To attain constant weight, cashew seeds were obtained from the major market in Ado Ekiti metropolis, and then further dried at sixty-degree Celsius right inside a cabinet dryer. Using a manual cashew kernel cutter, the nuts were isolated from the coat and roasted at 100 °C for 2 h before being clasped and sorted to remove the testa. Using a Kenwood blender, cream-colored nuts were ground into flour after cooling. In an attempt to sieve the flour, it was made to pass through a Z400122 Aldrich fine test SS frame sieve that has one hundred and twenty five microliter pore size, to produce a smooth powder. This was placed in a refrigerator and kept there until use in an airtight container. This was incorporated into the diet plan (Table 1). The sample's close examination was done to determine the various nutritional contents that were used in the diet formulation (Table 2) (Akomolafe et al., 2022) (Table 1).

Table 1. Diet formulation for basal and supplemented diets for control and test groups.

Treatment	Group I	Group II	Group III	Group IV	Group V	Group VI
Skimmed milk	40.0	40.0	31.3	22.6	31.3	22.6
Oil	10.0	10.0	5.71	1.42	5.71	1.42
Vitamin premix	4.0	4.0	4.0	4.0	4.0	4.0
Corn starch	46.0	46.0	48.99	51.98	48.99	51.98
Cashew nut	-	-	10.0	20.0	10.0	20.0
Total	100 g	100 g	100 g	100 g	100 g	100 g

Note: Skimmed milk = 32% protein; The vitamin premix (mg or IU/g) h was the following composition; 3200 IU vitamin A, 600 IU vitamin D3, 2.8 mg vitamin E, 0.6 mg vitamin K3, 0.8 mg vitamin B1, 1 mg vitamin B2, 6 mg niacin, 2.2 mg pantothenic acid, 0.8 mg vitamin B6, 0.004 mg vitamin B12, 0.2 mg folic acid, 0.1 mg biotin H2, 70 mg choline chloride, 0.08 mg cobalt, 1.2 mg copper, 0.4 mg iodine, 8.4 mg iron, 16 mg manganese, 0.08 mg selenium, 12.4 mg zinc, 0.5 mg antioxidant. Group I: (Control) normal control rats fed basal diet; Group II: (Induced) serve as cisplatin group placed on a basal diet; Group III: cisplatin induced rats fed diet supplemented with 10% processed cashew nut Group IV: cisplatin induced rats fed diet supplemented with 20% processed cashew nut; Group V: normal rats fed diet supplemented with 10% processed cashew nut; Group VI: normal rats fed diet supplemented with 20% processed cashew nut.

Table 2. Proximate component of roasted cashew nut.

Components	%
Moisture	4.33 ± 0.03
Ash	2.14 ± 0.10
Crude fat	40.32 ± 0.24
Crude protein	25.48 ± 0.12
Crude fibre	3.50 ± 0.04
Carbohydrate	24.23 ± 0.10
PEF %	64.45
PEP %	18.22
PEC %	17.33
UEDP %	10.93
Caloric value (KJ/100g)	2,377.23 ± 0.46

Results represent mean ± standard deviation of three determinations. PEP = Proportion of total energy due to protein, PEF = Proportion of total energy due to fat, PEC = Proportion of total energy due to protein, UEDP = Utilizable energy due to protein. Source: Akomolafe et al. (2022).

2.4. Animal care, formulation of diets and experimental protocol

In accordance with the National Council for the Control of Animal Experiments and the Institutional Ethics Committee's regulations, 48 Wistar albino male rats (weighing between 230 and 250 g) were housed with unlimited access to food and water throughout the course of the study. The animals were divided into six groups of eight rats each, with an average weight of 239 ± 6 animals each. Rats in Group I were normal controls (NC) and were provided a basal diet consisting of forty percent skim milk, ten percent vegetable oil, four percent vitamin and mineral premix, and forty-six percent corn starch. Rats in Group II were induced with 7 mg/kg b.w.t (i.p) CP alone and fed a basal diet. Rats in Groups III to VI received meals enriched with 10 and 20 percent roasted cashew nuts, respectively, while Groups III and IV were given a single dose of CP (7 mg/kg body weight, i.p., Fallahzadeh et al., 2017) after receiving roasted cashew nuts for 28 days. On day twenty-eight, cisplatin was administered at seven in the morning. Animals were sacrificed 24 h after receiving CP injections. The diets were newly made in accordance with Table 1 and expert recommendations (Akinyemi et al., 2014).

2.5. Necropsy and preparation of tissue

Under a minimal amount of diethyl ether anesthesia, cervical dislocation was used to sacrifice the rats. The post-mitochondrial fraction of the brain was obtained by isolating it, centrifuging it for 15 min at 12,000 g while rinsing it in 1.15 percent KCl, homogenizing it in phosphate buffer (with a concentration of 0.1 M and a pH of 7.4), and storing it at −20 °C for biochemical analysis (Akomolafe et al., 2015b).

2.6. Biochemical assays

The resulting supernatant was tested for the activities of adenosine deaminase (Giusti and Gakis, 1971), arginase (Zhang et al., 2001), glutathione-S-transferase (Habig et al., 1974), glutathione peroxidase (Paglia and Valentine, 1967), cholinesterases (Ellman et al., 1961), superoxide dismutase (Misra and Fridovich, 1972), catalase (Clairborne, 1995), monoamine oxidase (MAO) (Green and Haughton, 1961) activities; as well as), total antioxidant capacity (Kambayashi et al., 2009), nitric oxide (Miranda et al., 2001), non-protein thiol (Ellman, 1959), total thiol (Ellma, 1959), reactive oxygen species (ROS) (Hayashi et al., 2007) and thiobarbituric acid reactive species (TBARS) (Jentzsch et al., 1996) levels. According to the findings of Lowry et al. (1951) the total protein content of the tissue was determined.

2.7. Histopathological examination

Bouin's fixative was used for 6 h to conduct the histopathological analysis. The fixed tissue was cleaned with xylene, dried with alcohol, and then placed inside paraffin wax. The tissue was cut into segments of between four to five micrometer with a microtome, placed on slides, and stained with hematoxylin and eosin (H and E). The tissue was then seen with an Olympus/3H light microscope at X400 magnification.

2.8. Data analysis

All data were examined for normality and Prism was used for analysis (Graph cushion, San Diego, CA, USA). While fitting post-hoc treatment was used, one way analysis of variance (ANOVA) was used to analyze the mean. The threshold for statistical significance was set at 0.05, and the data were presented as mean ± SD or SEM.

