Therapeutic effects of calcium disodium edetate and alpha-lipoic acid combined and moringa seeds powder on neurotoxicity in rats

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Abstract:

The current study was aimed to investigate the therapeutic effects of calcium disodium edetate (CaNa2EDTA) and Alpha lipoic acid (ALA) combined and moringa seeds powder (MOS.P) against lead and cadmium-induced neurotoxicity in rats. Twenty-four Albino male rats, weighing 158 ± 3 g were randomly divided into four groups (6 each). The first group served as a negative control group (-ve), second group served as untreated neurotoxicity group (+ve) and two treated groups with CaNa2EDTA and ALA combined and MOS.P. The experiment lasted for 60 days. Food intake and rat's weight were recorded to obtain nutritional parameters. Blood samples were collected to assays the levels of Cyclooxygenase-2 (COX-2), C- reactive protein (CRP), Lactic Dehydrogenase (LDH), Acetyl cholinesterase (AChE), Dopamine (DA), Serotonin (ST), lipid peroxidation, antioxidant enzymes activity, some kidney and liver functions. Also, the histopathological examination changes in brain tissue. The study results treated with CaNa2EDTA and ALA combined and MOS.P showed a significant improvement in serum levels of COX-2, CRP, LDH, AChE, DA, ST, Lipid peroxidation, Antioxidant enzymes activity, and some kidney and liver functions, when compared to untreated neurotoxicity group (+ve).

We recommend consuming moringa seeds and Alpha-lipoic acid with diets because they have anti-neurotoxicity and antioxidant properties, which play a significantly safer role than calcium disodium edetate in the treatment of lead-cadmium toxicity and inhibit its complications.

Keywords: Moringa oleifera Lam., Neurotoxicity, Thioctic acid, Sodium calcium edetate, Lead, Cadmium and Rats.

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INTRODUCTION:

Neurotoxicity is a direct effect or indirect effect of chemical materials that deactivate the nervous system of humans and animals **(Sainio, 2015)**. Lead (Pb) and Cadmium (Cd) are ecologically prevalent neurotoxic heavy metals **(Diaconu *et al.*, 2020)**. They accumulate in the brain causing a disturbance in the homeostatic equilibrium in the central nervous system, which accelerates the appearance of neurotoxicity and neurodegeneration diseases. **(Abd El-Ghany *et al.*, 2017 and Li *et al.*, 2021)**.

Sodium calcium edetate or calcium disodium edetate (CaNa2EDTA) is an EDTA derivative salt with two sodium atoms and one calcium atom **(Barton, 2014)**. CaNa2EDTA can be useful for chelating metal ions to prevent inflammatory changes from taking place, such as short-term and long-term poisoning of Pb, and Cd **(Mostafalou *et al*, 2015)**.

Alpha-lipoic acid (ALA) "also known as thioctic acid" is an antioxidant naturally occurring compound that's produced in the body to protect against body cell damage. ALA can form complex compounds with metal ions such as manganese, cadmium, lead, nickel, cobalt, and iron to prevent free radical-induced tissue damage or inactivation of the antioxidant enzymes **(Yuan *et al.*, 2019 and Bilska-Wilkosz *et al.*, 2019)**. ALA can be obtained from natural sources, such as Animal products like red meat, liver, heart and kidneys, but plant foods like beets, carrots, tomatoes, spinach, broccoli, potatoes, and yeast **(Liu *et al.*, 2022)**.

Moringa (*Moringa oleifera Lam.*) is a perennial, fast-growing, and drought-resistant tree **(Fahey, 2005)**. The moringa seeds (MOS) have attracted scientific interest due to their containing lipids of about 19-47% including a high-quality fatty acid composition, therefor its considered oilseed. The seeds are also rich in protein (31.4%), carbohydrate (18.4%), fiber (7.3%), ash (6.2%), and Moisture (7%). MOS also contains pro-vitamin A, vitamin E, and vitamin B group, in particular, Thiamin (B1). It also good source of minerals, micronutrients, and bioactive elements like Phytates, Flavonoids, Saponins, Trypsin inhibitors, and Sterols **(Velázquez-Zavala *et al.*, 2016 and Leone *et al.*, 2016)**. The Ayurvedic medicine books

include records about the use of moringa for the treatment of pain in joints, stomach, headache, ears, arthritis, as a cardiac and circulatory stimulant, to treat physical weakness, kidney and liver problems, colds, fever, stomach worms, epilepsy, ulcers, anemia, delirium, snakebite, chelating metal and as a rubefacient **(Kumar *et al.*, 2015 and Dhakad *et al.*, 2019)**. Accordingly, this study aimed to assess the potential impact of a combination of Alpha-lipoic acid and CaNa2EDTA, as well as moringa seeds powder, in mitigating neurotoxicity induced by lead (Pb) and cadmium (Cd) in rats.

