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IN VIVO ANTI-INFLAMMATORY EFFECTS OF ANTI-TOXIC PRINCIPLES FROM MORINGA OLEIFERA(MO11) AND MUSA SAPIENTUM (MS06) VIA NF-KB/IL-4/IL-10-MEDIATED PATHWAY IN CADMIUM CHLORIDE-INDUCED HEPATO-TOXICITY.

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ABSTRACT

Cadmium-induction of hepato-toxicity and inflammation in animal models have been reported. The mechanism underlying hepatic inflammation is poorly understood. This study evaluated anti-inflammatory potentials of MO11 (isolated from *Moringa oleifera* leaves) and MS06 (isolated from *Musa sapientum* suckers) in Cadmium Chloride (CdCl)-induced hepato-toxicity and inflammation in rats.Twenty-eight adult male wistar rats (average weight of 155 g) were randomly divided into 7 groups (n = 4). Group 1 was control. Groups 2 - 4 and 7 received single intraperitoneal administration of 1.5 mg/Kg bodyweight of CdCl on Day 1. Thereafter, Groups 3, 4 and 7 were post-treated with 15 mg/Kg bodyweight of MO11, 15 mg/Kg bodyweight of MO11 + 7 mg/Kg bodyweight of MS06 and single-dose of 3.35 mg/Kg bodyweight of Doxorubicin respectively (Days 1 - 17). Groups 5 and 6 received only MO11-dose and Olive Oil (vehicle) respectively (Days 1 - 17). Liver histopathology (Heamatoxyline and Eosin technique) and ELISA concentrations of pro-inflammatory biomarkers (IL-1β, IL-6, IL-8 and NF-kB) and anti-inflammatory biomarkers (IL-4 and IL-10) in liver homogenates of rats of Groups 1 - 7 were evaluated. Computed data were statistically analysed using Mann-Whitney-U test at $P \leq 0.05$. Histo-pathological analyses showed normal liver histology in Groups 1 - 7. Post-treatments of CdCl-induced hepato-toxicity and hepatic inflammation with MO11 and MO11+MS06 resulted in downregulations of IL-1β, IL-6, IL-8 and NF-kB, but upregulations of IL-4 and IL-10 in Groups 3, 4 and 7, compared with Group 2. MO11 and MS06 possess hepato-protective and anti-inflammatory potentials.

Key words: anti-inflammation; hepato-protection; plants' drug candidates; toxicology.

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INTRODUCTION

Moringa oleifera (MO) and *Musa sapientum* (MS) are ethno-medicinal plants with reported anticancer potentials (Akinlolu et al., 2021). We previously isolated MOF6,

which is a sub-fraction of ethanolic extracts of MO leaves and tested its antioxidant and neuro-protective potentials. MOF6 showed significant antioxidant and neuro-protective potentials against Cuprizone-induced cerebellar damage in rats (Omotoso et al., 2018). MOF6 equally showed neuro-protective potentials against dysregulated Acetylcholinesterase concentrations in Sodium arsenite-induced neurotoxicity in rats (Akinlolu et al., 2020a). In addition, MOF6 possessed hepato-protective, anti-drug resistance and anti-proliferation potentials in 7,12-Dimethylbenz(a)anthracene-induced hepato-toxicity in rats (Akinlolu et al., 2021). Furthermore, MSF1, which was fractionated from MS suckers ameliorated 7,12-Dimethylbenz(a)anthracene-induced hepatic mutagenesis and showed hepato-protective, anti-drug resistance and anti-proliferation potentials in rats (Akinlolu et al., 2021).