3. Results

3.1. Effect of CN-supplemented diet on cholinesterases activities in cisplatin-intoxicated rats

The impact of cisplatin on AChE activity of rats took care of with roasted cashew nut enhanced diet is appeared in Figure 1A. Cisplatin significantly ($P < 0.05$) increased AChE activity contrasted with the control, 10% CN and 20% CN groups. Treatment with roasted cashew nut enhanced eating regimen significantly ($P < 0.05$) diminished the activity of acetylcholinesterase in the rats' brain in CIS +10% CN and CIS +20% CN groups. In any case, a critical diminishing in the activity of AChE was seen in rats' brain homogenates in CIS +20% CN contrasted with CIS +10% CN. A comparative outcome was acquired for the activity of butyrylcholinesterase in the rats' brain in CIS group contrasted with different groups as uncovered by Figure 1B. A lessening in BChE activity was seen in CIS +10% CN and CIS +20% CN. There was no conspicuous distinction in the activity of butyrylcholinesterase in rats' brain homogenates in these two groups (CIS +10% CN and CIS +20% CN).

3.2. Effect of CN-supplemented diet on adenosine deaminase and monoamine oxidase activities in cisplatin-intoxicated rats

After every day treatment, roasted cashew nut enhanced diet didn't influence ADA activity in normal rats fed 10% CN and 20% CN supplemented diet as appeared in Figure 2A, although there was decrease in the activity of ADA when compared with normal control rats but there was no statistical difference between them. Be that as it may, the administration of cisplatin set off a significant increment in ADA activity contrasted with the control, 10% CN and 20% CN groups. Roasted cashew nut enhanced eating routine decreased adenosine deaminase activity in the brain of rats in CIS +10% CN and CIS +20% CN groups. There was no undeniable contrast in adenosine deaminase action in rats' brain homogenate in these two groups. A comparative outcome was acquired for the activity of MAO activity in the rats' brain in CIS group contrasted with different groups as uncovered by Figure 2B. A decline in MAO activity was seen in CIS +10% CN and CIS +20% CN. In any case, a significant lessening in MAO activity was seen in brain homogenates of rats in CIS +20% CN contrasted with CIS +10% CN while 20% roasted cashew nut upgraded diet caused a critical decline in MAO action when contrasted with control.

3.3. Effect of CN-supplemented diet on nitric oxide level and arginase activity in cisplatin-intoxicated rats

Figure 3A portrays the NO amounts of test rats. This outcome shows that cisplatin significantly decreased NO levels in rat brain in CIS group contrasted with different groups. Be that as it may, the administration of roasted cashew nut enhanced eating routine set off the formation of NO

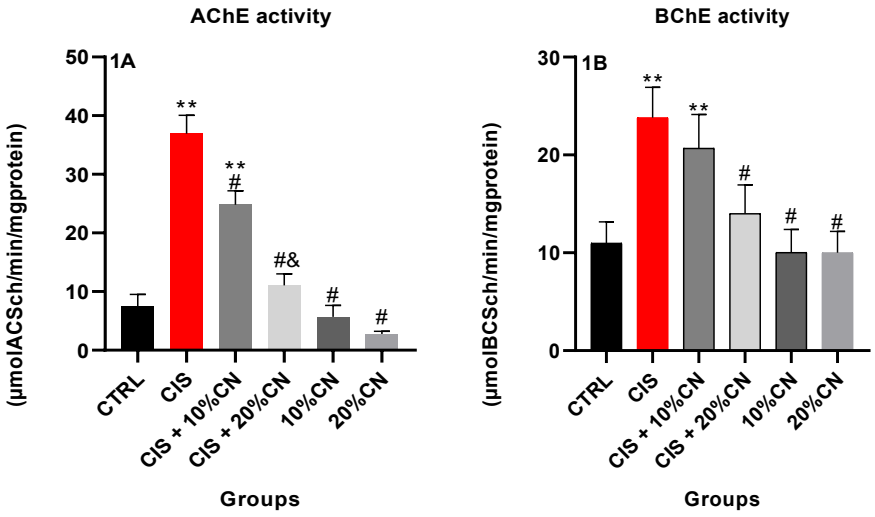

Figure 1. Effect of roasted cashew nut enhanced diet on (A) acetylcholinesterase and (B) butyrylcholinesterase activities in brain homogenates of cisplatin-initiated rats. The data are expressed as mean ± SEM. **P < 0.05 against control; #P < 0.05 against CIS; &P < 0.05 against CIS +10% CN.

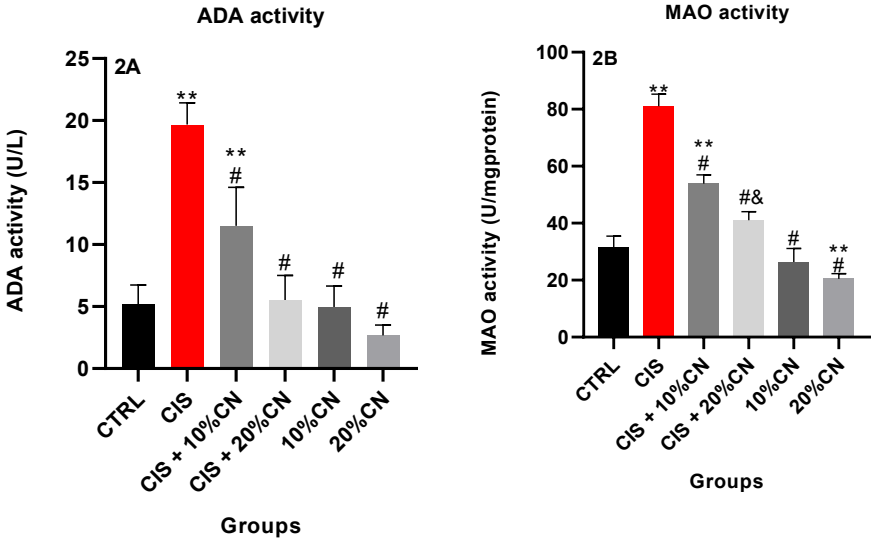

Figure 2. Effect of roasted cashew nut enhanced diet on (A) adenosine deaminase and (B) monoamine oxidase activities in brain homogenates of cisplatin-initiated rats. The data are expressed as mean ± SEM. **P < 0.05 against control; #P < 0.05 against CIS; &P < 0.05 against CIS +10% CN.

in CIS +10% CN and CIS +20% CN groups, though there was contrast in NO levels in the rats' brain homogenates in these two groups. The outcome in Figure 3B uncovered that there is no noteworthy distinction in the activity of arginase in homogenates of brain of the control, 10% CN and 20% CN groups. In any case, raised arginase activity was seen in CIS group because of treatment with cisplatin. Roasted cashew nut enhanced diet diminished arginase activity in CIS +10% CN and CIS +20% CN groups and was not significantly (P < 0.05) not quite the same as the control.

