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Anti-toxic Extracts from Moringa Oleifera (MO11) and Musa Sapientum (MS06) Ameliorated Cadmium Chloride-induced Neuroalterations of Catalase, Cyclo-oxygenase-2, Superoxide Dismutase and Cytochrome p450 Levels in Rat

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ABSTRACT

Introduction: this study evaluated neuroprotective potential of MO11 (isolated from *Moringa oleifera* leaves) and MS06 (isolated from *Musa sapientum suckers*) in cadmium chloride (CdCl2)-induced neurotoxicity in rats. Twenty-four adult male rats were randomly divided into 6 groups. Group 1 was control. Groups 2-4 and 6 received intraperitoneal single-dose of CdCl2 (Day 1). Groups 3, 4 and 6 were post-treated with MO11-dose, MO11+MS06-doses and Doxorubicin-dose respectively, while Group 5 received Olive Oil-dose (vehicle) from Days 1-17. Quantitative tissue enzyme-linked immunosorbent assays of catalase, superoxide dismutase, cyclo-oxygenase-2 and cytochrome p450 in rats' cerebri were evaluated. Data were statistically analysed using Mann-Whitney-U test at p≤0.05. Post-treatments of CdCl2-induced neurotoxicity with MO11, MS06 and Doxorubicin resulted in increased catalase levels, similar superoxide dismutase levels and decreased levels of cyclo-oxygenase-2 and cytochrome p450 in Groups 3, 4 and 6, compared with Group 2. MO11 and MS06 possess neuroprotective, antioxidant, neuroregenerative and anticancer potential.

Keywords: Cadmium; Neurotoxicity; *Moringa oleifera*; *Musa sapientum*; Neuroprotection.

Introduction

Cadmium (Cd), according to the World Health Organization, is one of the 10 chemicals of concern for human health[8]. Cd was classified as a human carcinogen by the National Toxicology program and the International Agency for Research on Cancer[16]. Cd-induced toxicity resulted in systemic dysfunctions such as neurotoxicity[9,28], inflammation and hepatotoxicity[8].

Human Cd exposure is associated with dysfunctions of the nervous system resulting in symptoms such as impaired learning capacity, headache and vertigo, decreased cognitive functions, olfactory dysfunction, poor vasomotor functioning, Parkinsonian-like symptoms, peripheral neuropathy and poor equilibrium and balance co-ordination[28]. Cd exposure has also been suspected as an etiological factor in the development of Parkinson's disease and Alzheimer's disease[28]. Increased concentrations in total Cd exposure was associated with dyslexia or learning difficulties, decreased visual motor capacity and mental retardation in children[28]. It is therefore, scientifically relevant to develop drug candidates from plants or other sources which can prevent or eliminate resulting dysfunctions of the nervous system due to Cd-induced neurotoxicity.

Moringa oleifera (MO) and *Musa sapientum* (MS) are ethno-medicinal plants which are well grown in Nigeria[3]. Furthermore, MOF6, which was fractionated from MO leaves using column chromatography methods showed significant antioxidant and neuroprotective potential against Cuprizone-induced cerebellar damage in rats[25], as well as neuroprotective potential against dysregulated acetylcholinesterase concentrations in sodium arsenite-induced neurotoxicity in rats[2]. MOF6 equally showed hepatoprotective, anti-proliferation and anti-

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drug resistance potential in 7,12-Dimethylbenz[a] anthracene-induced hepatotoxicity in rats[3]. Similarly, MSF1, which was fractionated from MS sucker using column chromatography methods possesses hepatoprotective, anti-proliferation and anti-drug resistance potential in 7,12-Dimethylbenz[a] anthracene-induced hepatotoxicity in rats[3].

Cd-induced neurotoxicity has been suggested to result from increased oxidative stress, dysregulation and dysfunction of neurotransmitters, estrogen-like effect, interactions with heavy metals such as zinc and cobalt and epigenetic effects[9,28]. The mechanism underlying Cd-induced neurotoxicity remains poorly understood and unresolved to date. Cd generally exists as a divalent cation, complexed with other elements, such as cadmium chloride ($CdCl_2$)[8].

In this study, the most active antioxidant and antimicrobial cytotoxic compounds were isolated from MO leaves (MO11) and MS suckers (MS06) respectively following series of chromatography and spectroscopic techniques. Therefore, in order to further understand the mechanisms underlying Cd-induced neurotoxicity and to determine the neuroprotective, antioxidant and neuroregenerative potential of MO and MS, this study evaluated the effects of MO11 and MS06 on $CdCl_2$-induced neurotoxicity, oxidative stress and neurodegeneration in the cerebral cortices of adult male Wistar rats.