MATERIALS AND METHODS

A-Materials:

Moringa (*Moringa oleifera Lam.*) seeds was purchased from the products selling unit at the National Research Center, Dokki, Egypt. Cadmium Chloride (CdCl2.H2O) 98% pure and Lead Acetate [Pb (CH3COO)2.3H2O] 99% pure were obtained from El-Gomhouria Company for trading Drugs and Chemicals, situated in Mansoura city branch, Dakahlia Governorate, Egypt. Thioctic acid drugs were purchased from a local pharmacy at Mansoura city. Ethylenediaminetetraacetic acid calcium disodium salt (CaNa2EDTA) was purchased commercially from Sigma-Aldrich Corporation in St. Louis, Missouri, USA. The basal diet was prepared according to **NRC (1995)**. Twenty-four healthy Albino male rats of Sprague–Dawley strain weighing 158 ± 3 g were purchased from the laboratory animal farm of Veterinary Medicine at Zagazig University in Egypt.

B-Methods:

Moringa seeds powder:

Moringa seeds were thoroughly checked to remove any impurities and then ground into a powder. Then, the whole seeds powder was saved in well-closed, opaque glass jars in the refrigerator to prevent lipid oxidation until used in diet preparation. The basic diet was supplemented with 5% moringa seeds powder by substituting some of the diet components.

Induction of Neurotoxicity (NT):

Lead Acetate Pb (CH_3COOH_2) and Cadmium chloride ($CdCl_2$) are used for experimental induction of neurotoxicity in rats. Pb and $CdCl_2$ were prepared as a mixture of a toxic solution by dissolving the following doses in 1 ml distilled water at a dose of Pb (30 mg/kg b.w.) according to **Saleh & Meligy (2018)**, combined with the dose of Cd (5 mg/kg b.w.) according to **Mohammed *et al.*, (2014)**. The toxic solution was freshly prepared daily and administered orally gavage in a volume of 1 mL/kg b.w. once daily for 30 days before treatment.

Alpha lipoic acid solution:

Thioctic tablets, manufactured as a pack of contained 30 film-coated tablets. Each tablet contains 300 mg of alpha lipoic acid. The tablets were crushed and suspended in distilled water, and administrated orally gavage as a freshly prepared daily solution at a therapeutic once daily dose of (54 mg/kg b.w.) for 30 days after toxicity according to **El-Sayed *et al.*, (2016).**

CaNa2EDTA solution:

The solution was made fresh daily by dissolving CaNa2EDTA in sterile saline to a concentration of 50 mg/mL, then was given as intraperetinoel injection in a therapeutic once daily dose of (50 mg/kg) for 5 sequential days depending on the body weight of each rat according to **Sánchez-Fructuoso *et al.*, (2002)**.

Experimental Animals Protocol:

Rats were kept under surveillance for seven days for adaptation and fed on basal diet. Six rats served as negative control group (-ve) and eighteen rats were orally gavage received a mixture of a toxic solution of Pb (30 mg/kg b.w.) according to **Saleh & Meligy (2018)**, combined with the dose of Cd (5 mg/kg b.w.) according to **Mohammed *et al.*, (2014)** for 30 days to induce Neurotoxicity. Then, rats were randomly divided into three groups (6 each), one group served as untreated neurotoxicity group (+ve) and two served as treated groups as the following: group with combined of CaNa2EDTA (50 mg/kg b.w. i.p) a once-daily dose for 5 consecutive days according to **Sánchez-Fructuoso *et al.*, (2002)**, along with Thioctic acid

tablets (ALA) administrated by oral gavage as a freshly prepared daily solution at a once-daily dose of (54 mg/kg b.w.) according to **El-Sayed *et al.*, (2016)** for 30 days, and group treated with moringa seeds powder (+MOS.P): treated with 5% moringa seeds powder by substituting some of the basic diet components, for 30 days. Food and water was provided *ad-libtum*. Food intake was recorded daily and body weight of rats was measured once weekly, until the end of experimental period (60 days). All the biological experimental procedures were performed according to Internationally Ethical Guidelines for the care and use of laboratory animals. Permission to conduct the experiment was obtained from the Research Ethics Committee at the Faculty of Specific Education, Mansoura University.

Chemical composition of Moringa seeds samples:

Moisture, fat, protein, fiber and ash contents in dry weight (D.w) were determined according to the methods of the **AOAC (2005**). Total carbohydrates and Nitrogen-free extract (NFE) were calculated by difference as following:

Total carbohydrates% = 100 - (moisture % + protein % + fat % + ash %).

Nitrogen-free extract% = 100 - (moisture% +protein% +fat % +ash %+ fiber %).