Cadmium (Cd) is one of the 10 chemicals of carcinogenic concerns according to the World Health Organization, and Cd-induced carcinogenesis has been reported in humans and animal models (Huff et al., 2007; Bernhoft, 2013; Wang and Du, 2013; Andjelkovic et al., 2019). Cd usually exists as a divalent cation, complexed with other elements, such as Cadmium Chloride (CdCl) (Lansdown et al., 2001; Huff et al., 2007; Bernhoft, 2013; Wang and Du, 2013; Andjelkovic et al., 2019). Commercially, Cd is used in television screens, lasers, batteries, paint pigments, cosmetics, in galvanizing steel and as a barrier in nuclear fission.[6] Approximately 30% of Cd deposits in the liver and 30% in the kidneys, with the rest distributed throughout the body, thus resulting in systemic dysfunctions such as inflammation and hepato-toxicity (Lansdown et al., 2001; Huff et al., 2007; Bernhoft, 2013; Wang and Du, 2013; Andjelkovic et al., 2019), neurotoxicity (Bernhoft, 2013), skin alopecia and ulceration (Lansdown et al., 2001). In humans, Cd-exposure following absorption resulted in Cd-Metallothioneins complexes via which bound-Cd is re-distributed to other body organs potentiating systemic toxicity (Godt et al., 2006; Bernhoft, 2013). In addition, Cd-exposure resulted in hepatocyte necrosis and apoptosis (Godt et al., 2006), mild dilation of sinusoids and infiltration of lymphocytes in liver portal spaces (Andjelkovic et al., 2019), reduction in hepatic antioxidant defense system and increased hepatic lipid peroxidation (Renugadevi et al., 2010) in animal models. Despite reported Cd-induced hepato-toxicity in experimental studies, the mechanism underlying Cd-induced hepato-toxicity and hepatic inflammation remains poorly understood.

Plants have been great sources of therapeutic drug candidates (Akinlolu et al., 2021). There is paucity of studies which evaluated the mechanisms underlying Cd-induced hepatic inflammation, Therefore, this study evaluated the effects of MO11 (isolated from *Moringa oleifera* leaves) and MS06 (isolated from *Musa sapientum* suckers) on biomarkers of pro-inflammation (IL-1β, IL-6, IL-8 and NF-kB) and anti-inflammation (IL-4 and IL-10) in CdCl-induced hepato-toxicity and hepatic inflammation in the liver of adult male wistar rats.

MATERIALS AND METHODS

Ethics Statement

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).

Collection, authentication and deposition of MO leaves and MS suckers

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

Extraction and partitioning of fractions of MO leaves and MS suckers

MO leaves and MS suckers were air-dried, powdered, weighed and kept in an air tight container until ready for further analyses. 4.0 Kg weight of powdered MO leaves and 5.2 kg weight of powdered MS suckers were extracted with distilled ethanol and evaporated to a dry form using a rotary evaporator. 210.2 g of MO leaves and 159.32 g of MS suckers were consequently separated into dichloromethane (DCM), ethyl acetate (EA), methanol (MeOH) and n-hexane (NH) soluble fractions in an increasing order of polarity to obtain 12 fractions (MO1 – MO12) and 8 fractions (MS01 – MS08) respectively.

Column chromatography

Column chromatography of the MO and MS fractions was executed on silica gel (70 – 230 and 240 – 300 mesh size, Merck, Germany), Merck alumina (70 – 230 mesh ASTM). Thin Layer Chromatography (TLC) was executed on pre-coated silica gel 60 F_{254} aluminium foil (Merck, Germany) in-order to obtain pure isolates. Spots on TLC were evaluated using an ultraviolet lamp which operates at a wavelengths of 366 nm and 254 nm for fluorescence and fluorescence quenching spots respectively.

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 by Chaves et al., 2020. In addition, antimicrobial activities of plants' extracts were evaluated by testing the cyto-toxic potentials of each fraction against the growths of *Escherichia coli* and *Salmonella tiphimurium* as previously described by Elisha et al., 2017.

Purification of MO fractions

MO8 and MO11 fractions which had the best antioxidant and antimicrobial potentials were selected and further purified on a silica gel open column, using NH, DCM, EA and MeOH in an increasing order of polarity until the most active antioxidant and anti-microbial isolates ($MO11_{8,3}$ and $MO11_{8,4}$) were obtained. Phytochemical screenings of $MO11_{8,3}$ and $MO11_{8,4}$ showed the presence of flavonoids, saponin, tannins, alkaloids, glycosides and steroids. The resulting grams of $MO11_{8,3}$ and $MO11_{8,4}$ were mixed together as 1.43 g of MO11, which was further tested for its anticancer and anti-inflammatory potentials in $CdCl_2$-induced skin carcinogenesis in this study.