Materials and Methods

Ethics approval

Ethical approval for this study was sought and received from the Ethical Review Committee of the University of Ilorin, Nigeria. Appropriate measures were observed to ensure minimal pain or discomfort of rats used in this study. The ethical approval number is UERC/ASN/2018/1161. Furthermore, this research study was conducted in accordance with the internationally accepted principles for laboratory animal use and care as provided in the European Community guidelines (EEC Directive of 1986; 86/609/EEC), the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes and the Guidelines of the U.S. Public Health Service and NIH regarding the care and use of animals for experimentation (NIH publication #85-23, revised in 985).

Authentication and deposition of MO leaves and MS suckers

Freshly cut MO leaves and MS suckers were obtained from forest reserves in Ilorin, Kwara State of Nigeria. The plants' samples were authenticated and assigned Herbarium Identification Numbers: UILH/001/1249 and UILH/002/1182 respectively at the Department of Botany of study institution.

Evaluations of antioxidant and antimicrobial activities of MO and MS fractions

Antioxidant activities of plants' extracts were evaluated using modified 2,2- diphenyl-1-picrylhydrazyl method as previously described[11]. Antimicrobial activities of plants' extracts were evaluated by testing cytotoxic potential of each fraction against growths of *Escherichia coli* and *Salmonella typhimurium* as previously described[12].

Extractions of MO11 and MS06 from MO leaves and MS suckers

MO11 and MS06 were extracted as final therapeutic isolates from MO leaves and MS suckers following series of antioxidant analyses, antimicrobial cytotoxicity potential, column chromatography and liquid chromatography-mass spectrometry as previously reported[5,6].

Animals

Twenty-four (24) adult male Wistar rats (average weight of 155 g and 2 months of age) were purchased from a colony breed at Badagry in Lagos state, Nigeria. The rats were acclimatized for a week, and randomly divided into 6 groups with 4 rats per group. The rats were kept under standard conditions. The body weights of rats in grams were computed on daily bases using electronic SF-400C compact weighing scale (Valid Enterprise, Mumbai, India).

Experimental design

MO11 and MS11 were dissolved in Olive Oil (vehicle). Rats of Control Group 1 received physiological saline only for 17 Days (Days 1 – 17). The dose of 1.5 mg/kg body weight of $CdCl_2$ was determined from a previous study which investigated the effects of low dose of $CdCl_2$ on the testis[5,19]. Doses of Doxorubicin, MS06 extract and MO11 extract were determined from previous studies, which investigated cytoprotective potential of the extracts in comparison with Doxorubicin against $CdCl_2$ induced toxicity in rats[5,6].

Each rat of Experimental Groups 2 – 4 and 6 received single intra-peritoneal administration of 1.5 mg/kg body weight of $CdCl_2$ (Sigma-Aldrich, Japan Co.) on Day 1. Rats of Group 2 (Toxic Control) were left untreated throughout experimental procedure for 17 Days (Days 1 – 17). Thereafter, rats of Group 3 were post-treated with oral administration of 15 mg/kg body weight of MO11 for 17 Days (Days 1 – 17). Rats of Group 4 were post-treated with oral administration of combined mixture of 15 mg/kg body weight of MO11 and 7 mg/kg body weight of MS06 for 17 Days (Days 1 – 17). Rats of Group 5 received only oral administration of 1 ml/kg body weight of Olive Oil (vehicle) for 17 Days (Days 1 – 17), and were not exposed to administration of $CdCl_2$. Rats of Group 6 were post-treated with oral administration of 3.35 mg/kg body weight of Doxorubicin (standard

anticancer drug – Positive Control) for 17 Days (Days 1 - 17).

Completion of experimental procedures

No anesthesia was used for animal sacrifice as approved by the University Ethical Review Committee after evaluation of experimental protocol based on the fact that the biomarkers to be examined include enzymes such as Caspase-3 and metabolic agents such as Cytochrome p450 (P450), which may be endogenously altered by anesthetic agents requiring post-experimental control of confounding factors. Hence, the rats were sacrificed by cervical dislocation as previously applied[25].

Tissue-biochemical analyses of levels of Catalase (CAT) and Superoxide dismutase (SOD) in rat cerebrum

Tissue-biochemical analyses of levels of CAT and SOD in rat cerebrum were evaluated using standard spectrometric methods of Sinha, 1972 and Misra and Fridovich (1972) respectively as modified by Akinlolu *et al*., 2013[1].

