The Pharmaceutical and Chemical Journal, 2018, 5(4):81-96

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Evaluation of Low and High Daily Intakes of Cinnamon against Cadmium-induced Liver and Brain Toxicity in Rats

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Abstract Cinnamon is commonly used as a spice and has also been broadly employed in the treatment and prevention of disease. Cadmium is a heavy metal of considerable toxicity with destructive impact on most organ systems and in some cases it can cause deaths annually. The study was designed to evaluate the impact of low and high intake of cinnamon against cadmium-induced liver and brain toxicity in rats. Adult male albino rats were randomly classified into six groups. Group I control rats received distilled water for 45 days. Group II and III were given daily oral administration of cinnamon aqueous extract as 20 mg/kg (Cin-20) and 120 mg/kg (Cin-120), respectively. Group IV received 2 mg/kg $CdCl_2$, once daily for 45 consecutive days. Group V and VI received $CdCl_2$+Cin-20 and $CdCl_2$+Cin-120, respectively. The evaluation of the effects of both doses of cinnamon was measured using open field test, cerebral neurotransmitters, GABA, and choline esterase. Cerebral and hepatic oxidative biomarkers, myeloproxidase activity, liver functional tests, lysosomal enzymes, as well as histopathological examination of liver, cerebral cortex, and hippocampus were also estimated. The significantly disturbed brain-liver biomarkers by cadmium toxicity were restored to nearly normal values by administration of cin-20. While, cin-120 showed less improvement in some parameters. Also, the histopathological effect of cadmium on brain and liver was also markedly overturned by co-administration of cin-20. Our findings concluded that cinnamon aqueous extracts at the low dose rather than high dose possessed protective activity against cadmium induced hepatic-cerebral toxicity in rats.

Keyword: Cadmiumm, Cinnamon, Neurotoxicity, Neurotransmitters, Cortex and hippocampus, Hepatotoxicity

Introduction

Environmental pollution by cadmium is documented as a worldwide problem [1]. Cadmium is an abundant, nonessential element that occurs either naturally or used in agriculture and industrial applications [2,3]. Beside occupational exposure, it enters the body through food and drinking water as well as through inhalation [4]. Cadmium is classified by the International Agency for Cancer Research as a type I carcinogen [5]. Having a long biological half-life and low rate of excretion from the body, its soluble salts accumulate by time in a variety of tissues causing toxicity [6,7,8]. Being a multitarget toxicant, cadmium causes intracellular ROS accumulation, elevates lipid peroxidation in tissues and disturbs antioxidant defense system by chronic exposure [9]. Noteworthy, cadmium indirectly causes oxidative stress by depleting cellular GSH. It competes with essential metals such as zinc, selenium, cupper and calcium interfering with various cellular processes, enzyme activities, DNA repair

systems, and redox state of the cell [10].The metal also affects cell proliferation, differentiation, apoptosis and other cellular activities [11].

Liver is a major target organ of cadmium toxicity following acute and chronic exposure and cadmium hepatotoxicity is the major cause of its acute lethality [12,13], where apoptosis plays a primary role in cadmium-induced hepatotoxicity [14]. The hepatotoxicity of cadmium has also been attributed to the formation of toxic metabolites as a result of its activation by hepatic cytochrome P 450 to a highly active metabolite [15].

Concerning brain, previous reports indicated a correlation between cadmium exposure and certain alterations in behavior of both humans and animals [16,17]. Cadmium enters the CNS either through the olfactory pathway or by altering the permeability of the blood–brain barrier [18] causing damage to DNA [19], and alteration of calcium homeostasis [20]. By reaching the CNS, cadmium is targeting the cortical and hippocampal neurons causing a disturbance in the higher functions [21,22]. Cadmium causes neurochemical changes on catecholaminergic and serotoninergic, as well as cholinergic transmission [23]. Noteworthy, the brain is highly vulnerable to lipid peroxidation because of its high rate of oxygen utilization, an abundant supply of polyunsaturated fatty acids, a deficient antioxidant defense and a high content of transition metals like copper and iron in several regions [24]. Therefore, deregulation of the homeostasis of transition metals by cadmium contributes to its toxicity [25]. Furthermore, cadmium has an inhibitory action on the antioxidant enzymes and membrane bound ATPases indicating the alterations in membrane and neurotransmitter functions [26,27].

Antioxidants are supposed to antagonize the harmful effects of ROS and adjust the physiological defense system; consequently they are beneficial for lessening oxidative stress related diseases [28]. The antioxidant compounds can counteract the decrease in ATPase activity and the increase in oxidative stress induced by cadmium [29].

Cinnamon (Cinnamomum cassia, Family Lauraceae) bark is commonly used in Asian countries as a spice for most foods. It has a wide range of historical use as a medicine. In eastern and western folk medicine; it is used for treating kidney disorders, abdominal and chest pains. It has strong antioxidant, analgesic, anti-ulcer, hypocholesterolaemic, antimutagenic, as well as, antibacterial activities [30,31,32]**.** Cinnamon also offered anti-diabetic and cognition improving properties [33]. Hepato-protective activity of cinnamon against carbontetrachloride and alcohol induced liver injury was proved [34,35]. Its beneficial health promoting properties is mainly attributed to inducing the antioxidant-defense system through its polyphenolic composition. Cinnamon has an extended diversity of phytochemicals procyanidins, coumarins, flavonoids, catechins, terpenes, volatile essential oils and minerals [15,36].