3.4. Effect of CN-supplemented diet on oxidative stress markers in cisplatin-intoxicated rats

In the treated rats, antioxidative status was assessed utilizing the degree of TBARS, ROS, T-SH, NPSH and TAC just as activities of CAT, SOD, GST and GPx (Figure 4A, B, C, D, E, F, G, H, I). As introduced in Figure 4A, a critical (p < .05) decline in the activity of SOD was seen in CIS group contrasted with control and roasted cashew nut enhanced diet treated groups. Also, the action of SOD in CIS +10% CN and CIS +20% CN was significantly (P < 0.05) higher contrasted with CIS. Likewise, as appeared in Figure 4B, C and D, comparable pattern was seen in CAT, GST and GPx activities. Treatment with roasted cashew nut enhanced diet didn't influence the action of CAT, GST and GPx in 10% CN and 20% CN groups when contrasted with the control as appeared in Figure 4B, C and D. Be that as it may, cisplatin set off a decline in CAT, GST and GPx activities past normal levels in CIS group contrasted with control, 10% CN and 20% CN groups. A significant increment in CAT, GST and GPx activities was seen in CIS +10% CN and CIS +20% CN yet the enzymes activities were not up to control levels. Figure 4E, F, and G uncovered the impact of roasted cashew nut enhanced diet on protein thiol, non-protein thiol and total antioxidant capacity. Treatment with cisplatin set off a significant abatement in protein thiol, non-protein thiol and total antioxidant capacity in CIS group as appeared in Figure 4E, F and G separately. In any case, roasted cashew nut improved eating routine caused a

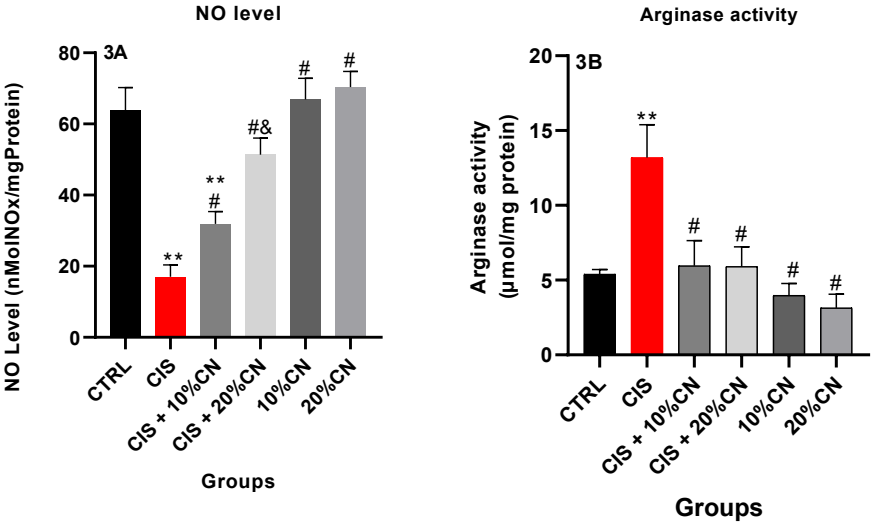

Figure 3. Effect of roasted cashew nut enhanced diet on (A) nitric oxide level and (B) arginase activity in brain homogenates of cisplatin-initiated rats. The data are expressed as mean ± SEM. **P < 0.05 against control; #P < 0.05 against CIS; &P < 0.05 against CIS +10% CN.

noteworthy increment in protein thiol, non-protein thiol and total antioxidant capacity in CIS +10% CN and CIS +20% CN. Moreover, Figure 4H and I uncovered that treatment with cisplatin set off the formation of TBARS and ROS individually in CIS group contrasted with the control and roasted cashew nut enhanced diet treated groups. Be that as it may, treatment with roasted cashew nut enhanced diet weakened the release of TBARS and ROS in CIS +10% CN and CIS +20% CN.

3.4.1. Histological examination

CIS treatment indicated more structures of neuronal degeneration contrasted with control and roasted cashew nut enhanced diet treated only groups, especially in the brain section demonstrating misshaped nuclei in the granular layer (red arrows) as delineated in Figure 5(II). Neurodegenerative structure are likewise seen in group treated with both CIS and 10% CN (yellow arrows), though less significantly.

4. Discussion

Cisplatin-incited neurotoxicity is the significant dose constraining unfavorable impact of cisplatin, there are various investigations managing this issue (Abdel-Wahab and Moussa, 2019). Verification is storing up to recommend that dietary patterns may expect a critical capacity in protecting the brain from chemotherapy-initiated brain weakness. The viability of dietary enhancement with different sustenance has been seemed to induce a collection of protective effects against neurotoxicity related with platinum-based chemotherapeutic regimens (Yehuda et al., 2005; Morris et al., 2005; Engelhart et al., 2002; Commenges et al., 2000). In this current investigation, we plainly analyzed the effect of roasted cashew nuts enhanced diet on enzymes related with brain function in cisplatin-initiated brain damage in adult male Wistar rat. As far as anyone is concerned, the anticipation of neurotoxic impact of cisplatin with roasted cashew nuts enhanced diets treatment has been shown in this investigation for the first time.

The result of proximate composition of roasted cashew nut is shown in Table 2. Comparably higher than the values recorded for various edible nuts consumed in Nigeria was the crude protein content (25.48 ± 0.12%): 4.13% (Tiger nut) (Okorie and Nwanekezi, 2014), 14.40% (pea nut) (Stevens-Barrón et al., 2019), 20.44% (Bambara nut) (Anhwange and Atoo, 2015); but favourably compared with the values reported for walnut (29.81%) (Stevens-Barrón et al., 2019). The amount of minerals or inorganic components in a sample of roasted cashew nuts is indicated by their 2.14 percent ash content. The absence of certain minerals may lead to altered metabolism since they serve as inorganic co-factors in metabolic processes (Adesina and Akomolafe, 2014). Other parameters derived from the proximal values are still listed in Table 2. It displays the different energy values that protein, fat, and carbohydrates contribute. Depending on his physiological state, an adult's daily energy demand ranges from 2500 to 3000 kCal (10455–12548 kJ), but an infant's daily energy requirement is 740 kCal (3094.68 kJ) (Bingham, 1978). This suggests that while an adult man would need between 934 and 1,123 g to meet his energy needs, newborns would only need 276.9 g to do so (based on the projected energy of 2,377 kJ/100 g). Overall, this meant that fewer samples would need to be used to meet the energy requirements of adults and newborns than samples with lower energy values. Also, at the end of feeding treatment, Table 3 revealed that all the rats eat the same ration of food as there was no significant difference between their average feeding intake.