Tissue-ELISA analyses of Cyclo-oxygenase-2 (COX-2) and P450 in rat cerebrum

Tissue-ELISA analyses of levels of COX-2 and P450 in rat cerebrum using ELISA technique as described by Akinlolu *et al*., 2023[5]. ELISA kits for COX-2 and P450 were products of CUSABIO Technology LLC, Houston, USA. AgileReader™ ELISA plate reader was employed with absorbance read at the wavelength of 450 nm.

Data analysis

Computed data of concentrations of each biomarker was expressed as arithmetic means ± standard deviation. Mann-Whitney U test (Wilcoxon-Mann-Whitney Test, 2016) was used for statistical comparison of the concentration of each of CAT, SOD, COX-2 and P450 between two groups because the sample size of 24 is less than 30. Significant difference was confirmed at 95% confidence interval with associated p-value of less than 0.05 ($p \leq 0.05$).

Results

Concentrations of CAT in cerebral cortices of rats

Results showed statistically non-significant lower levels of CAT in rats of $CdCl_2$-only treated Group 2, when compared with normal saline-treated Control Group 1 ($p = 1.00$), as presented in Table 1. In addition, results showed significantly higher levels of CAT in $CdCl_2$-exposed + MO11 + MS06 post-treated Group 4 ($p<0.001$), Olive Oil-only treated Group 5 ($p = 0.03$) and $CdCl_2$-exposed + Doxorubicin post-treated Group 6 ($p<0.001$) when compared to Group 2. An increase in CAT levels was also observed in $CdCl_2$-exposed + MO11 post-treated Group 3 when compared to Group 2, although statistically non-significant ($p = 0.21$).

Concentrations of SOD in cerebral cortices of rats

Results showed similar levels of SOD in rats of $CdCl_2$-only treated Group 2, when compared with normal saline-treated Control Group 1 ($p = 0.19$), as presented in Table 1. No statistically significant changes in SOD levels were found in $CdCl_2$-exposed + MO11 post-treated Group 3 ($p = 0.17$), $CdCl_2$-exposed + MO11 + MS06 post-treated Group 4 ($p = 0.28$), Olive Oil-only treated Group 5 ($p = 0.16$) and $CdCl_2$-exposed + Doxorubicin post-treated Group 6 ($p = 0.10$), when compared to Group 2.

Concentrations of COX-2 in cerebral cortices of rats

Results showed statistically significant higher levels of COX-2 in rats of $CdCl_2$-only treated Group 2, when compared with normal saline-treated Control Group 1 ($p<0.001$), as presented in Table 1. COX-2 levels were found significantly decreased in $CdCl_2$-exposed + MO11 post-treated Group 3 ($p<0.001$), $CdCl_2$-exposed + MO11 + MS06 post-treated Group 4 ($p<0.001$), Olive Oil-only treated Group 5 ($p<0.001$) and $CdCl_2$-exposed + Doxorubicin post-treated Group 6 ($p<0.001$) when compared to Group 2.

Table 1. Concentrations of Catalase, Superoxide dismutase, Cyclo-oxygenase-2 and Cytochrome p450 in cerebral cortices of rats. Data are presented as mean + SD (n = 4 per group).

Drug/Extract Administered	CAT (U/L)	SOD (U/L)	COX-2 (pg/mL)	P450 (pg/mL)
Normal saline-only treated Group 1	145.90±2.55	2356.65±0.21	31.78±2.81	52.62±10
CdCl2 only treated Group 2	104.09±1.43	2355.02±0.40	112.17±5.25a	199.77±5.57a
CdCl2-exposed + MO11 post-treated Group 3	544.87±26.05	2356.71±0.56	32.3±2.78***	66.02±21.58***
CdCl2-exposed + MO11 + MS06 post-treated Group 4	1558.7±331.78***	2356.51±0.30	24±1.98***	44.42±2.56***
Olive Oil only Group 5	776.3±214.80*	2357.62±0.69	17.63±1.22***	43.52±6.47***
CdCl2-exposed + Doxorubicin post-treated Group 6	1387.33±54.83***	2358±1.79	21.78±1.33***	164.45±45.15

[a] - significant difference compared with the normal saline-treated control Group 1, $p \leq 0.001$.
* $p \leq 0.05$, *** $p \leq 0.001$ – significant difference compared with $CdCl_2$-only treated Group 2.

Concentrations of P450 in cerebral cortices of rats

Results showed statistically significant higher levels of P450 in rats of $CdCl_2$-only treated Group 2, when compared with normal saline-treated Control Group 1 ($p<0.001$), as presented in Table 1. P450 levels were found significantly decreased in $CdCl_2$-exposed + MO11 post-treated Group 3 ($p<0.001$), $CdCl_2$-exposed + MO11 + MS06 post-treated Group 4 ($p<0.001$) and Olive Oil-only treated Group 5 ($p<0.001$) when compared to Group 2.