To our knowledge, no previous data are available on the effect of cinnamon extract on neuronal injury in cerebral cortex and hippocampal brain area caused by cadmium toxicity. Therefore, this study was designed to inspect the efficacy of daily intake of two doses of cinnamon on cerebrum neurotoxicity as well as, hepatotoxicity induced by metal (cadmium) noxiousness.

Materials and Methods

Animals

Adult male albino rats weighing approximately 150-180 g at the beginning of the experiment were used in the present study. They were obtained from the breeding colony maintained at the animal house of the National Organization for Drug Control and Research (NODCAR, Cairo, Egypt). Animals were housed for at least one week prior to testing under standard housing conditions (room temperature 24-27° C) with alternating 12hr light and dark cycles and will allowed free access to food (standard pellet diet), water ad libitum. Animals housing and raring followed standard rules. Animals were treated gently; squeezing, pressure and tough maneuver were avoided. The investigation was complied with the Guide for Care and Use of Laboratory Animals of the National Institutes of Health (NIH publication No. 85–23, revised 1996).

Preparation of Cinnamon Aqueous Extract

For preparation of cinnamon extract, 10 g cinnamon was weighed, dissolved in 100 ml distilled water and boiled for 10 minutes. Then the solution was cleared with filter paper and was ready for administration by gavage tube [37]. The dose of cinnamon was 20 and 120 mg/kg, p.o. according to Mahmoud et al. [38] and Ismail [39], respectively.

Induction of Metal Toxicity

Selection of the dose was based on the published literature of Hejazy and Koohi [40], Cadmium chloride ($CdCl_2$) was used in a dose 2mg/kg; p.o.

Experimental Design

Sixty adult male albino rats weighing approximately 150-180 g at the beginning of the experiment were randomly allocated into six groups. Each group consisted of 10 rats.

The animals were treated for 45 consecutive days according to the following scheme:

Group1: animals received saline and served as normal group.

Group2: animals received cinnamon (20mg/kg; p.o.; daily).

Group3: animals received cinnamon (120mg/kg; p.o.; daily).

Group4: animals received $CdCl_2$ (2mg/kg; p.o.; daily) and served as (+ve) control group.

Group5: animals received cinnamon (20mg/kg; p.o.; daily) after 1hr from $CdCl_2$ (2mg/kg; p.o.; daily).

Group6: animals received cinnamon (120mg/kg; p.o.; daily) after 1hr from $CdCl_2$ (2mg/kg; p.o.; daily).

Open field test was performed in the last day of the experiment. On the day (46^{th}) after completion of the experiments, animals were sacrificed by decapitation then blood was collected and sera were separated for the estimation of the liver and kidney function tests by colorimetric assay kits.

Tissue Sampling

Liver and brain of each rat were immediately excised, and divided into two portions, one was kept in 10% formalin for histopathological examination, while the other was reserved for estimating the other biochemical parameters. As the liver and the cerebrum (cerebral cortex and hippocampus) were dissected, each of them was weighed and bisected. The first half of either liver or cerebrum was homogenized in ice cold PBS to prepare 10% homogenate that was used for the assessment of oxidative stress biomarkers, myeloperoxidase activity (MPO), as inflammatory marker, as well as, ɤ-aminobutyric acid (GABA) and cholinesterase (ChE) cerebral contents. The other half of liver was used to determine the liver lysosomal enzymes, while that of cerebrum was homogenized in ice cold solution of acidified n-butanol to obtain 10% homogenate for the determination of brain contents of serotonin (5-HT) and dopamine (DA). Finally, the used animals will be frozen till being incinerated.

Open Field Behavioral Test

It is a general test for motor activity, excitability, emotionality and exploratory behavior in rodents [41]. It consists of a square wooden box 80 cm x 80 cm × 40cm height, with red sides and white floor divided by black lines into 16 equal squares 4 × 4 [42]. Latency time was measured in seconds, while ambulation frequency, expressed by number of squares crossed by the animal was counted during 3 min. Numbers the animal stood stretched on its hind limbs with and without forelimbs support during 3 min was identified as rearing frequency [43].

Determination of Liver and Kidney Functions in Serum

Estimation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were done according to Burtis et al. [44] using Diamond Diagnostics kits (Egypt, Cairo).

Stanbio Laboratory kits (Boerne, TX, USA) were used for the determination of the serum albumin, bilirubin and the total protein levels. The estimation of blood urea nitrogen and creatinine was carried out according to the method of Wybenga et al. [45], Henry et al. [46], respectively using Bio-diagnostic kits (Egypt, Giza). All procedures were performed according to the manufacturers' instructions.

Determination of Liver Lysosomal Enzymes Activities

The activity of liver lysosomal acid hydrolases, acid phosphatase, β-galactosidase, and N-acetyl-β-glucosaminidase were measured according to the method described by Van Hoof and Hers [47].

Determination of Liver and Cerebral Inflammatory and Oxidative Stress Parameters

Determination of myeloperoxidase (MPO) activity was done using a kinetic colorimetric method described by Bradley et al. [48]. Malondialdehyde (MDA) was determined according to the method of Buege and Aust [49] and expressed as nmol/g wet tissue. Determination of reduced glutathione (GSH) was done according to the method described by Beutler et al. [50] and expressed as mg/g wet tissue.