Purification of MS fractions

Phytochemical screening of MS showed the presence of saponins, saponin glycosides, tannins, alkaloids and indole alkaloids. The antioxidant and antimicrobial activities of the obtained 8 MS fractions (MS01 – MS08) were determined. MS06 which had the best antioxidant and antimicrobial potential was selected and further purified on a silica gel open column, using NH, DCM, EA and MeOH in an increasing order of polarity to afford seven fractions ($MS06_{1-7}$). $MS06_5$ showed the best antioxidant and antimicrobial potential. The resulting 1.24 g of $MS06_5$ was further tested for its anticancer and anti-inflammatory potentials in $CdCl_2$-induced skin carcinogenesis in this study.

Liquid chromatography-mass spectrometry (LC-MS) analyses of $MO11_{8,3}$, $MO11_{8,4}$ and $MS06_5$

The MO isolates ($MO11_{8,3}$ and $MO11_{8,4}$) and MS isolate ($MS06_5$) were submitted for LC-MS analysis at the Chemical Purification Analysis and Screening Core -+Facility, University of South Florida, Tampa, Florida, USA. Low resolution mass spectra were recorded on an Agilent Technologies LC/MSD VL electrospray ionization mass spectrometer. High resolution mass spectra were recorded on an Agilent Technologies LC/MSD TOF electrospray ionization spectrometer.

Animal care and feeding

Twenty-eight (28) 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 randomly divided into 7 groups with 4 rats per group. The rats were acclimatized for a week at the animal house of Faculty of Pharmacy of the primary study institution before the beginning of experimental procedures. The rats were kept under standard conditions and permitted unlimited access to food and drinking water ad libitum. The bodyweights of the rats were computed on daily bases using electronic compact scale (SF-400C weighs in gram) weighing scale (Valid Enterprise, Kalbadevi, Mumbai, India).

Grouping of rats and extracts/drugs administration

MO11 and MS11 were dissolved in Olive Oil (vehicle). Rats of Control Group 1 (Baseline Control) received physiological saline only for 17 Days (Days 1 - 17). Each rat of Experimental Groups 2 - 4 and 7 received single intra-peritoneal administration of 1.5 mg/Kg bodyweight CdCl (Sigma-Aldrich, Japan Co.) on Day 1. Rats of Group 2 (Negative Control) were left untreated throughout experimental procedure for 17 Days (Days 1 - 17). Thereafter, rats of Group 3 were post-treated with 15 mg/Kg bodyweight of MO11 for 17 Days (Days 1 - 17). Rats of Group 4 were post-treated with combined mixture of 15 mg/Kg bodyweight of MO11 and 7 mg/Kg bodyweight of MS06 for 17 Days (Days 1 - 17). Rats of Group 5 received only 15 mg/Kg bodyweight of MO11 for 17 Days (Days 1 - 17). Rats of Group 6 received only 1 ml/Kg bodyweight of Olive Oil (vehicle) for 17 Days (Days 1 - 17). Rats of Group 7 were post-treated with single-dose of 3.35 mg/Kg bodyweight of Doxorubicin (standard anticancer drug – Positive Control) on Day 1 and the rats left untreated from Days 2 - 17.

Completion of experimental procedures

Twenty-four hours after the last day of administration of drugs and extracts on Day 17, the experimental procedures were completed following rats' sacrifice on Day 18.

Histo-pathological evaluations of the liver

Liver samples were excised following the opening of the thoracic and abdominal cavities of each rat, and fixed in 10% formol-saline and processed for light microscopy using conventional histological procedures. Histo-pathological evaluations of the liver were conducted as using Heamatoxyline and

Eosin technique as earlier described by Akinlolu et al., 2021.

Evaluations of concentrations of biomarkers in homogenates of skin of rats using Enzyme Linked Immunosorbent Assay (ELISA)

Homogenates of excised liver lobes of all rats of Control and Experimental Groups 1 - 7 were obtained. Thereafter, the excised liver lobes were isolated and thoroughly homogenized using porcelain mortar and pestle in ice-cold 0.25 M sucrose. 1 g of liver tissue was homogenized in 4 ml of 0.25 M sucrose solution. The tissue homogenates were additionally filled up to 5 ml with sucrose in a 5 ml serum bottle. Liver homogenates were consequently centrifuged at 3000 revolution per minute for 15 minutes using a centrifuge (Model 90-1). The supernatant was collected with Pasteur pipettes and placed in a freezer at -4^{O}C, and thereafter assayed for concentrations of IL-1β, IL-4, IL-6, IL-8, IL-10 and NF-kB in the liver of all rats of Control Group 1 and Experimental Groups 2 – 6 using ELISA technique as previously described by Akinlolu et al., 2021.