Energy was expressed in kilocalories per 100g according to **Watt & Merrill (1963)**, using the following formula:

Energy (kcal.100g) = (g of protein x 4) + (g of fat x 9) + (g of carbohydrate x 4).

Nutritional Parameters:

The amounts of food intake was recorded daily, while rat's weighted once a week to identify body weight gain. Body weight gain, feed efficiency ratio (FER), and protein efficiency ratio (PER) calculate according to **Chapman *et al*., (1959)**.

Biological analyzes:

At the end of experimentation, animals were anesthetized by di-ethyl ether and blood samples were gathered from the inner canthus of the rat's eye using heparinized capillary tubes, and then the serum was taken after

centrifugation at 3000 rpm for 10 minutes. The serum biochemical analysis includes the following:

Cyclooxygenase-2 (COX-2), C-reactive protein level (CRP), Lactic Dehydrogenase (LDH),) were measured depending on the method of **(Van Weemen & Schuurs, 1971; Vaishnavi, 1996 and Vassault, 1983, respectively)**. Acetyl cholinesterase (AChE) levels were assessed by using the manufacturer's protocol of a Rat Acetylcholinesterase ELISA Kit Principles (No. DEIASL417; Creative Diagnostics Co., Shirley, New York, USA). Dopamine (DA) level was assessed by enzyme-linked immunosorbent assay using the manufacturer's protocol of a Mouse/Rat Dopamine ELISA Assay Kit (No. DOU39-K01; Eagle Biosciences, Inc., Boston, USA). Serotonin (ST) levels were assessed by using the manufacturer's protocol of a Rat Serotonin ELISA Kit (No. LS-F27987; LifeSpan Biosciences, Inc., Seattle, Washington, USA), were determined according to **(Kelishadi *et al*., 2018)**.

Serum Lipid peroxidation (Malondialdhyde "MDA") and Antioxidant enzymes: Catalase (CAT), superoxide dismutase (SOD), Reduced Glutathione (GSH). Glutathione Peroxidase (GPx) were determined according to the method described by **(Paoletti & Macali, 1990; Eze *et al.*, 2008; Sinha, 1972; Rice-Evans & Miller, 1994 and Paglia & Valentine, 1967, respectively)**. Some serum kidney and liver functions: Urea, Creatinine, Total Bilirubin (T.BiL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) were determined according to **(Rock *et al*., 1987; Henry *et al*., 1974; Young *et al.*, 1975; Belfield & Goldberg, 1971 and Orlowski & Meister, 1963, respectively)**.

Histopathological examination of the brain tissue:

The brain tissues were stained with hematoxylin and eosin (H&E) for histopathological examination according to **Bancroft *et al.*, (1996).**

Statistical data analysis:

Gathered data were analysis according to SPSS program according to **Abu-Bader (2011)**.

RESULTS AND DISCUSSION:

Chemical composition of chia seeds samples:

The data in table (1) showed moringa seeds chemical composition as a percentage as the following: moisture content is 6.77 ± 0.08%, fat content is 29.23 ± 0.06%, protein content is 31.17 ± 0.07%, ash content is 4.31 ± 0.04%, total carbohydrate (T. Carb) content is 28.51 ± 0.24%, fiber content is 5.13 ± 0.05%, Nitrogen-free extract (NFE) content is 23.39 ± 0.29% and energy is 501.83 ± 0.20 kcal.100g. This finding is nearly similar to a study showed the chemical composition of whole moringa seeds contains as the following: 6.70% moisture, 31:30% protein, 28.85% fat, 26.71% dietary fiber, and 4.22% Ash **(Salama *et al.,* 2018)**. The chemical compositions of seeds are good source of essential nutritional compounds associated with human's health promotion and disease prevention **(Senila *et al.,* 2021).**

Table (1): Chemical composition (%) of raw moringa seeds:

Component	Values
Moisture	**6.77 ± 0.08 %**
Fat	**29.23 ± 0.06 %**
Protein	**31.17 ± 0.07 %**
Ash	**4.31 ± 0.04 %**
T. Carb	**28.51 ± 0.24%**
Fibers	**5.13 ± 0.05 %**
NFE	**23.39 ± 0.29 %**
Energy (kcal.100g)	**501.83 ± 0.20**

Each value is average repetition three times, whereas illustrating mean ± SD

Nutritional indicators of neurotoxicity rats treated by calcium disodium edetate with alpha-lipoic acid and moringa seeds powder at the end of study:

The arithmetical data in table 2 showed: the untreated neurotoxicity rats group (+ve) had a significant decrease in body weight gain, body weight gain %, food intake, feed efficiency ratio (FER), protein intake, and protein efficiency ratio (PER), when compared with control group (-ve). While, the

neurotoxicity rat groups treated with the combination of CaNa2EDTA & ALA and moringa seeds powder showed significant decrease in body weight gain, body weight gain %, food intake, FER, protein intake, and PER when compared with the control group (-ve). While, nutritional indicators at CaNa2EDTA & ALA and moringa seeds powder treated groups marked a significant increase when compared with the untreated neurotoxicity group (+ve).