Cholinergic dysfunction is an essential indication of neurotoxicity. In this, the toxicity of cisplatin in the brain was portrayed by a significant increment in AChE and BChE activities which concurs with past examinations (Abdel-Wahab and Moussa, 2019; Jangra et al., 2016; Chtourou et al., 2015). The neurotoxic effects of cisplatin, which damage neurons, disrupt the cholinergic system, and cause rapid acetylcholine breakdown, may be the origin of the observed increase in the activities of AChE and BChE. The elevation in AChE activity may potentially be caused by an increase in ROS generation. ROS has been observed to speed up the peroxidation of the plasma membrane, which impacts the cholinergic system's functionality and integrity (Melo et al., 2003). Notwithstanding, treatment with roasted cashew nuts enhanced diets decreased AChE activity which proposes lessening of cholinergic deficiency. This outcome recommends that roasted cashew nuts enhanced diets may improve cholinergic and brain function in cisplatin-initiated rats. Additionally, our discoveries uncovered that there is noteworthy distinction between CIS +10% CN and CIS +20% CN treatment groups. This outcome shows that higher utilization of roasted cashew nut might be progressively advantageous as against that of a lower utilization.

Adenosine or 2^{I}-deoxyadenosine is irreversibly deaminated to inosine by the catalyst ADA (Burnstock et al., 2011). ADA is similarly essential for regulating the impact of adenosine on various systems, including the CNS, despite adenosine breakdown (Burnstock et al., 2011). As an endogenous antihypoxic, anticonvulsant, and modulator of platelet aggregation, lipolysis, glycogenolysis, circulatory system, and neurotransmission, adenosine

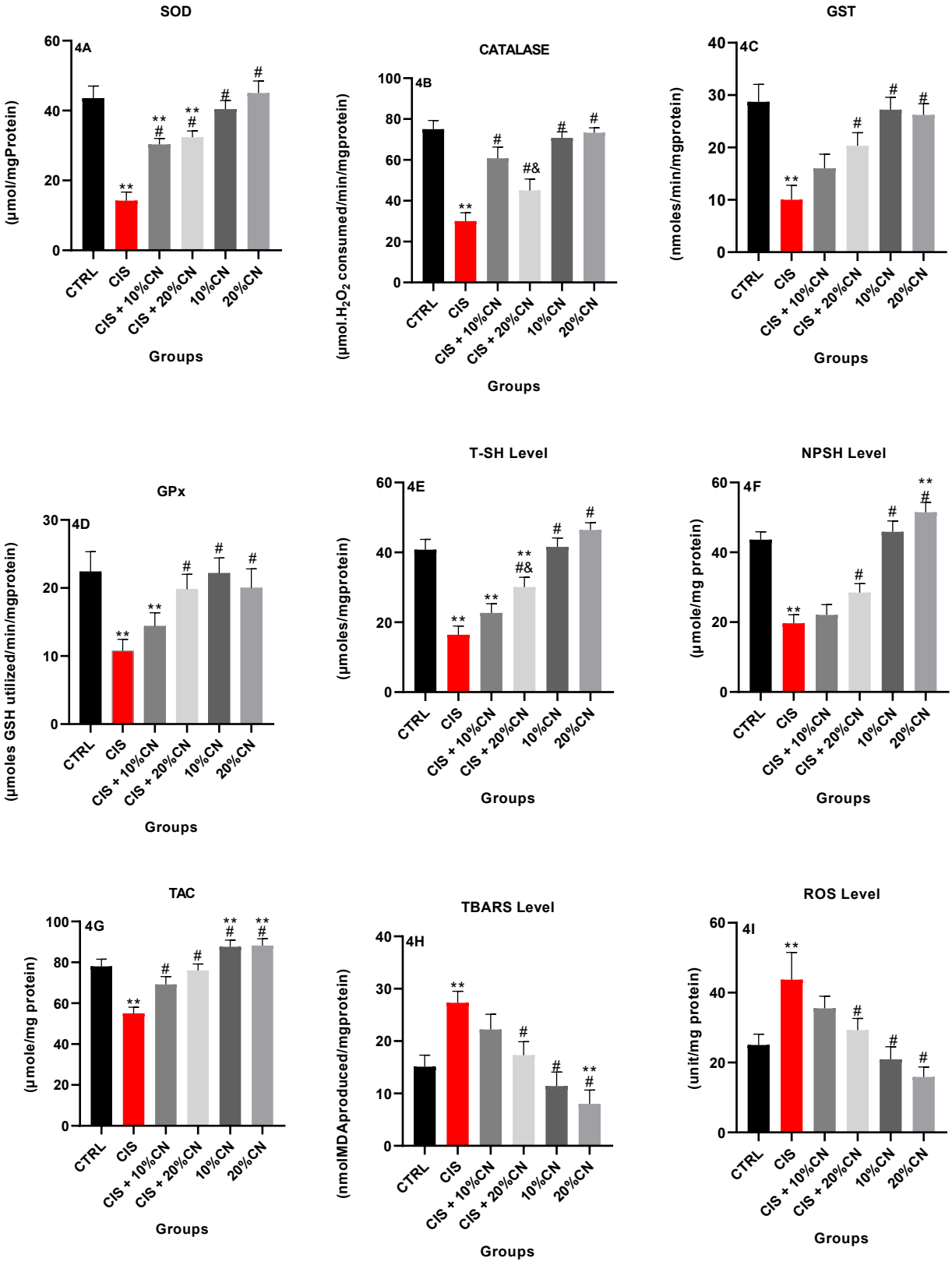

Figure 4. Effect of roasted cashew nut enhanced diet on (A) superoxide dismutase activity, (B) catalase activity, (C) glutathione-S-transferase activity (D) glutathione peroxidase activity, (E) total thiol level, (F) non protein thiol level, (G) total antioxidant capacity, (H) thiobarbituric acid level and (I) reactive oxygen species level in brain homogenates of cisplatin-initiated rats. The data are expressed as mean ± SEM. **P < 0.05 against control; $^{\#}$P < 0.05 against CIS; $^{\&}$P < 0.05 against CIS +10% CN.