P450 levels were also found decreased in rats of $CdCl_2$-exposed + Doxorubicin post-treated Group 6 compared to $CdCl_2$-only treated Group 2, although statistically non-significant ($p = 0.34$).

Discussion

In our previous study by Akinlolu *et al.*, 2022[4], we reported that $CdCl_2$-induced neurotoxicity caused increased number of chromatolytic cells and neurodegeneration in the prefrontal cortices of rats of $CdCl_2$-only treated Group 2. However, post-treatments of $CdCl_2$-induced neurotoxicity with MO11, MO11 + MS06, and Doxorubicin resulted in decreased number of chromatolytic cells in the prefrontal cortices of rats. Hence, MO11, MS06 and Doxorubicin possess neuroprotective potential and were able to gradually reverse $CdCl_2$-induced chromatolysis and neurodegeneration within 17 days[4].

CAT and SOD are antioxidant enzymes, which catalyse the conversion of hydrogen peroxide to water and molecular oxygen, and break down potentially harmful oxygen molecules in cells respectively[1,32]. CAT and SOD, therefore, protect against tissue damage by scavenging free radicals and reversing the effects of oxidative stress. CAT is a peroxisomal marker enzyme and the role of brain CAT in ethanol oxidation as well as in central nervous system disorders due to hereditary peroxisomal diseases such as Zellweger syndrome has been reported[28]. Schad *et al.*, 2003[28] demonstrated marked cytoplasmic staining of CAT mRNA in a large number of neurons throughout the rat brain using tyramine/CARD (catalyzed reporter deposition)-enhanced nonradioactive in situ hybridization protocol. Hence, evaluation of CAT levels in the cerebrum is of interest in neuroregenerative studies.

The decreased CAT level in $CdCl_2$-only treated Group 2, when compared with normal saline-only treated Control Group 1 confirmed $CdCl_2$-induction of oxidative stress and reduction of antioxidant enzymes levels. This observation is in agreement with those of Elkhadragy *et al.*, 2018[13] and Mohammed *et al.*, 2019[23], which reported cadmium-induced decreased CAT levels. Contrariwise, our results showed higher CAT levels in $CdCl_2$-exposed + MO11 post-treated Group 3, $CdCl_2$-exposed + MS06 post-treated Group 4, Olive Oil-treated Group 5 and Doxorubicin-treated Group 6 when compared with normal saline-treated Group 1, confirming pro-antioxidant potential of the extracts, Olive Oil and Doxorubicin.

Post-treatments of $CdCl_2$-induced neurotoxicity and oxidative stress confirmed that MO11, MS06 and Doxorubicin possess antioxidant, neuroprotective and neuroregenerative potential which resulted in increased CAT levels in cerebral cortex homogenates of rats of Groups 3, 4 and 6 respectively, when compared with Group 2.

Low to high levels of Mn-SOD mRNA were expressed in cholinergic neurons of nuclei of basal forebrain, striatum, and reticular formation of upper brainstem (laterodorsal tegmental and pedunculopontine nuclei)[18]. These reported observations emphasizes the relevance of evaluating SOD-levels in the rat brain. The results of this study showed similar levels of SOD in cerebral homogenates of rats of Groups 1 – 6. These results indicate that $CdCl_2$ exposure and post-treatments with MO11, MS06 and Doxorubicin had no significant effects on SOD levels within the 18 days of experimental procedures.

COX-2 is the main cyclo-oxygenase isoform in the brain. Kawaguchi *et al.*, 2005[19] reported COX-2 expression in hippocampal CA3, dentate gyrus and cerebral cortex emphasizing the relevance of evaluating COX-2-levels in the rat brain. Increased COX-2 activity results in increased oxidative stress and increased release of prostaglandins with accompanied injurious effects[19]. Therefore, increased COX-2 levels results in increased oxidative stress causing induction of inflammation, apoptosis and carcinogenesis[24,25]. The higher level of COX-2 in $CdCl_2$-only treated Group 2, when compared with normal saline-only treated Control Group 1 confirmed $CdCl_2$-induction of oxidative stress and promotion of inflammation, neuronal cell death and carcinogenesis. The observed $CdCl_2$-induction of COX-2 upregulation in this study is in agreement with those of Liu and Kadiiska, 2009[20] and Junior *et al.*, 2020[17], which reported cadmium-induced increase in COX-2 levels with associated inflammation, apoptosis and carcinogenesis. In contrast, our results showed similar COX-2 levels in Groups 1 and 3, but lower COX-2 levels in Groups 4 - 6, when compared with normal saline-treated Group 1, confirming neuroprotective potential of the extracts, Olive Oil and Doxorubicin.