Statistical analyses

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 biomarker 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

Histo-pathological evaluations of the liver

Histo-pathological analyses showed normal histo-architectures of the liver with typically sized spaced central vein surrounded by densely distributed hepatocytes in rats of Groups 1 – 7 (Figures 1a – 1g).

Concentrations of IL-1β, IL-4, IL-6, IL-8, IL-10 and NF-kB in liver homogenates of rats: CdCl-only treated Group 2 versus Normal Saline-only Control Group 1

Results showed statistically significant higher ($P \leq 0.05$) levels of IL-1β, IL-6, IL-8 and NF-KB in rats of Group 2, when compared with Control Group 1 (Table 1 and Figures 2 - 7). In addition, results showed statistically non-significant lower ($P \geq 0.05$) levels of IL-4, but statistically significant lower ($P \leq 0.05$) levels of IL-10 in rats of Group 2, when compared with Control Group 1 (Table 1 and Figures 2 - 7).

Concentrations of IL-1β, IL-4, IL-6, IL-8, IL-10 and NF-kB in liver homogenates of rats: CdCl-only treated Group 2 versus CdCl-exposure + MO11 post-treated Group 3 and CdCl-exposure + MO11 + MS06 post-treated Group 4

Results showed statistically significant higher ($P \leq 0.05$) levels of IL-1β, IL-6, IL-8 and NF-KB in rats of Group 2, when compared with Groups 3 and 4 (Table 1 and Figures 2 - 7). In addition, results showed statistically non-significant lower ($P \geq 0.05$) levels of IL-4 and IL-10 in rats of Group 2, when compared with Groups 3 and 4 (Table 1 and Figures 2 - 7).

Concentrations of IL-1β, IL-4, IL-6, IL-8, IL-10 and NF-kB in liver homogenates of rats: CdCl-only treated Group 2 versus CdCl-exposure + Doxorubicin post-treated Group 7

Results showed statistically significant higher ($P \leq 0.05$) levels of IL-1β, IL-6 and IL-8 in

rats of Group 2, when compared with Group 7 (Table 1 and Figures 2 - 7). In addition, results showed statistically non-significant higher ($P \geq 0.05$) levels of NF-KB in rats of Group 2, when compared with Group 7 (Table 1 and Figures 2 - 7). Furthermore, results showed statistically significant lower ($P \leq 0.05$) levels of IL-4 and IL-10 in rats of Group 2, when compared with Group 7 (Table 1 and Figures 2 - 7).


Figure 1a

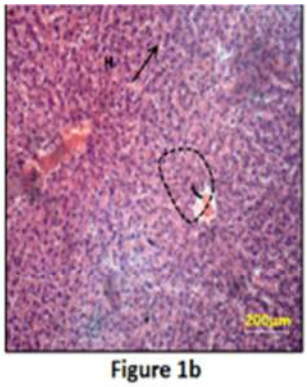
Figure 1b

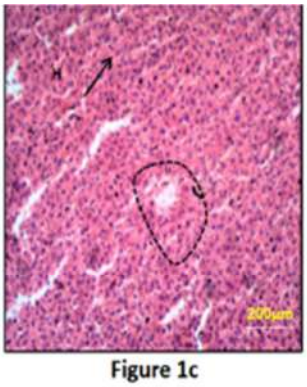
Figure 1c


Figure 1d

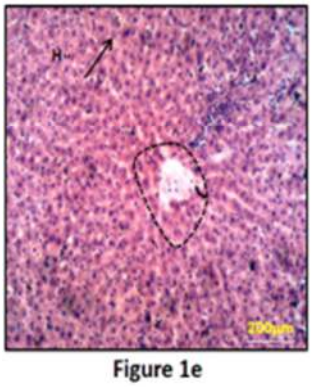
Figure 1e

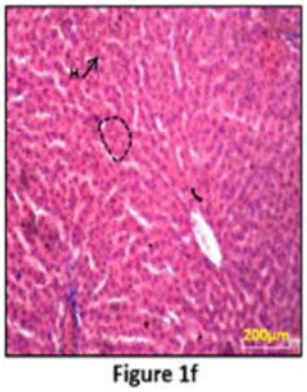
Figure 1f

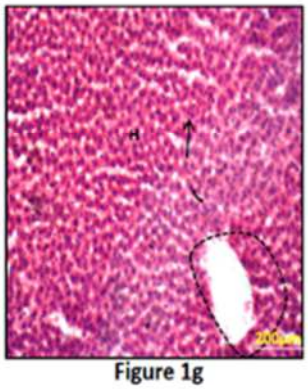
Figure 1g

Legends for Figures 1a – g.