Chronic administration of Cd and Pb is related to lessening body weight, anorexia, vomiting, nausea, muscle wasting and oxidative stress **(Fiati Kenston *et al.*, 2018 and Lopotych *et al.*, 2020)**. Treated with moringa seeds achieved significant improvement in the weight gained and different nourishment effects **(Al-Malki & El Rabey 2015 and Sardabi *et al.*, 2022)**. Seeds are usually rich sources of fatty acids, sterols, dietary fiber and phenolic which have shown ability to enhances metabolism, anti-obesity promotion, increase satiety and used as nutritional medicine for some chronic degenerative diseases **(Roy *et al.*, 2022)**.

Table (2): Nutritional indicators of neurotoxicity rats treated by calcium disodium edetate with alpha-lipoic acid and moringa seeds powder:

	Parameters / groups	Weight Gain (g)	Weight Gain %	Food Intake (g)	feed efficiency ratio (FER)	Protein Intake (g)	Protein efficiency ratio (PER)
untreated	Control (-ve)	79.83 ±2.32^{a}	50.43 ±1.82^{a}	18.08 ±0.34^{a}	0.073 ±0.003^{a}	3.62 ±0.07^{a}	0.37 ±0.02^{a}
	Control (+ve)	34.17 ±2.86^{d}	21.61 ±1.83^{d}	11.99 ±0.34^{c}	0.047 ±0.004^{c}	2.40 ±0.07^{c}	0.24 ±0.02^{c}
treated	+CaNa2EDTA & ALA	55.33 ±1.21^{b}	35.06 ±0.52^{b}	15.33 ±0.34^{b}	0.060 ±0.002^{b}	3.07 ±0.07^{b}	0.30 ±0.01^{b}
	+MOS.P	50.17 ±1.17^{c}	31.69 ±0.64^{c}	14.63 ±0.34^{b}	0.057 ±0.002^{b}	2.93 ±0.07^{b}	0.29 ±0.01^{b}

The results were illustrating as mean ± SD values in each column having different combinations of superscript letters (a, b, c, d...).

Biological analyzes:

1- Serum Cyclooxygenase-2 (COX-2), C- reactive protein (CRP), and Lactic Dehydrogenase (LDH) levels of neurotoxicity rats treated by CaNa2EDTA with ALA and moringa seeds powder:

The arithmetical data in table 3 showed a significant increase in COX-2, CRP, and LDH levels in the untreated neurotoxicity rats group (+ve) when compared with the control group (-ve). While the neurotoxicity group treated with the combination of CaNa2EDTA & ALA showed a significant increase in COX-2, and LDH levels, while CRP showed non-significant differences when compared with the control group (-ve). Also, the neurotoxicity group treated with moringa seeds powder (+MOS.P) showed a significant increase in COX-2, CRP, and LDH levels when compared with the control group (-ve). Moreover, treated groups with combination of CaNa2EDTA & ALA and MOS.P marked a significant decrease in the levels of COX-2, CRP, and LDH, when compared with the untreated neurotoxicity group (+ve).

Moringa seed contain different concentrations of essential unsaturated fatty acids, which help to reduced inflammation by restoring the antioxidant system, increased fatty acid oxidation, and reduced metabolic disorders **(Hamdy *et al.,* 2019 and Chen *et al.,* 2022)**. The anti-inflammatory effect of Moringa seeds treatment was confirmed by the low circulating levels of CRP due to its photochemical compounds **(Randriamboavonjy *et al.,* 2017)**. Also, the phenolic glycosides that exist in Moringa oleifera seeds suppress inducible production of COX-2 proteins and significantly inhibited LDH leakage in treated rat cells **(Sun *et al.,* 2019 and Akter *et al.,* 2021)**.

Table (3): Serum Lactic Dehydrogenase (LDH), C- reactive protein (CRP), and Cyclooxygenase-2 (COX-2) levels of neurotoxicity rats treated by CaNa2EDTA with ALA and moringa seeds powder:

groups \ Parameters		COX-2 (pg/mL)	CRP (mg/mL)	LDH (U/L)
untreated	Control (-ve)	33.85 ±4.15^{cd}	2.14 ±0.17^{d}	1377.83 ±12.95^{d}
	Control (+ve)	79.90 ±2.07^{a}	5.55 ±0.62^{a}	4195.67 ±12.83^{a}
treated	+CaNa2EDTA & ALA	43.95 ±7.14^{c}	2.29 ±0.25^{c}	1551.67 ±12.55^{c}
	+MOS.P	53.93 ± 3.68^{b}	2.73 ± 0.20^{b}	2290.17 ± 9.66^{b}

The results were illustrating as mean ± SD values in each column having different combinations of superscript letters (a, b, c, d...).