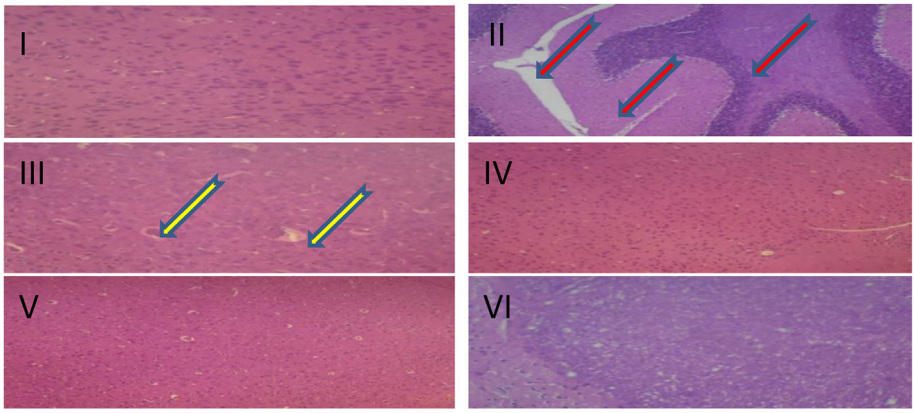

Figure 5. H&E (X400 mag) brain photomicrographs of: (I) normal control rats fed basal diet section showing normal nuclei and white matter, (II) cisplatin treated rats fed basal diet brain section showing distorted nuclei in the granular layer (red arrows), (III) cisplatin induced rats fed diet supplemented with 10% roasted cashew nut section showing partially reduced damage with few shrunken cell bodies along with normal nucleus and cytoplasm (yellow arrows), (IV) cisplatin induced rats fed diet supplemented with 20% roasted cashew nut section resembles control group, (V) rats fed diet supplemented with 10% roasted cashew nut section resembles control group and (VI) rats fed diet supplemented with 20% roasted cashew nut section resembles control group.

Table 3. Average feed intake of cisplatin-induced rats fed diet supplemented with processed cashew nut.

Group	Treatment	Average feed intake (g per rat per 28 days)
I	Normal control	$1,364.38 \pm 69.16^{a}$
II	Cisplatin induced	$1,327.31 \pm 75.44^{a}$
III	Cisplatin +10% CN	$1,359.45 \pm 66.80^{a}$
IV	Cisplatin +20% CN	$1,393.17 \pm 72.56^{a}$
V	Normal +10% CN	$1,334.48 \pm 84.28^{a}$
VI	Normal +20% CN	$1,341.82 \pm 87.84^{a}$

Values represent mean ± standard deviation ($n = 8$). Values with different superscript letters are significantly ($P < 0.05$) different. CN = Cashew nut. Source: Akomolafe et al. (2022).

also acts as an inhibitor of hypoxia and an inducer of hypoxia (Mcilwain, 1983; Stone, 1989). It serves as a significant factor for adenosine level modulation in the purinergic system. Adenosine accepts a notable neuromodulatory role in mammals' central nervous systems (CNS) in the brain (Burnstock, 2006; Burnstock et al., 2011). Under extreme circumstances, it accepts a protective role by adjusting the release of neurotransmitters and trophic components (Burnstock et al., 2011). The discoveries uncovered that cisplatin increased the activity of ADA in the brain. High ADA activity decreases adenosine levels significantly and has been associated with memory impairment. In this investigation, CN use stopped an excessive rise in ADA activity brought on by CIS-administration. Outstandingly, treatment with roasted cashew nuts enhanced diet diminished ADA activity which proposes that the exhaustion of extracellular adenosine can disturb memory development since it has been accounted for to be a significant neuromodulator in the foundation of long-term potentiation (LTP) and long-term depression (LTD), just as in synaptic flexibility (Burnstock, 2006; Gutierres et al., 2012). In the brain homogenates of the rats in the cisplatin-actuated groups treated with 10% and 20% roasted cashew nut increased diet, there was no discernible difference in the adenosine deaminase activity. The observed decrease in ADA activity showed by CN-fed rats may be explained by an increase in adenosine levels, which have been shown to protect against memory loss through their interaction with adenosine receptors (Olasehinde et al., 2020).

In our study, cisplatin also markedly increased the brain's MAO activity. The creation of H_2O_2 as a consequence of the oxidative deamination of monoamine synapses, which is catalyzed by MAO, was explained (Akomolafe et al., 2017; Ooi et al., 2015). In this way, the improved action of MAO might be a significant method in increasing the formation of H_2O_2, along these lines increasing oxidative stress. Increased oxidative stress has the potential to initiate and spread neurodegenerative processes as well as cause oxidative damage to diverse brain regions (Akomolafe et al., 2017). Treatment with roasted cashew nuts enhanced diet in the current examination reestablished the usual action of MAO. The antioxidant action and free radical-suppressing properties of roasted cashew nuts may be found responsible for the ameliorative effects of improved diets. Regardless, 20% roasted cashew nut enhanced diet caused a serious decrease in MAO activity when contrasted with 10% roasted cashew nut enhanced diet.

Inflammation has been accounted for to be embroiled in the pathophysiological forms related with brain injury (Abdel-Wahab and Moussa, 2019; Kadhim et al., 2008) and appear to be the fundamental components in the neurotoxicity of cisplatin (Jaggi and Singh, 2012). Our discoveries likewise indicated that cisplatin may incite neuroinflammation and neurodegeneration because of an increase in NO formation and arginase action upregulation as saw in CIS groups. Test examinations have indicated that high arginase action and changes in NO levels may add to neurodegeneration (Caldwell et al., 2015; Olasehinde et al., 2019b; Akomolafe et al., 2020). Arginase and nitric oxide synthase (NOS) compete for the same substrate, therefore increasing the activity of the former decreases arginine levels, modifies NOS activity, and inhibits NO production (Zhou et al., 2015). Low NO levels and increased arginase activity cause nitrosative stress, which may cause neurodegeneration by producing superoxide and peroxynitrite (Kim et al., 2009; Polis and Samson, 2018). Therefore, the rise in arginase activity and notable decline in nitric oxide in rat brains from CIS groups may affect memory functions, inhibit long-term potentiation, and hasten neurodegeneration (Virarkar et al., 2013). Our outcomes indicated that treatment with roasted cashew nut enhanced diet turned around arginase action and NO levels in CIS +10% CN and CIS +20% CN gatherings. The watched decrease in arginase action in CIS +10% CN and CIS +20% CN may forestall neuronal dysfunction and neuroinflammation.