Figure 1a: Liver photomicrograph of rats of Group 1 which received physiological saline only. Haematoxylin and Eosin X 100. Histological analyses show normal histoarchitecture of the liver. (Dotted circle: Central vein, H: Hepatocyte).

Figure 1b: Liver photomicrograph of rats of Group 2 which received single 1.5mg/kg bodyweight of CdCl *i.p.* Heamatoxylin and Eosin X 100. Histological analyses show normal histoarchitecture of the liver. (Dotted circle: Central vein, H: Hepatocyte).

Figure 1c: Liver photomicrograph of rats of Group 3 which received single CdCl-dose *i.p.* and post-treated with MO11-dose. Haematoxylin and Eosin X 100. Histo-pathological analyses show normal liver histology. (Dotted circle: Central vein, H: Hepatocyte).

Figure 1d: Liver photomicrograph of rats of Group 4 which received single CdCl-dose *i.p.* and post-treated with MO11-dose + MS06-dose. Haematoxylin and Eosin X 100. Histo-pathological analyses show normal liver histology. (Dotted circle: Central vein, H: Hepatocyte).

Figure 1e: Liver photomicrograph of rats of Group 5 which received 15mg/Kg bodyweight of MO11 only. Haematoxylin and Eosin X 100. Histo-pathological analyses show normal liver histology. (Dotted circle: Central vein, S: Sinusoidal space, H: Hepatocyte).

Figure 1f: Liver photomicrograph of rats of Group 6 which received 1ml/Kg bodyweight of Olive oil only. Haematoxylin and Eosin X 100. Histo-pathological analyses show normal liver histology. (Dotted circle: Central vein, H: Hepatocyte).

Figure 1g: Liver photomicrograph of rats of Group 7 which received single CdCl-dose *i.p.* and post-treated with 3.35mg/Kg bodyweight of Doxorubicin. Haematoxyline and Eosin X 100. Histo-pathological analyses show normal liver histology. (Dotted circle: Central vein, H: Hepatocyte).

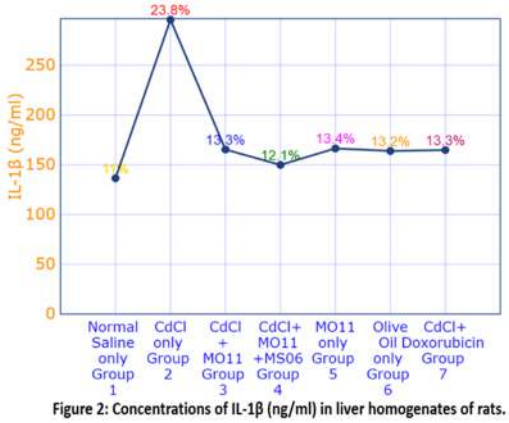

Figure 2: Concentrations of IL-1β (ng/ml) in liver homogenates of rats.

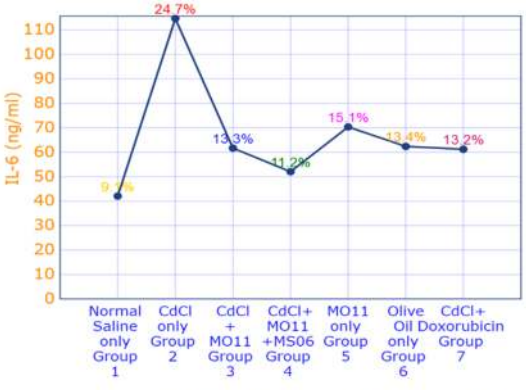

Figure 3: Concentrations of IL-6 (ng/ml) in liver homogenates of rats.