2- Serum Acetylcholinesterase (AChE), Serotonin (ST), and Dopamine (DA) levels of neurotoxicity rats treated by CaNa2EDTA with ALA and moringa seeds powder:

The data in table 4 showed a significant increase in of AChE and DA levels, and a significant decrease in ST level in the untreated neurotoxicity rats group (+ve) when compared with the control group (-ve). While, the neurotoxicity groups treated with CaNa2EDTA & ALA and moringa seeds powder (+MOS.P) showed a significant increase in AChE and DA levels, While, ST level showed a significant decrease when compared with the control group (-ve). Moreover, neurotoxicity groups treated with CaNa2EDTA & ALA and MOS.P marked a significant decrease in the levels of AChE and DA While, ST level showed a significant increase when compared with the untreated neurotoxicity group (+ve). Inhibition of AchE is a therapeutic target using the inhibitory natural products. Therefore, using moringa seeds fats could modulate AchE activity in the cerebrum and reduces the neurotoxicity effects **(Famurewa *et al.*, 2018)**. Also, Moringa seeds act as a neuroprotective agent, had the ability to activate serotonin

receptors on gastric tissues, and are potentially used as an alternative therapy for neurodegenerative disorders **(Liaqat *et al.*, 2022)**.

Table (4): Serum Dopamine (DA), Serotonin (ST), and Acetylcholinesterase (AChE) levels of neurotoxicity rats treated by CaNa2EDTA with ALA and moringa seeds powder:

groups \ Parameters		AChE (pg/ml)	ST (ng/ml)	DA (ng/ml)
untreated	Control (-ve)	25.98 ±2.80^{d}	184.72 ±4.81^{a}	11.55 ±0.51^{d}
	Control (+ve)	127.43 ±11.10^{a}	136.50 ±7.05^{c}	23.22 ±0.41^{a}
treated	+CaNa2EDTA & ALA	39.67 ±7.68^{c}	170.17 ±6.45^{b}	13.88 ±0.60^{c}
	+MOS.P	70.22 ±3.37^{b}	156.18 ±9.72^{bc}	16.12 ±0.79^{b}

The results were illustrating as mean ± SD values in each column having different combinations of superscript letters (a, b, c, d...).

3- Serum free radical (Malondialdhyde "MDA") concentration levels and antioxidant enzymes Catalase (CAT), superoxide dismutase (SOD), Reduced Glutathione (GSH) and Glutathione Peroxidase (GPX) levels of the experimental rat groups:

The data in table 5 showed a significant increase in MDA levels, and showed a significant decrease in CAT, SOD, GSH and GPX levels in the untreated neurotoxicity rats group (+ve) when compared with the control group (-ve). While, the neurotoxicity groups treated with a combined of CaNa2EDTA & ALA and moringa seeds powder (+MOS.P) showed a significant increase in MDA levels, and showed a significant decrease in the levels of CAT, SOD, GSH and GPX when compared with the control group (-ve). Also, the CaNa2EDTA & ALA and MOS.P treated groups marked a significant increase in CAT, SOD, GSH and GPX levels, and showed a significant decrease in MDA levels when compared with the untreated neurotoxicity group (+ve).

Neurotoxicity related to Pb and Cd exposure causes an increase in MDA levels could be the result of a series of perturbations in brain metabolism and the production of free radicals which lead to impair the functions and ultrastructure of the central nervous system **(Antonio *et al.*, 2003 and Zhang *et al.*, 2009)**. The free radicals will attack proteins, DNA, polysaccharides, and cell membranes that consist of polyunsaturated fatty acids, leading to an increase in MDA levels and a decrease in antioxidant enzymes activity, which causes progressive damage of cellular structures. **(Halliwell, 2011 and Poljsak *et al.*, 2013)**.

Alpha-lipoic acid has a promising natural and soft chelating agent, due to an amphiphilic property which allows it to easily cross the blood-brain barrier and cell membranes and also helps to activate other antioxidants such as vitamin E, vitamin C and coenzyme Q10 **(AlMomen & Blaurock-Busch, 2022)**. Furthermore, rats fed on moringa seed showed a significant decrease in MDA and a significant increase in the antioxidant enzymes activities including CAT, SOD, GSH and GPX. Seed powder antioxidant activity are due to its contents of bioactive components such as phenolics and flavonoids, because it's scavenging effect on the free radicals **(Al-Malki & El Rabey 2015 and Mahmoud, 2021)**.