Determination of Cerebral Dopamine (DA) and Serotonin (5-HT) Contents

For the determination of neurotransmitters, a 10% (w/v) homogenate was prepared in acidified n-butanol. Each homogenate was centrifuged at 2000 rpm (4 °C) for 5 min. The resultant supernatant was used for monoamines determination; namely dopamine (DA) and serotonin (5-HT) according to Ciarlone [51] and they were expressed as µg/g wet tissue.

Determination of Cerebral ɤ-aminobutyric Acid (GABA) content

Determination of cerebral GABA content in brain was carried out according to the method described by Sutton and Simmonds [52].

Determination of Cerebral Cholinesterase (ChE) content

Cholinesterase (ChE) in cerebrum was determined according to the method of Ellman et al. [53] using DTNB-phosphate reagent after 10 min incubation of the brain homogenate with acetyl thiocholine iodide.

Histopathological Examination

Liver and brain tissues from every rat were fixed with 10% formalin for 24h and embedded in paraffin. Then, they were cut into 5µm-thick sequential sections with a microtome, stained with hematoxylin and eosin (H&E) and liver were also examined with Masson's Trichrome stain.

Statistical Analysis

Results were expressed as mean ± SEM. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey–Kramer Multiple Comparison Test. Probability values of less than 0.05 were considered statistically significant. Whereas the graphs were drawn using a prism computer program (GraphPad software Inc. V5, San Diego, CA).

Results

Effect of Treatments on Open Field Behavioral Test

In open field test, latency time was elevated, while ambulation and rearing frequencies were significantly reduced by cadmium administration compared to normal group (Figure 1-A, B, and C). On administration of either cin-20 or cin-120 in cadmium treated rats, ambulation frequency was elevated but did not reach normal values. Meanwhile, latency was normalized by treatment with low dose of cinnamon rather than high dose in cadmium received rats. Still, rearing frequency was not affected by cin-20, cin-120 intake in cadmium- intoxicated rats. Noteworthy, cin-120 treatment in normal rats caused significant rise in ambulation and rearing frequencies.

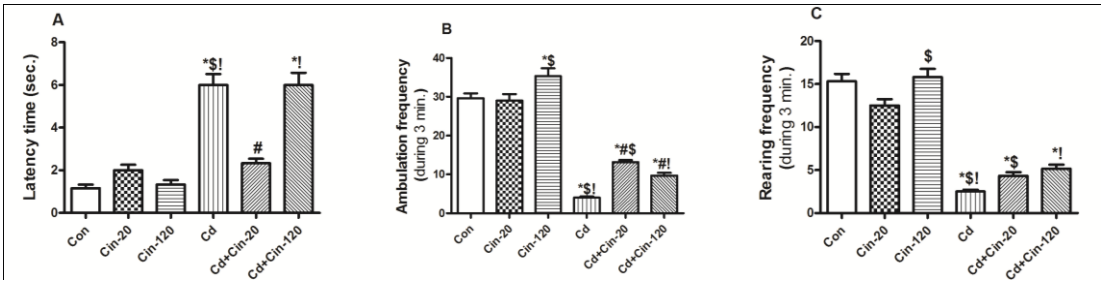

Figure 1: Effects of low and high dose of cinnamon on latency [A], ambulation frequency [B], and rearing frequency [C] of open field behavioral test in Cd induced liver-brain injury in rats

Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

*Data represents mean (n = 8-10) ±S.E.M. *$!# P<0.05 compared to the Con, Cin-20, Cin-120, and Cd-treated rats, respectively. Statistical analysis was carried out by one way ANOVA followed by Tukey- Kramer Multiple Comparison Test.*

Effect of Treatments on Liver Functions and Kidney Functions in Serum

In serum, cinnamon administration in high dose elevated ALT and AST levels. Serum ALT was also raised by cin-20 and cadmium intake in normal rats. Conversely, cinnamon low dose co-administration with cadmium

significantly renormalized serum ALT. Although, high dose of cinnamon reduced serum ALT in cadmium treated rats, serum AST was still elevated (Table 1).

Table 1: Effect of low and high dose of cinnamon on liver and kidney functions in Cd induced liver-brain injury in rats

	Serum ALT (U/L)	Serum AST (U/L)	Total Protein (g/dl)	Serum Albumin (g/dl)	Serum creatinine (mg/dl)	Blood urea nitrogen (mg/dl)
Con	13.98±1.16	17.00±0.52	6.15±0.47	4.17±0.04	1.78±0.01	16.37±0.60
Cin-20	26.23±0.88*	12.83±0.87	5.98±0.21	2.72±0.11*	1.87±0.01	28.30±0.18*
Cin-120	28.80±0.49*	40±2.56*$	5.25±0.14	2.24±0.12*$	1.96±0.01*	20.17±0.40$
Cd	33.14±2..29*$	21.83±0.54$!	4.55±0.16*$	2.90±0.04*!	2.07±0.02*$!	27.80±0.77*!
Cd+Cin-20	15.81±1.42#$	22.83±1.38$	5.40±0.16	3.10±0.15*!	1.84±0.04#	30.65±1.70*
Cd+Cin-120	25.86±1.20*#	35.33±1.61*#	5.80±0.26#	2.49±0.12*	2.07±0.03*!	46.28±2.77*#!

Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

*Data represents mean (n = 8-10) ±S.E.M. *$!# P<0.05 compared to the Con, Cin-20, Cin-120, and Cd-treated rats, respectively. Statistical analysis was carried out by one way ANOVA followed by Tukey- Kramer Multiple Comparison Test.*

Intake of cin-20 elevated blood urea nitrogen, while intake of cin-120 elevated serum creatinine of normal rats. Noteworthy, normal groups received cinnamon in either dose showed marked decrease in serum albumin compared to control group. Moreover, cadmium intoxicated rats displayed significant increase in urea, creatinine versus reduction in albumin and total protein compared to their respective control values. Concomitant administration of cinnamon in low dose with cadmium restored serum creatinine with no effect on the remaining parameters. The combined intake of high dose of cinnamon with cadmium elevated blood urea nitrogen upper than the normal levels and restored total protein with no effect on either albumin or creatinine (Table 1).

Effect of Treatments on Lysosomal Enzymes in Liver

Administration of cin-120, cadmium, concurrent cadmium and cinnamon in both doses revealed significant reduction in acid phosphatase, B-galactosidase, N-acetyl-glucosaminidaselysosomal enzymes compared to control. Further reduction in N-acetyl-glucosaminidase was shown by cin-120 compared to cadmium treated rats (Table 2).

Table 2: Effect of of low and high dose of cinnamon on liver lyzosomal enzymes in Cd induced liver-brain injury in rats

	Acid phosphatise (nmol/g)	β-Galactosidas (nmol/g)	N-acetyl-glucosaminidas (nmol/g)
Con	4727±137.0	1836±74.62	1622±34.13
Cin-20	4382±67.0	1810±102.4	1576±15.10
Cin-120	3383±201.6*$	1368±80.25*$	1389±23.75*$
Cd	3108±117.6*$	1057±8.98*$!	1222±7.92*$!
Cd+ Cin-20	3259±128.3*$	1253±77.77*$	1356±61.64*$
Cd+ Cin-120	3030±22.83*	1022±9.09*!	963±31.13*#!

Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

*Data represents mean (n = 8-10) ±S.E.M. *$!# P<0.05 compared to the Con, Cin-20, Cin-120, and Cd-treated rats, respectively. Statistical analysis was carried out by one way ANOVA followed by Tukey- Kramer Multiple Comparison Test.*

Effect of Treatments on Neurotransmitters, DA, 5-HT, GABA, ChE in Cerebrum

Cerebral monoamines contents, DA and 5-HT were significantly decreased by 39 and 35% in cadmium treated rats compared to normal rats.The level of DA in cerebrum of rats under the toxicity of cadmium was restored bycinnamon administration in each dose. Moreover, cerebral 5-HT was renormalized by high dose of cinnamon,

however, low dose of cinnamon did not affect the cerebral level of 5-HT of cadmium toxicant rats. Worth mentioning that normal rats received cin-120 displayed lower cerebral DA content in respect to control rats (Figure 2-A and B).