Post-treatments of $CdCl_2$-induced neurotoxicity confirmed that MO11, MS06 and Doxorubicin possess neuroprotective, neuroregenerative, anti-inflammatory and anticancer potential which resulted in significant reduction of COX-2 levels in cerebral cortex homogenates of rats of Groups 3, 4 and 6 respectively, when compared with Group 2.

P450s are monooxygenases that oxidize fatty acids, steroids and xenobiotics thereby enhancing the water-solubility and expulsion of foreign compounds. P450 thus plays regulatory roles in the clearance of drugs and compounds, detoxification of drugs

and xenobiotics, vitamin D metabolism, synthesis of cholesterols and hormones, cellular metabolism and homeostasis[21]. P450 is involved in activation/inactivation of carcinogen as well as activation/inactivation of anticancer drugs, and clearly plays strong roles in cancer therapy[26]. The liver is the major site of xenobiotic metabolism and detoxification, and the brain P450 is very low constituting about 0.5%-2%[15] or 0.2%-0.5%[30] of hepatic P450. Hence, the brain P450 does not appear significantly involved in regulatory roles of pharmacokinetics of the body's hormones and drugs. The brain P450 rather regulates brain cholesterol homeostasis, retinoids elimination and levels of endogenous GABA receptor agonists[15,31]. Wojciech *et al.*, 2021[31] reported expression of different forms of P450 in the frontal cortex, thalamus, hypothalamus, striatum and hippocampus of rat brain. Therefore, the profiling of brain P450 in neurotoxicology becomes very important in understanding the mechanism of action of the neurotoxin and in the design of appropriate chemotherapy.

The higher P450 level in $CdCl_2$-only treated Group 2, when compared with normal saline-only treated Control Group confirmed induction and increased P450 level. This observation is similar to those of Bhattacharyya *et al.*, 2014[10], which reported that increased P450 levels are associated with increased oxidative stress via oxygen activation. Hence, the observed increased P450 levels could have resulted from $CdCl_2$-induced increased oxidative stress and decreased CAT levels in rats of $CdCl_2$-only treated Group 2. Contrari-wise, our results showed similar or lower P450 levels in Groups 3 – 5, when compared with Group 1. However, results showed higher P450 level in Group 6 compared with Group 1. These observations imply that the extracts and Olive Oil have pro-P450 potential.

The increased P450 levels in cerebral cortex homogenates of rats in this study is in contrast with previously reported significant decrease in liver P450 levels in cadmium-induced hepatotoxicity in hamsters[29] and significant decrease in testes P450 levels in cadmium-induced testicular damage in rats[7]. These differences could have been due to low brain P450 content versus high liver P450 content. In addition, the reason for the cadmium-induced increased brain P450 levels versus cadmium-induced liver and testicular decreased P450 levels could have been due to the shielding effect of the protective components of the brain resulting in increased P450 levels to aid clearance of $CdCl_2$ brain content.

Post-treatments of $CdCl_2$-induced neurotoxicity confirmed that MO11, MS06 and Doxorubicin possess neuroprotective and neuroregenerative potential which resulted in significant reduction of P450 levels in cerebral cortex homogenates of rats of Groups 3 and 4 respectively, when compared with Group 2. Contrari-wise, results of higher P450 levels in Group 6 compared with Group 2 indicate that Doxorubicin possesses lower neuroprotective and neuroregenerative potential, when compared with MO11 and MS06.

Conclusion

Overall, the findings of this study suggest that post-treatments of $CdCl_2$-induced neurotoxicity with MO11 (isolated from *Moringa oleifera* leaves) and MS06 (isolated from *Musa sapientum* suckers), and Doxorubicin resulted in significant increased CAT levels, but significant decreased COX-2 levels in rat brain. In addition, post-treatments of $CdCl_2$-induced neurotoxicity with MO11 and MS06 resulted in significant decreased levels of P450, however post-treatments with Doxorubicin resulted in non-significant decreased levels of P450 in rat brain. These observations indicate that MO11 and MS06 conferred a higher degree of neuroprotection against $CdCl_2$-induced neurotoxicity, oxidative stress and promotions of inflammation, apoptosis and carcinogenesis, when compared with Doxorubicin. Hence, MO11 and MS06 are recommended for further evaluations as potential drug candidates for the treatments of neurodegenerative diseases and disorders of the central nervous system.

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