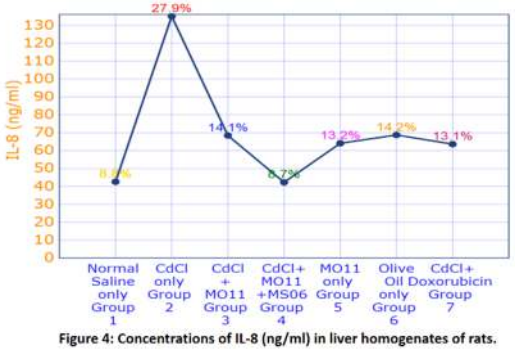

Figure 4: Concentrations of IL-8 (ng/ml) in liver homogenates of rats.

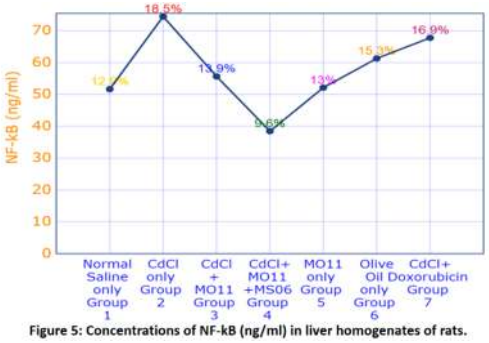

Figure 5: Concentrations of NF-kB (ng/ml) in liver homogenates of rats.

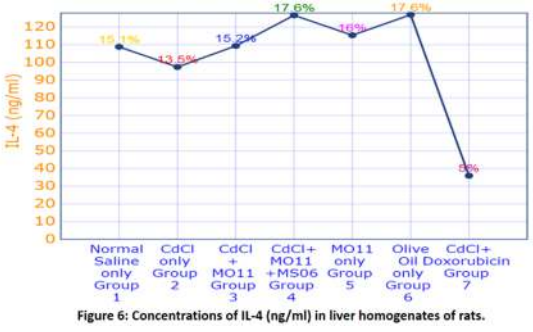

Figure 6: Concentrations of IL-4 (ng/ml) in liver homogenates of rats.

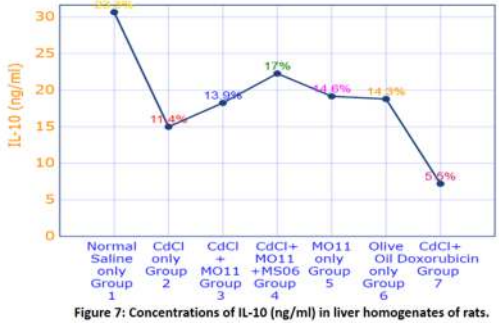

Figure 7: Concentrations of IL-10 (ng/ml) in liver homogenates of rats.

Table 1: Concentrations of IL-1β, IL-6, IL-8, NF-kB, IL-4 and IL-10 in liver homogenates of rats.

Drug/Extract →	**Normal Saline only Group 1**	**CdCl only Group 2**	**CdCl-exposure + MO11 post-treated Group 3**	**CdCl-exposure + MO11 + MS06 post-treated Group 4**	**MO11 only Group 5**	**Olive Oil only Group 6**	**CdCl-exposure + Doxorubicin post-treated Group 7**
IL-1β (ng/ml)	*136.48± 19.44	295.80 ±7.20	165.37*± 1.30	*149.89± 10.19	*166.48±0.93	*163.89 ±7.59	*164.81±24.07
P - value	P < 0.01		P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01
IL-6 (ng/ml)	*42.04±0.03	114.66 ±4.55	*61.67±0.22	*52.04±4.93	*70.33 ±2.31	*62.37± 1.89	*61.22±0.64
P – value	P < 0.01		P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01
IL-8 (ng/ml)	*42.57±1.32	135.02 ±5.09	*68.42±0.19	*42.28±6.89	*64.08 ±2.64	*68.72± 1.82	*63.60±4.05
P – value	P < 0.01		P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01
NF-kB (ng/ml)	*51.65±0.12	74.45± 3.18	*55.65±1.91	*38.47±2.22	*52.12 ±0.92	*61.29± 1.06	67.76±0.82
P – value	P < 0.01		P < 0.01	P < 0.01	P < 0.01	0.03	0.38
IL-4 (ng/ml)	108.79±0.12	97.40± 2.56	109.31±0.17	126.62±1.36	115.36 ±1.92	126.93± 7.56	**35.96±14.27
p-value	0.98		0.98	0.42	0.89	0.50	0.02
IL-10 (ng/ml)	**30.66± 3.10	14.99± 0.92	18.26±0.07	**22.28± 0.65	19.16± 0.20	18.79±0.76	**7.20±0.12
P – value	P < 0.01		0.59	0.03	0.34	0.43	0.04

P - value at P ≤ 0.05: Group 2 versus Groups 1 and 3 – 7 (** = significant increase, * = significant decrease).