Antioxidants have a well demonstrated role in the neuroprotective pathways of brain function (Zaki, Abd-EL-Fattah, and Attia, 2014). The outcome uncovered that cisplatin administration brought about a significant ($p < .05$) increment in TBARS and ROS levels with an attendant synergistic diminishing in TAC, T-SH, NPSH, levels, SOD, CAT, GST and GPx activities in brain of rats contrasted with control. Therefore, a reduction in TAC, protein and non-protein thiols, SOD, CAT, GST, and GPx activities as well as an associated synergistic upsurge in TBARS and ROS levels in the brain of rats in the CIS group may result in oxidative damage to the neurons (Akomolafe et al., 2020; Akomolafe, 2017; Valko et al. 2007). In any case, treatment with roasted cashew nut enhanced diet caused a noteworthy increment in TAC, protein and non-protein thiols, SOD, CAT, GST and GPx activities and an attendant synergistic diminishing in TBARS and ROS levels which recommend guard against CIS-instigated oxidative harm to the brain cells. These perceptions could bring about adequacy of the brain antioxidant status to adequately forestall initiation of oxidative stress in the treated rats. These perceptions because of presentation of the dietary cashew nut to the eating regimen could be connected to the synergistic impact of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), flavonoids, proanthocyanidins, phenolic acids,

vitamin E, and folate present in the nut. Tree nuts are a significant source of essential nutrients like fiber, vitamin E, and folate, according to Carey et al. (2012). They also include a number of nutrients, including mono-unsaturated, omega-3, and omega-6 polyunsaturated fatty acids, as well as phytochemicals like flavonoids, proanthocyanidins, and phenolic acids that may help fight brain dysfunction.

Photomicrographs got from histological examinations uncovered that treatment with cisplatin actuated neuronal harm in the brain of the rodents in CIS group. The watched neuronal degeneration and distorted nuclei in the granular layer in the brain areas might be expected to cisplatin-initiated oxidative harm. Upsurge in free radical levels have been linked to the onset of neurodegeneration in the brain (Akomolafe et al., 2020). In any case, treatment with roasted cashew nut enhanced diet forestalled neuronal degeneration in the brain particularly in CIS +20% CN group.

5. Conclusion

The goal of this study was to see if a roasted cashew nut supplemented diet may improve neurochemicals linked with brain function in cisplatin-treated rats. Cisplatin inhibited purinergic, monoaminergic, and cholinergic transmission in the rat brain and caused oxidative stress, according to the findings. However, a diet supplemented with roasted cashew nuts can help to protect these neurochemicals by lowering purinergic, monoaminergic, and cholinergic enzymes, inhibiting ROS and TBARS generation, and increasing antioxidant enzymes and thiol levels. These findings shed light on the biochemical and therapeutic benefits of a roasted cashew nut supplemented diet for neurological impairments caused by cisplatin treatment. Be that as it may, higher utilization of roasted cashew nut might be progressively valuable as against that of a lower utilization. Notwithstanding, clinical investigations are required for forestalling the neurotoxicity in malignancy patients.

Declarations

Author contribution statement

Seun F. Akomolafe: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Abiola M. Asowata-Ayodele: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

Abdallah, H.M., Abdel-Rahman, R.F., El Awdan, S.A., Allam, R.M., El-Mosallamy, A.E., Selim, M.S., Mohamed, S.S., Arbid, M.S., Farrag, A.R.H., 2019. Protective effect of some natural products against chemotherapy-induced toxicity in rats. Heliyon 5 (5), 01590.

Abdel-Wahab, W.M., Moussa, F.I., 2019. Neuroprotective effect of *N*-acetylcysteine against cisplatin-induced toxicity in rat brain by modulation of oxidative stress and inflammation. Drug Des. Dev. Ther. 13, 1155–1162.

Adesina, A.J., Akomolafe, S.F., 2014. Nutritional and anti-nutritional composition of *bridelia ferruginea* benth (euphorbiaceae) stem back sample. Int. J. Sci. Res. Knowl. 2 (2), 92–104.

Ahles, T.A., Saykin, A.J., 2007. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat. Rev. Cancer 7, 192–201. PMID: 17318212.

Akinyemi, A.J., Ademiluyi, A.O., Oboh, G., 2014. Inhibition of angiotensin-1-convertingenzyme activity in high cholesterol fed diet in rats by two varieties of ginger (Zingiber officinale). J. Med. Food 17 (3), 317–323.

Akomolafe, S.F., Akinyemi, A.J., Ogunsuyi, O.B., Oyeleye, S.I., Oboh, G., Adeoyo, O.O., Allismith, Y.R., 2017. Effect of caffeine, caffeic acid and their various combinations on enzymes of cholinergic, monoaminergic and purinergic systems critical to neurodegeneration in rat brain—*In vitro*. NeuroToxicol. 62, 6–13.

Akomolafe, S.F., 2017. The effects of caffeine, caffeic acid, and their combination on acetylcholinesterase, adenosine deaminase and arginase activities linked with brain function. J. Food Biochem., e12401

Akomolafe, S.F., Oboh, G., Akindahunsi, A.A., Afolayan, A.J., 2015. Antiperoxidative activity of Tetracarpidium conophorum leaf extract in reproductive organs of male rats. Evid. base Compl. Alternative Med. Article ID 798491, 8.

Akomolafe, S.F., Olasehinde, T.A., Oyeleye, S.I., Aluko, B.T., Adewale, O.O., Ijomon, O.M., 2020. Curcumin administration mitigates cyclophosphamide-induced oxidative damage and restores alteration of enzymes associated with cognitive function in rats' brain. Neurotox. Res. 38, 199–210.

Akomolafe, S.F., Oyeleye, S.I., Oboh, G., 2022. Effect of cashew (*Anacardium occidentale* L.) nut-supplemented diet on steroidogenic enzymes, hormonal and oxidative imbalances, and sperm parameters in cisplatin-induced reproductive toxicity in male rats. J. Food Biochem., e14100

Anhwange, B.A., Atoo, G.H., 2015. Proximate composition of indigenous Bambara nuts (vigna subterranean (L.) verdc). SCSR J. Pure Appl. Sci. 2 (1), 11–16.

Bingham, S., 1978. Nutrition: A Consumer's Guide to Good Eating. Transworld Publishers, London.

Bost, F., Sahra, I.B., Le Marchand-Brustel, Y., Tanti, J.F., 2012. Metformin and cancer therapy. Curr. Opin. Oncol. 24, 103–108.

Burnstock, G., 2006. Purinergic signalling. Br. J. Pharmacol. 147, 172–181.

Burnstock, G., Fredholm, B.B., Verkhratsky, A., 2011. Adenosine and ATP receptors in the brain. Curr. Top. Med. Chem. 11, 973–1011.