Table (5): Serum Malondialdhyde (MDA) and antioxidant enzymes Catalase (CAT), superoxide dismutase (SOD), Reduced Glutathione (GSH), and Glutathione Peroxidase (GPX) levels of the experimental rat groups:

groups \ Parameters		MDA nmol/ml	CAT (U/L)	SOD (U/L)	GSH (µmol/L)	GPX (mU/ml)
untreated	Control (-ve)	6.07 ±0.20^{d}	0.95 ±0.01^{a}	42.49 ±0.90^{a}	2.06 ±0.08^{a}	96.12 ±2.92^{a}
	Control (+ve)	21.18 ±3.23^{a}	0.23 ±0.02^{d}	8.11 ±4.19^{d}	0.69 ±0.03^{d}	25.57 ±8.46^{d}
treated	+CaNa2EDTA & ALA	9.93 ±0.72^{c}	0.79 ±0.01^{b}	38.35 ±0.93^{b}	1.57 ±0.12^{b}	72.36 ±5.78^{b}
	+MOS.P	13.23 ± 0.85^{b}	0.69 ±0.03^{c}	27.21 ±2.95^{c}	1.29 ±0.16^{c}	63.17 ±1.83^{c}

The results were illustrating as mean ± SD values in each column having different combinations of superscript letters (a, b, c, d...).

4- Some serum Kidney and Liver function: Urea, Creatinine, Total Bilirubin (T.BiL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) and Gamma-glutamyl Transferase (GGT) levels of the experimental rat groups:

The data in table (6) showed significant increase in Urea, Creatinine, T.BiL ALT, AST, ALP and GGT levels in the untreated neurotoxicity group (+ve) when compared with the control group (-ve). While the neurotoxicity group treated with the combined of CaNa2EDTA & ALA showed a significant increase in Urea, ALT and AST Levels when compared with the control group (-ve). While, the neurotoxicity rats group treated with moringa seeds powder (+MOS.P) showed significant increase in Urea, Creatinine, T.BiL ALT, AST, ALP and GGT levels when compared with the control group (-ve). Moreover, neurotoxicity treated groups with the combined of CaNa2EDTA & ALA and MOS.P marked a significant decrease in Urea, Creatinine, T.BiL ALT, AST, ALP and GGT levels when compared with the untreated neurotoxicity group (+ve).

Pb and Cd cause the increase in liver enzymatic activities specifically AST and ALT **(Zou *et al.*, 2020 and Hassan *et al.*, 2022)**. CaNa2EDTA effectively slowness the progression of chronic kidney disease in patients with body Pb burden by increased levels of creatinine clearance and glomerular filtration. While, ALA has a protective effect on Cd-induced oxidative stress, due to its potent antioxidant and metal chelator activity that can repair oxidative damaged and exert antioxidant cellular activities, also, significantly decreased the activity of serum AST, ALT, LDH, and GGTP, which counteracts organ damage caused by cadmium **(Luo *et al.*, 2016 and Markiewicz-Górka *et al.*, 2019)**. Simultaneous treatment of moringa seeds reduced Cd-induced hepatotoxicity by improving liver function as indicated by reducing ALT, AST, and ALP activities and raising albumin levels, also, had shown significant improvement in Urea and Creatinine levels. The hepatoprotective property of Moringa is attributed to its high antioxidant

activity and free radical scavenging activity which caused stabilization of cell membrane activity preventing enzymes **(Saleh *et al.*, 2019; Alshubaily & Almotairi, 2020 and Mahmoud, 2021)**.

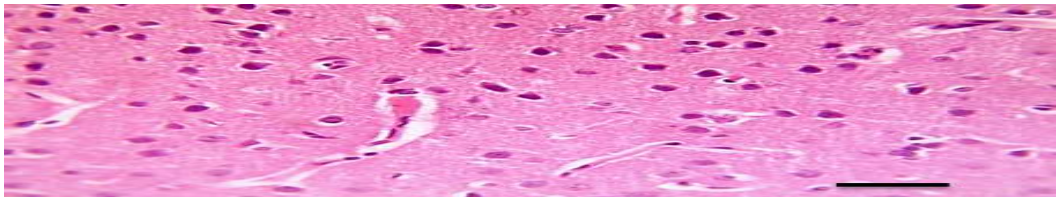
Table (6): Some serum Kidney and Liver function: Creatinine, Urea, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Gamma-glutamyl Transferase (GGT) and Total Bilirubin (T.BiL) levels of the experimental rat groups:

groups \ Parameters		Urea (mg/dl)	Creatinine (mg/dl)	T.BiL (mg/dl)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)
untreated	Control (-ve)	25.65 ±4.62^{d}	0.53 ±0.02^{d}	0.31 ±0.09^{bc}	34.67 ±5.20^{bc}	140.50 ± 9.20^{d}	86.00 ±10.99^{c}	3.29 ± 0.46^{d}
	Control (+ve)	101.17 ±9.56^{a}	1.57 ±0.12^{a}	1.56 ±0.20^{a}	83.33 ±3.56^{a}	419.33 ±8.82^{a}	344.00 ±11.20^{a}	19.28 ±3.28^{a}
treated	+CaNa2EDTA & ALA	37.33 ±3.51^{c}	0.59 ±0.02^{c}	0.41 ±0.14^{b}	44.17 ±6.27^{c}	170.17 ±7.28^{c}	95.33 ±8.29^{c}	4.30 ±0.54^{c}
	+MOS.P	51.50 ±7.35^{b}	0.67 ±0.05^{b}	0.49 ±0.19^{b}	57.33 ±4.55^{b}	232.67 ±6.98^{b}	153.00 ±7.97^{b}	7.55 ±0.70^{b}

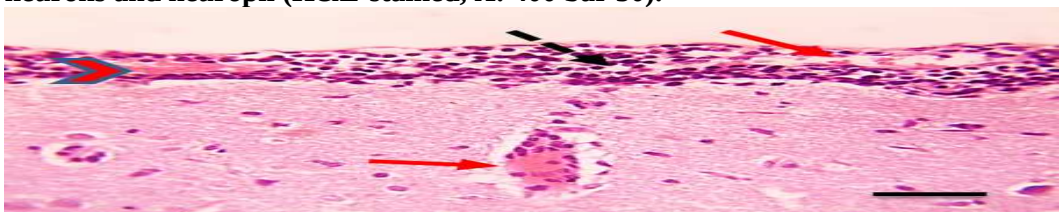
The results were illustrating as mean ± SD values in each column having different combinations of superscript letters (a, b, c, d...).

Histopathological analysis of Brain specimens:

The microscopic pictures from the Brain cortical sections appear as the following: the control group (-ve) and CaNa2EDTA & ALA treated group showing normal neurons and neuropil in pictures 1&3 respectively. While, the untreated neurotoxicity rats group (+ve) showing leukocytic cell infiltration, congestion and hemorrhage in meninges, congested blood vessels, focal area of necrosis infiltrated by leukocytic cells, and vacuolation in the neuropil in picture 2. The neurotoxicity rat groups treated with moringa seeds powder (+MOS.P) showing mildly congested blood vessels in pictures 4.

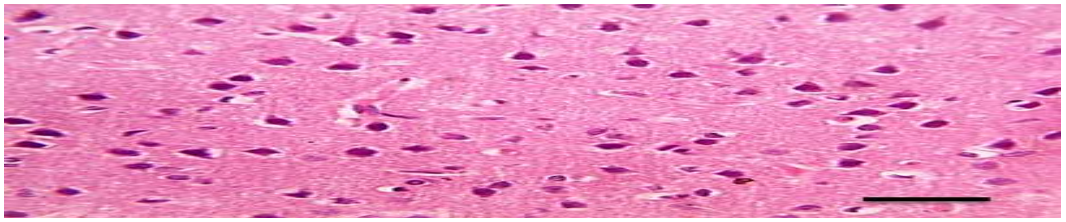


Pic (1): Brain cortical sections for negative control group (-ve) showing normal neurons and neuropil (H&E-stained, X: 400 bar 50).

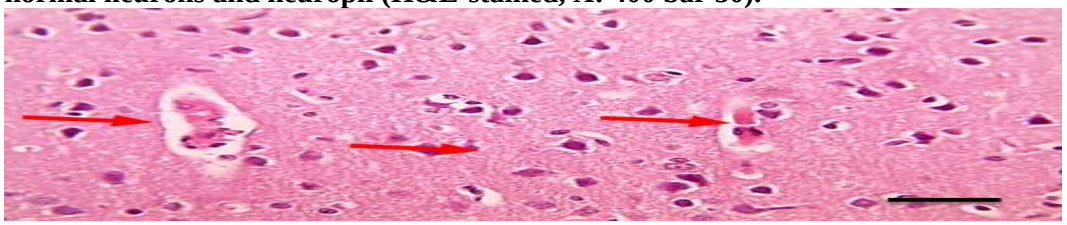


Pic (2): Brain cortical sections for untreated neurotoxicity group (+ve) showing leukocytic cells infiltration (dashed black arrows), congestion (red arrow) and hemorrhage (red arrowhead) in meninges, congested blood vessels (red arrows), focal area of necrosis (black arrows) infiltrated by leukocytic cells (blue arrows), and vacuolation (arrowheads) in the neuropil (H&E-stained, X: 400 bar 50).