DISCUSSION

Spectroscopic analyses showed the presence of Leucine, Glutamic acid, Guanine, Phenylalanine and other therapeutic compounds in MO11 and MS06 isolates (Ameen and Akinlolu, 2022). Glutamic acid (Dutta et al., 2013), Guanine (Dasari and Tchounwou, 2014), Phenylalanine (Lieu et al., 2020; Ziyu et al., 2020) and Leucine (Lee et al., 2017) are established anti-inflammatory and antioxidant compounds. Hence, the observed anti-ulceration and anti-inflammatory effects of MO11 and MS06 in this study could have been due to the presence of Leucine, Glutamic acid, Guanine and Phenylalanine and other anticancer compounds in MO11 and MS06 isolates. Furthermore, the observed significant anti-inflammatory potentials in rats of Group 3 and Group 4, which were post-treated with MO11 and MO11+MS06 (Group 4) following $CdCl_2$-induced hepato-toxicity (Table 1 and Figures 2 – 7), could have been due to the fact that MO11 and MS06 contain anticancer and anti-inflammatory compounds such as Leucine, Glutamic acid, Guanine and Phenylalanine.

Histo-pathological analyses showed normal histo-architectures of the liver with typically sized spaced central vein surrounded by densely distributed hepatocytes in rats of Groups 1 – 7 (Figures 1a – 1g). These observations suggest that the administrations of CdCl, MO11, MS06, Olive Oil and Doxorubicin from Days 1 – 17 of experimental procedures did not result in evident histo-pathology of the liver. This is possibly because results of cyto-toxicity are first elicited at the molecular level and when sustained result in evident tissue histo-pathology.

Inflammation is associated with the release of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, TNFα and NF-kB (Shih et al., 2015; Akinlolu et al., 2020b). NF-kB upregulation results in the release and increased levels of other pro-inflammatory cytokines, hence NF-kB is opined to be the central regulator of inflammation (Shih et al., 2015). Furthermore, IL-4 and IL-10 inhibit the release of NF-kB and pro-inflammatory cytokines, and are involved in the resolution of inflammation (Shih et al., 2015).

What mechanism underlies CdCl-induced hepatic inflammation? Results of this study showed upregulations of IL-1β, IL-6, IL-8 and NF-kB, but downregulations of IL-4 and IL-10 in liver homogenates of rats of CdCl-only treated Group 2, when compared with Normal saline-only treated Control Group 1 (Table 1 and Figures 2 – 7). These observations confirm CdCl-induction of hepatic inflammation, and equally indicate that CdCl-induced hepatic inflammation possibly occurs via the NF-kB pathway. The findings of this study are in agreement with those of Ebrahimi et al. 2020, which reported Cd-induction of inflammation via upregulations of IL-1β, IL-6 and IL-8 in plasma of rats, but downregulations of IL-4 in mice.

Do MO11 and MS06 have anti-inflammatory potentials against CdCl-induced hepatic inflammation? Post-treatments of CdCl-induced hepatic inflammation in rats with MO11 (Group 3) and MO11 + MS06 (Group 4) resulted in downregulations of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and NF-kB), but upregulations of anti-inflammatory cytokines (IL-4 and IL-10), when compared with CdCl-only treated Group 2 (Table 1 and Figures 2 – 7). These observations indicate that MO11 and MS06 possess anti-inflammatory potentials which were possibly mediated via the NF-kB pathway.

CONCLUSION

Overall, the findings of this study suggest that post-treatments with MO11 and MS06 conferred a degree of hepato-protective and anti-inflammatory potentials against CdCl-induced hepatic inflammation and resulted in

downregulations of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and NF-kB), but upregulations of anti-inflammatory cytokines (IL-4 and IL-10), when compared with CdCl-only treated Group 2. Hence, MO11 and MS06, are recommended for further evaluations as potential drug candidates for the treatments of hepatic inflammation.

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CONFLICTS OF INTEREST
Authors declare no conflicts of interest

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