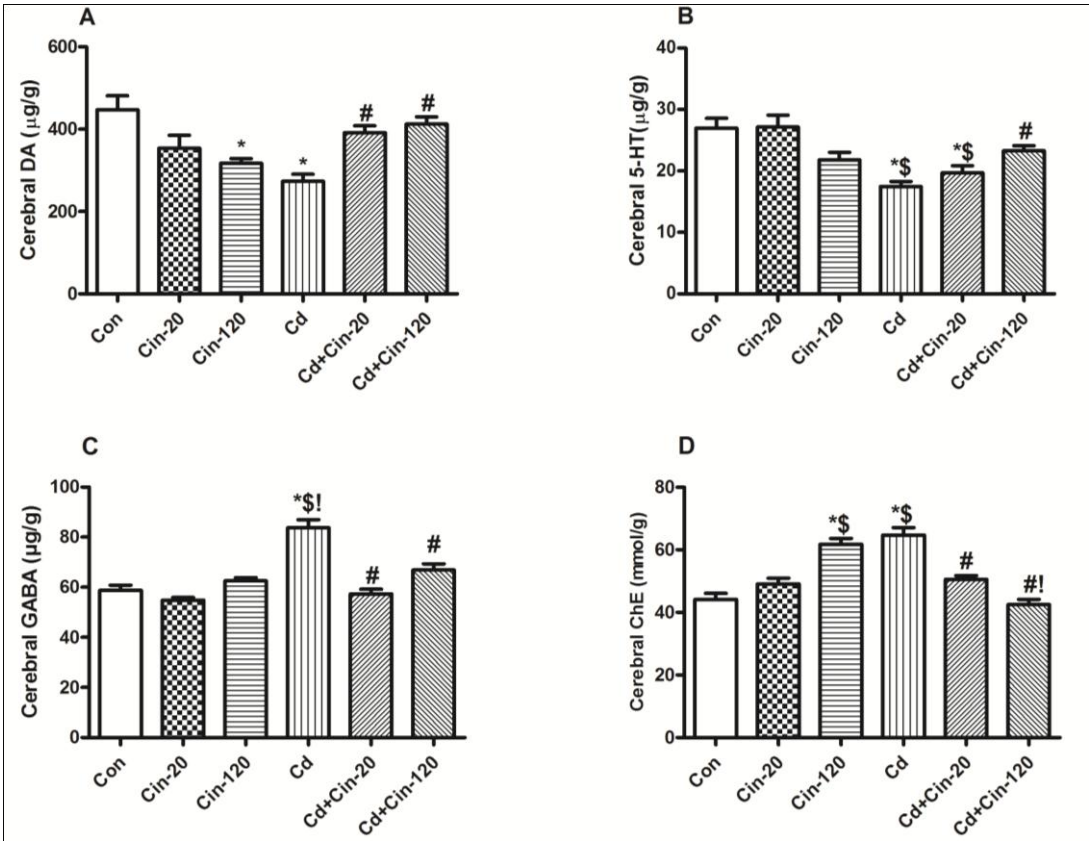

Figure 2: Effects of low and high dose of cinnamon on cerebrum Dopamine (DA) [A] , Serotonin (5-HT) [B], ɤ-Amino butyric acid (GABA) [C], cholinesterase (ChE) [D] contents in Cd induced liver-brain injury in rats.

Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

*Data represents mean (n = 8-10) ±S.E.M. *$!# P<0.05 compared to the Con, Cin-20, Cin-120, and Cd-treated rats, respectively. Statistical analysis was carried out by one way ANOVA followed by Tukey- Kramer Multiple Comparison Test.*

Cadmium administration elevated cerebral GABA content by 43% in respect to control. Co-administration of either Cin-20 or Cin-120 with cadmium restored its content to nearly normal value (Figure 2-C).

Normal ChE content in cerebrum was 44.2±1.87 (mmol/g). Administration of either cin-120 or cadmium raised the enzyme activity by 40 and 46% compared to normal rats. Administration of either dose of cinnamon in cadmium-treated rats normalized the cerebral enzyme content (Figure 2-D).

Effect of Treatments on Inflammatory and Oxidative Stress Parameters in Liver

Hepatic MPO as well as MDA was elevated in case of treatment with high dose of cinnamon, cadmium, and their combination compared to normal rats. Conversely, low dose of cinnamon restored MPO and MDA hepatic concentration in cadmium exposed rats (Figure 3-A and B).

Additionally, GSH concentration in liver was decreased in cadmium treated rats, while co-treatment of cin-120 in cadmium treated rats caused significant elevation in GSH above normal (Figure 3-C).

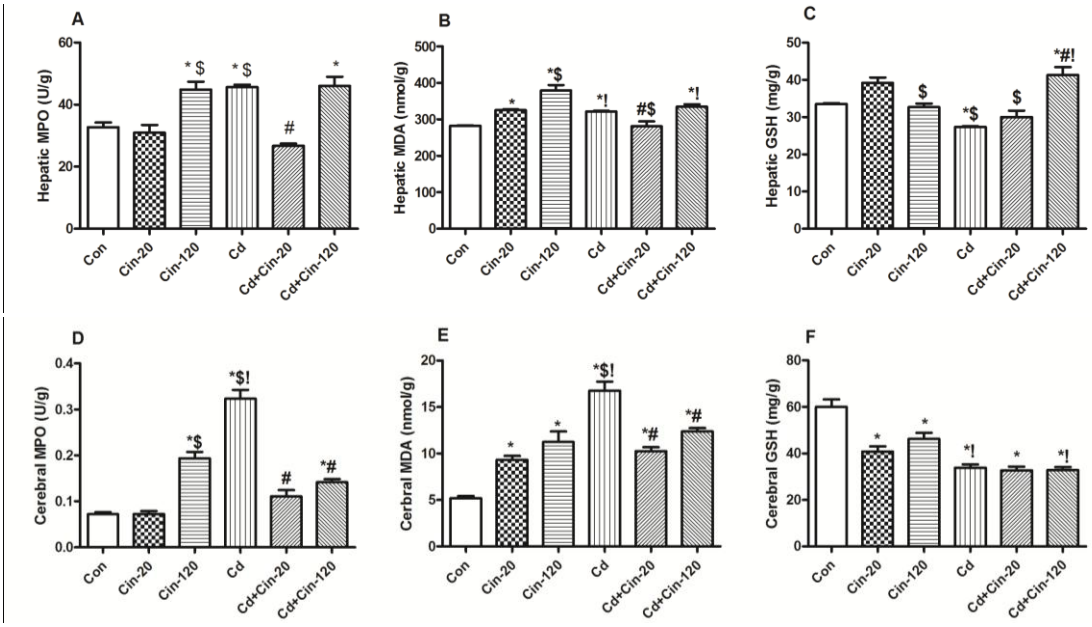

Figure 3: Effects of low and high dose of cinnamon on hepatic and cerebrum myeloperoxidase activity (MPO) [A, D], lipid peroxidation (LPO) [B, E], and reduced glutathione (GSH) [C, F] in Cd induced liver-brain injury in rats. Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

*Data represents mean (n = 8-10) ±S.E.M. *$!# P<0.05 compared to the Con, Cin-20, Cin-120, and Cd-treated rats, respectively. Statistical analysis was carried out by one way ANOVA followed by Tukey- Kramer Multiple Comparison Test.*

Effect of Treatments on Inflammatory and Oxidative Stress Parameters in Cerebrum

Low and high intake of cinnamon in normal rats showed elevation in cerebral MDA in opposition to reduction in cerebral GSH. In addition, elevated content of cerebral MPO by the intake of cin-120 was observed. Cadmium administration enhanced cerebral concentration of MPO and MDA to 2 and 3.5 folds, respectively. Conversely, low and high dose of cinnamon intake in cadmium-received rats caused significant reduction in MPO and MDA. Furthermore, MPO touched normal level by cin-20 co-administration in cadmium treated rats (Figure 3-D and E).