The ability of Pb to replace calcium ions accumulation in the brain using calcium-ATPase pumps, which might play a significant role in the development of neurodegenerative diseases. Also, heavy metals-induced neuronal injury interferes with oxidative balance, neuroinflammation, and programmed cell death. **(Shaban *et al.*, 2021 and Enogieru & Egbon, 2022)**. The use of different nutrients from medicinal plants may reduce the toxic effect of heavy metals mediated oxidative damage in different organs of the body, especially the brain **(Abd El-Ghany *et al.*, 2019 and Abdulidha *et al.*, 2020)**. Furthermore, the harmful effect of the drugs and chemicals on the histological state and functions of the brain can be prevented and treated through the administration of healthy medicinal plants such as nuts, chia seeds and moringa seeds **(Henrich, 2020 and Usman *et al.*, 2022)**.



Pic (3): Brain cortical sections for treated group by CaNa2EDTA &ALA showing normal neurons and neuropil (H&E-stained, X: 400 bar 50).



Pic (4): Brain cortical sections showing mildly congested blood vessels (red arrows) (H&E-stained, X: 400 bar 50).

CONCLUSION:

In conclusion, we advocate for the incorporation of Alpha-lipoic acid and moringa seeds into diets for individuals exposed to lead and cadmium toxicity, as they exhibit potential in mitigating the adverse effects of these metals on the nervous system.

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التأثيرات العلاجية لإديتات الكالسيوم ثنائي الصوديوم مع حمض ألفا ليبويك وبذور المورينجا على السمية العصبية في الفئران

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الملخص العربي:

صممت الدراسة الحالية لدراسة تأثير خليط ايديتات كالسيوم ثنائي الصوديوم (CaNa2EDTA) مع حمض ألفا ليبويك (ALA) معاً ومسحوق بذور المورينجا (MOS.P) على السمية العصبية التي يسببها الكادميوم والرصاص. أجريت الدراسة على أربعة وعشرون من ذكور الفئران الألبينو البالغة، متوسط وزنها (١٥٨ ± ٣ جم) تم تقسيمها عشوائيًا إلى أربع مجموعات (ستة بكل مجموعة)، المجموعة الأولي الضابطة السالبة وثلاثة مجموعات تم اصابتهم بالسمية العصبية، ثم تم إعادة تقسيمهم على النحو التالى: المجموعة الثانية الضابطة الموجبة (غير معالجة)، والمجموعة الثالثة تم معالجتها بخليط ايديتات كالسيوم ثنائي الصوديوم مع حمض ألفا ليبويك، والمجموعة الرابعة تم معالجتها بمسحوق بذور المورينجا. وقد استمرت التجربة لمدة ٦٠ يومًا. تم تسجيل كمية الطعام المتناولة يومياً ووزن الفئران أسبوعياً، وفى نهاية التجربة تم جمع عينات الدم من الفئران لفحص المستويات التالية: إنزيمات الأكسدة الحلقية- ٢ (COX-2)، ومستوى البروتين التفاعلي (CRP)، إنزيم نازع لهيدروجين اللاكتات (LDH)، أسيتيل كولينستراز (AChE) ، السيروتونين (ST)، الدوبامين (DA)، بيروكسيد الدهون، نشاط إنزيمات مضادات الأكسدة، بعض مؤشرات وظائف الكلى و الكبد. كذلك، تم فحص التغيرات النسيجية في أنسجة المخ. أظهرت نتائج الدراسة تحسنًا معنوي في مستويات المصل من LDH، CRP، COX-2، DA، ST، AChE، بيروكسيد الدهون، نشاط الإنزيمات المضادات للأكسدة، وبعض وظائف الكلى والكبد في المجموعات المعالجة بخليط ايديتات كالسيوم ثنائي الصوديوم مع حمض ألفا ليبويك، وبمسحوق بذور المورينجا، عند مقارنتها بمجموعة الضابطة الموجبة الغير معالجة (+ve).

وتوصي الدراسة بضرورة استهلاك حمض ألفا ليبويك وبذور المورينجا في الوجبات الغذائية لتأثيراتهم المضادة للسمية العصبية وتثبيط مضاعفاتها، ولإحتوائهم على مضادات أكسدة تلعب دورًا هام وأكثر أمانً من مركبات إديتات الكالسيوم ثنائي الصوديوم في علاج سمية الرصاص والكادميوم.

الكلمات المفتاحية: مورينجا أوليفيرا لام. - السمية العصبية - ايديتات كالسيوم ثنائي الصوديوم - حمض الثيوكتيك - الكادميوم - الرصاص - فئران.

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