Caldwell, R.B., Toque, H.A., Narayanan, S.P., Caldwell, R.W., 2015. Arginase: an old enzyme with new tricks. Trends Pharmacol. Sci. 36 (6), 395–405.

Chtourou, Y., Gargouri, B., Kebieche, M., Fetoui, H., 2015. Naringin abrogates cisplatin-induced cognitive deficits and cholinergic dysfunction through the down-regulation of AChE expression and iNos signaling pathways in hippocampus of aged rats. J. Mol. Neurosci. 56 (2), 349–362.

Clairborne, A., 1995. Catalase activity. In: Greewald, A.R. (Ed.), Handbook of Methods for Oxygen Radical Research. CRC Press, Boca Raton, USA, pp. 237–242.

Commenges, D., Scotet, V., Renaud, S., Jacqmin-Gadda, H., Barberger-Gateau, P., Dartigues, J.F., 2000. Intake of flavonoids and risk of dementia. Eur. J. Epidemiol. 16 (4), 357–363.

Ellman, G.L., 1959. Tissue sulfhydryl groups. Arch. Biochem. Biophys. 82, 70–77.

Ellman, G.L., Courtney, K.D., Andres, V., Featherstone, R.M., 1961. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 7, 88–95.

Engelhart, M.J., Geerlings, M.I., Ruitenberg, A., van Swieten, J.C., Hofman, A., Witteman, J.C., 2002. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 287 (24), 3223–3229.

Fallahzadeh, A.R., et al., 2017. Evaluation of the effect of pentoxifylline on cisplatin-induced testicular toxicity in rats. Toxicol. Res. 33 (3), 255–263.

Fung, C., Vaughn, D.J., 2011. Complications associated with chemotherapy in testicular cancer management. Nat. Rev. Urol. 8, 213–222.

Gan, H.,K., Bernstein, L.J., Brown, J., Ringash, J., Vakilha, M., Wang, L., 2011. Cognitive functioning after radiotherapy or chemoradiotherapy for head-and-neck cancer. Int. J. Radiat. Oncol. Biol. Phys. 81, 126–134.

Giridharan, V.V., Thandavarayan, R.A., Bhilwade, H.N., Watanabe, K., Konishi, T., Schisandrin, B., 2012. Attenuates cisplatin-induced oxidative stress, genotoxicity and neurotoxicity through modulating NF-kappaB pathway in mice. Free Radic. Res. 46, 50–60.

Giusti, G., Gakis, C., 1971. Temperature conversion factors, activation energy, relative substrate specificity and optimum pH of adenosine deaminase from human serum and tissues. Enzyme 12, 417–425.

Green, A.L., Haughton, T.M., 1961. A colorimetric method for the estimation of monoamine oxidase. Biochem. J. 78, 172–175.

Gutierres, J.M., Carvalho, F.B., Schetinger, M.R., Rodrigues, M.V., Schmatz, R., Pimentel, V.C., Spanevello, R.M., 2012. Protective effects of anthocyanins on the ectonucleotidase activity in the impairment of memory induced by scopolamine in adult rats. Life Sci. 91, 1221–1228.

Habig, W.H., Pabst, U.J., Jakoby, W.B., 1974. Glutathione-S-transferase. J. Biol. Chem. 249, 7130–7139.

Hayashi, I., Morishita, Y., Imai, K., Nakamura, M., Nakachi, K., Hayashi, T., 2007. High-throughput spectrophotometric assay of reactive oxygen species in serum. Mutat. Res., Genet. Toxicol. Environ. Mutagen. 631 (1), 55–61.

Hinduja, S., Kraus, K.S., Manohar, S., Salvi, R.J., 2015. D-methionine protects against cisplatin-induced neurotoxicity in the Hippocampus of the adult rat. Neurotox. Res. 27 (3), 199–204.

Jaggi, A.S., Singh, N., 2012. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology 291 (1–3), 1–9.