On the other hand, cerebral concentration of GSH was reduced to almost half its value by cadmium exposure, and the administration of cin-20 or cin-120 either alone or in combination did not augment GSH cerebral concentration (Figure 3-F).

Effect of Treatments on Histopathological Study in Liver, Cerebral Cortex, and Hippocampus

By using H & E stain, figure (4) illustrated that rats in either control or cin-20 group revealed normal histopathological appearance, while sections of liver treated with cin-120 showed focal hepatic necrosis associated with inflammatory cells infiltration. The liver histopathological examination of animals treated with cadmium showed hyperplasia of biliary epithelium and appearance of newly formed bile ductuoles with fibroplasia in the portal triad along with focal hepatic necrosis associated with inflammatory cells infiltration. Co administration of either cin-20 or 120 with cadmium showed almost normal morphology except for slight congestion of hepatic sinusoids and fibroplasia in the portal triad, respectively (Figure 4).

Concerning brain, normal and cin-20 treated rats showed normal histopathological appearance, while cin-120 received rats exhibited necrosis of some sporadic hippocampal neurons although cerebral cortex appeared normal. Cadmium treatment resulted in necrosis, pyknosis and atrophy of cerebral cortex, as well as hippocampal neurons accompanied by neuronophagia. The neuron architecture was amended to some extent by the intake of cin-20 orcin-120 in cadmium toxicant rats (Figure 4).

By using Massosn's trichrome stain, figure (5) illustrated that normal and cin-20 treated rats showed normal appearance of hepatic cells, while cin-120 treated rats exhibited weak positive histochemical reaction for collagen fibers. An apparent increase in the collagen fibers in between hepatocytes were detected in cadmium received group as compared to that of the control group, whereas cin-20 and cin-120 displayed weak fibrosis, as compared to cadmium group.