Janelsins, M.C., Kesler, S.R., Ahles, T.A., 2014. Morrow GR.Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int. Rev. Psychiatr. 26, 102–113.
Jangra, A., Kwatra, M., Singh, T., 2016. Edaravone alleviates cisplatin-induced neurobehavioral deficits via modulation of oxidative stress and inflammatory mediators in the rat hippocampus. Eur. J. Pharmacol. 791, 51–61.
Jentzsch, A.M., Bachmann, H., Fürst, P., Biesalski, H.K., 1996. Improved analysis of malondialdehyde in human body fluids. Free Radic. Biol. Med. 20 (2), 251–256.
Kadhim, H., Duchateau, J., Sebire, G., 2008. Cytokines and brain injury. J. Intensive Care Med. 23 (4), 236–249.
Kambayashi, Y., Binh, T., Asakura, H.W., 2009. Efficient assay for total antioxidant capacity in human plasma using a 96-well microplte. J. Clin. Biochem. Nutr. 44 (1), 46–51.
Kim, J.H., Bugaj, L.J., Oh, Y.J., Bivalacqua, T.J., Ryoo, S., Soucy, K.G., Nyhan, D., 2009. Arginase inhibition restores NOS coupling and reverses endothelial dysfunction and vascular stiffness in old rats. J. Appl. Physiol. 107 (4), 1249–1257.
Lendvai, B., Vizi, E.S., 2008. Nonsynaptic chemical transmission through nicotinic acetylcholine receptors. Physiol. Rev. 88, 333–349.
Lepage, C., Smith, A.M., Moreau, J., Barlow-Krelina, E., Wallis, N., Collin, B., 2014. A prospective study of grey matter and cognitive function alterations in chemotherapy-treated breast cancer patients. SpringerPlus 3, 444.
Lowry, O.H., Rosenbrough, N.J., Farr, A.L., Randall, R.J., 1951. Protein measurement with folin phenol reagent. J. Biol. Chem. 193, 265.
Manohar, S., Jamesdaniel, S., Salvi, R., 2014. Cisplatin inhibits hippocampal cell proliferation and alters the expression of apoptotic genes. Neurotox. Res. 25, 369–380. PMID.
Mattison, C.P., Cavalcante, J.M., Gallão, MI. De., Brito, E.S., 2018. Effects of industrial cashew nut processing on anacardic acid content and allergen recognition by IgE. Food Chem. 240, 370–376.
Mcilwain, H., 1983. Central nervous system studies on metabolic regulation and function. In: Genazzari, E., Herken, H. (Eds.), Central Nervous System. Springer-Verlag, New York, pp. 3–11.
Melo, J.B., Agostinho, P., Oliveira, C.R., 2003. Involvement of oxidative stress in the enhancement of acetylcholinesterase activity induced by amyloid beta-peptide. Neurosci. Res. 45 (1), 117–127.
Mexis, S.F., Kontominas, M.G., 2009. Effect of γ-irradiation on the physicochemical and sensory properties of cashew nuts (Anacardium occidentale L.). LWT–Food Sci. Technol. 42 (9), 1501–1507.
Miranda, K.M., Espay, M.G., Wink, D.A., 2001. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric Oxide: Biol. Chem. 5, 62–71.
Misra, H.P., Fridovich, I., 1972. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J. Biol. Chem. 247, 3170–3175.
Morris, M.C., Evans, D.A., Tangney, C.C., Bienias, J.L., Wilson, R.S., Aggarwal, N.T., 2005. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am. J. Clin. Nutr. 81 (2), 508–514.
O'Farrell, E., MacKenzie, J., Collins, B., 2013. Clearing the air: a review of our current understanding of "chemo fog. Curr. Oncol. Rep. 15, 260–269.
Okorie, S.U., Nwanekezi, E.C., 2014. Evaluation of proximate composition and antinutritional factors of Cyperus esculentus (tigernut) as influenced by boiling. IOSR J. Environ. Sci. Toxicol. Food Technol. 8 (7), 70–73.
Olasehinde, T.A., Oyeleye, S.I., Ibeji, C.U., Oboh, G., 2020. Beetroot supplemented diet exhibit anti-amnesic effect via modulation of cholinesterases, purinergic enzymes, monoamine oxidase and attenuation of redox imbalance in the brain of scopolamine treated male rats. Nutr. Neurosci.
Olasehinde, T.A., Olaniran, A.O., Okoh, A.I., 2019. Neuroprotective effects of some seaweeds against Zn–induced neuronal damage in HT-22 cells via modulation of redox imbalance, inhibition of apoptosis and acetylcholinesterase activity. Metab. Brain Dis. 34 (6), 1615–1627.
Ooi, J., Hayden, M.R., Pouladi, M.A., 2015. Inhibition of excessive monoamine oxidase A/B activity protects against stress-induced neuronal death in Huntington disease. Mol. Neurobiol. 52 (3), 1850–1861.
Paglia, D.E., Valentine, W.N., 1967. Studies on quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J. Lab. Clin. Med. 70, 158–169.
Papanastasopoulos, P., Stebbing, J., 2013. Nuts and cancer: where are we now? Lancet Oncol. 14 (12), 1161–1162.
Polis, B., Samson, A.O., 2018. Arginase as a potential target in the treatment of Alzheimer's disease. Adv. Alzheimer's Dis. 7, 119–140.
Salas-Salvado, J., Casas-Agustench, P., Salas-Huetos, A., 2011. Cultural and historical aspects of Mediterranean nuts with emphasis on their attributed healthy and nutritional properties. Nutr. Metabol. Cardiovasc. Dis. 21 (Suppl 1), S1–S6.
Saura, J., Luque, J.M., Da Cesura, A.M., Prada, M., Chan-Palay, V., Huber, G., Loffler, J., Richards, J.G., 1994. Increased monoamine oxidase B activity in plaque- associated astrocytes of Alzheimer brains revealed by quantitative enzyme radioautography. Neuroscience 62 (1), 15–30.
Simo, M., Root, J.C., Vaquero, L., Ripolles, P., Jove, J., Ahles, T., 2015. Cognitive and brain structural changes in lung cancer population. J. Thorac. Oncol. 10 (1), 38–45.
Skoogh, J., Steineck, G., Stierner, U., Cavallin-Stahl, E., Wilderang, U., Wallin, A., 2012. Testicular-cancer survivors experience compromised language following chemotherapy: findings in a Swedish population based study 3–26 years after treatment. Acta Oncol 51, 185–197.
Stevens-Barrón, J.C., de la Rosa, L.A., Wall-Medrano, A., Álvarez-Parrilla, E., Rodríguez-Ramirez, R., Robles-Zepeda, R.E., Astiazaran-García, H., 2019. Chemical composition and in vitro bioaccessibility of antioxidant phytochemicals from selected edible nuts. Nutrients 11, 2303.
Stone, T.W., 1989. Purine receptors and their pharmacological roles. Adv. Drug Res. 18, 291–429.
Vichaya, E.G., Chiu, G.S., Krukowski, K., Lacourt, T.E., Kavelaars, A., Dantzer, R., 2015. Mechanisms of chemotherapy-induced behavioral toxicityies. Front. Neurosci. 9, 131.
Virarkar, M., Alappat, L., Bradford, P.G., Awad, A.B., 2013. L-arginine and nitric oxide in CNS function and neurodegenerative diseases. Crit. Rev. Food Sci. Nutr. 53 (11), 1157–1167.
Walker, W.H., Kearney, E.B., Seng, R.L., Singer, T.P., 1971. The covalently-bound flavin of hepatic monoamine oxidase. 2. Identification and properties of cysteinyl riboflavin. Eur. J. Biochem. 24 (2), 328–331.
Wefel, J.S., Schagen, S.B., 2012. Chemotherapy-related cognitive dysfunction. Curr. Neurol. Neurosci. Rep. 12, 267–275.
Yang, J.C., Hirsh, V., Schuler, M., Yamamoto, N., O'Byrne, K.J., Mok, T.S., 2013. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J. Clin. Oncol. 231, 3342–3350.
Yehuda, S., Rabinovitz, S., Mostofsky, D.I., 2005. Essential fatty acids and the brain: from infancy to aging. Neurobiol. Aging 26 (Suppl 1), 98–102.
Zhang, Q.Y., Wang, F.X., Jia, K.K., Kong, L.D., 2018. Natural product interventions for chemotherapy and radiotherapy-induced side effects. Front. Pharmacol. 9, 1253.
Zhang, C., Hein, T.W., Wang, W., Chang, C.I., Kuo, L., 2001. Constitutive expression of Arginase in microvascular endothelial cells counteracts nitric oxide mediated vasodilatory function. FASEB (Fed. Am. Soc. Exp. Biol.) J. 15, 1264–1266.
Zhou, L., Sun, C.B., Liu, C., Fan, Y., Zhu, H.Y., Wu, X.W., Li, Q.P., 2015. Upregulation of arginase activity contributes to intracellular ROS production induced by high glucose in H9c2 cells. Int. J. Clin. Exp. Pathol. 8 (3), 2728–2736.
Zhou, W., Kavelaars, A., Heijnen, C.J., 2016. Metformin prevents cisplatin-induced cognitive impairment and brain damage in mice. PLoS One 11 (3), e0151890.