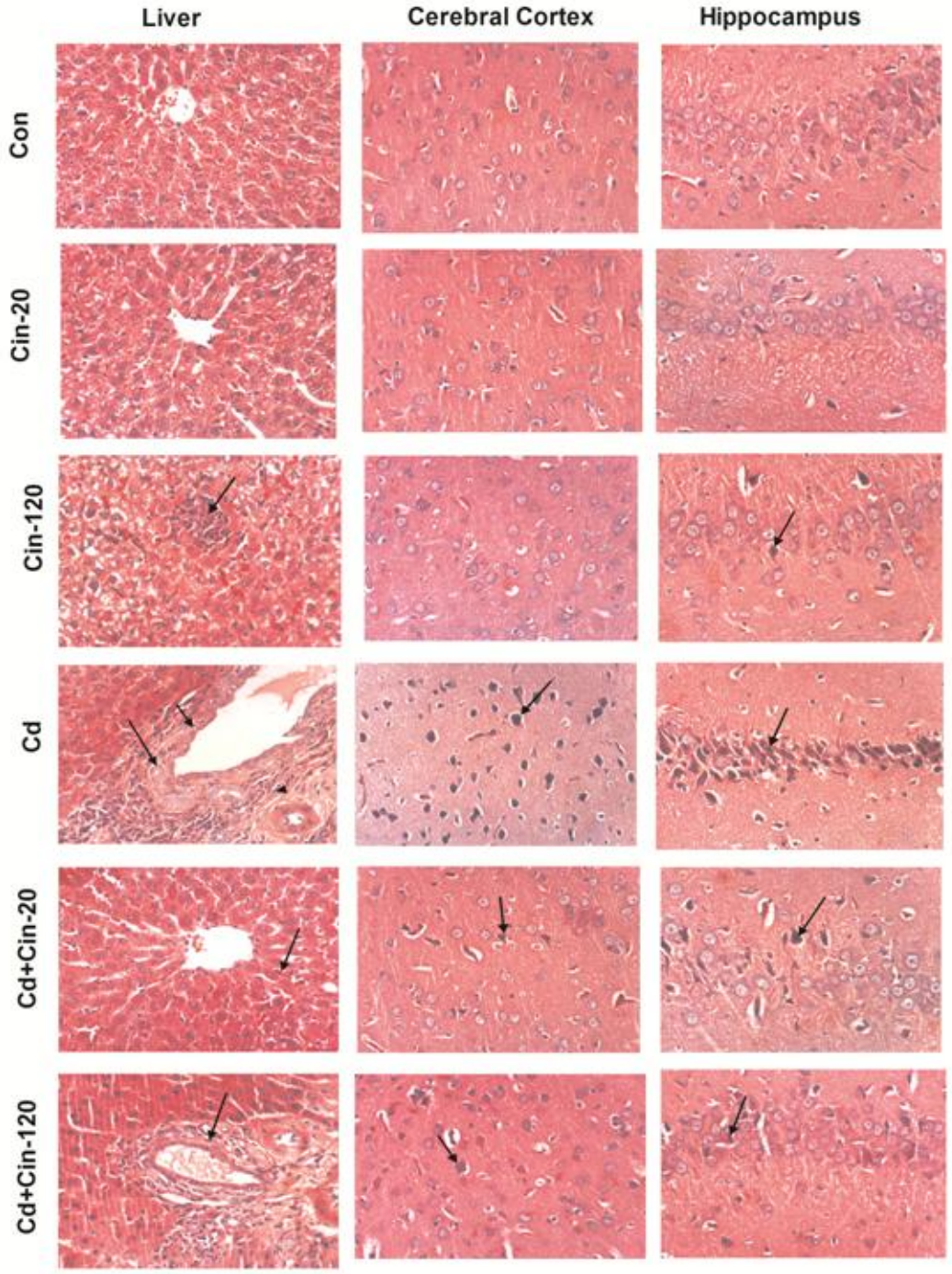

Figure 4: Photomicrographs of rat liver, cerebral cortex and hippocampus sections stained with H & E (X400). Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

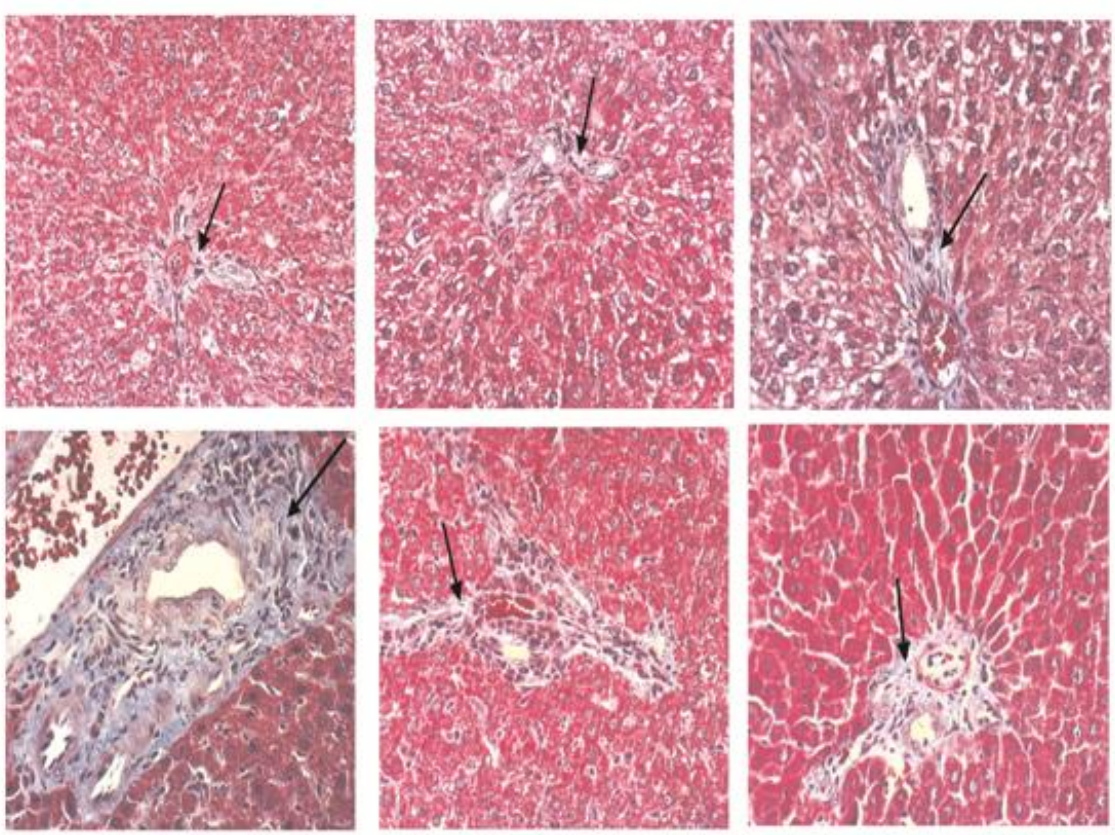

Figure 5: Photomicrographs of rat liver stained with Masson's Trichome (X400). Cadmium was given at a dose 2 mg/kg, p.o., 45 days, while cinnamon was given in two different doses (20 mg/kg, p.o., 45 days), (120 mg/kg, p.o., 45 days).

Discussion

Cadmium is a ubiquitous strong cell toxin, its toxicity occurs mainly by ingestion and inhalation and liver is the main site of its metabolism as well as accumulation. Brain is another organ also affected by cadmium exposure, where severe neurological damages take place as a result of its toxicity. The current study evaluates the hepato- and neuro-modulatory influence of low and high intake of cinnamon aqueous extract against liver and cerebrum injury in cadmium-toxicant rats.

Regarding to metal-induced hepatotoxicity observed in the current study, cadmium received group exhibited marked increase in serum ALT in respect to normal rats. Similarly, El-Maraghy et al. [54]; Renugadevi and Prabu [55]; Mladenović et al. [56], and Adefegha et al. [57] pointed to liver enzymes rise as a result of their release into circulation after hepatic cell damage by cadmium. On the contrary, liver lysosomal enzymes, acid phosphatase, B-galactosidase, and N-acetyl glucosaminides were reduced in cadmium- treated group. de Santiago-Martín et al. [58]; Simone et al. [59] referred to the inactivation of enzymes as a result of metal contamination. The lysosomal injury hypothesis proposes that excessive accumulation of metals within lysosomes can lead to lysosomal fragility, impaired lysosomal function, and eventual cellular injury [60].

In the current study, serum creatinine and urea were elevated as a result of cadmium administration. These alterations reflect renal toxicity and impaired glomerular function, as kidney is a further organ that retains cadmium at a high level. Researchers mentioned a specific metal binding protein that deliver cadmium efficiently to the epithelial cells of the proximal tubule called Metallothionein, where after degradation, high levels of free cadmium release locally and cause tubular injury [2,13,61]. Other molecules such as albumin, cysteine, and sulfhydryl (SH)-rich proteins, can also form associations with cadmium, subsequently hepato-renal toxicity of cadmium could be

also produced by direct effects of free cadmium initiating oxidative stress in organs as a result of binding to SH group [13,62]. The ability of liver to synthesize proteins was depressed by cadmium as mentioned by Cupertino et al. [63], therefore, the observed reduction in albumin and total protein in our study upon cadmium exposure mirrors a disturbance in hepatic function.

Our result revealed that the elevated serum ALT induced by cadmium were near normal levels or only slightly elevated by oral administration of low and high dose of cinnamon extract, indicating protection against liver damage. Total protein was reversed upon treatment with cin-120, reflecting its hepato- protective activity. Stimulation of protein synthesis has been advanced as an influential mechanism which accelerates the regeneration and production of liver cells [64]. Creatinine was reduced upon treatment with cin-20. In accordance, cinnamaldehyde administration restored kidney function and suppressed renal oxidative stress in the study of sharma et al. [65].

In the current study, cadmium induced oxidative stress displayed by increased hepatic and cerebral MPO, MDA, as well as glutathione depletion. The results are in accordance with [14,54,66,67]. Stohs and Bagachi [6] suggested that cadmium induce phagocytic cells for production of ROS which is involved in the initiation of lipid peroxidation (LPO) and oxidative stress in different tissues. Another suggestion was cadmium displacement of iron from its binding sites leading to acceleration of free radicals production [68]. Additionally, the content of GSH was greatly diminished in the liver and cerebral tissues of the cadmium-treated group compared with control group. As mentioned above, cadmium has a strong affinity for the SH group of cysteine moiety of glutathione, therefore, decreased GSH level is due to its consumption in cadmium reclamation and its utilization in the protective action against free radical-induced LPO [67,69,70]. Moreover, SH is exhausted in heavy metals detoxification, consequently, SH level reduction changes the activities of antioxidant enzymes and lead to peroxidation of polyunsaturated fatty acids initiating a prooxidant state in the biological system [6,71,72,73].

Besides, histopathological examination revealed marked changes in the structure of the studied tissues in cadmium-administered animals. In liver, the histological area occupied by collagen fibers in group exposed to cadmium was higher compared with the control, also showed in the study of Cupertino et al. [63]. Svegtiati Baroni et al. [74] referred to a common link between chronic liver damage and hepatic fibrosis. Changes in H & E stain demonstrated by congestion of central vein and sinusoids, focal hepatic necrosis, inflammatory cells infiltration, hyperplasia of biliary epithelium with fibroplasia in the portal triad were in line with other reports [1,75]. Liver injury from acute cadmium revelation is expected to originate from the activation of Kupffer cells and a cascade of events including cytokines, nitric oxide and ROS [76].

On the contrary, the use of cinnamon provided protection against the oxidative disorder by lowering the MPO and MDA levels in liver and cerebrum. The present protective capacity against MPO and LPO in both organs mostly by the low dose of cinnamon is attributed to its phytoconstituents, flavonoids, triterpenoids, saponins, and alkaloids [35]. Hepatoprotection from oxidative stress by cinnamon was also investigated by [32,77,78,79]. Hepatoprotective activity of cinnamon aqueous extract against the toxic effect of cadmium is also revealed in the histological studies. Cinnamon reduced the toxin-induced inflammatory cells infiltration and maintained an almost normal architecture. The current preservation of hepatic cells structure by cinnamon was according to Moselhy and Ali [78]. In a previous study, few collagen fibers were observed by cinnamon in high fructose diet model comparable to that of control group [80].

Concerning brain, oxidative stress induced by cadmium exposure was accompanied by histological damage in the examined tissue (cerebral cortex and hippocampus). Histological examination of each region revealed a change in internal morphology; increased nuclear pyknosis, necrosis, and atrophy of neurons in the cadmium-treated group. Barroso-Moguel et al. [81] explained that cell damage via the necrotic pathway is associated with the shrinkage and condensation of nuclear chromatin, leading to nuclear pyknosis. Brain histopathological examination was in accordance to [82,83,84]. However, there has been no prior report on the neuroprotective effects of cinnamon in the cadmium toxicity. Herein, cinnamon possesses neuroprotective effects interfering cerebral oxidative stress and histopathological alterations involved by cadmium. The observed improvement in cortical and hippocampal

neuronal cells in cinnamon- administered rats may be due to free radical scavenging activities of its polyphenolic derivatives and the capacity of cinnamon flavonoids to enter the brain upon crossing the blood brain barrier [36].

In our study, the content of the inhibitory amino acid GABA in cerebrum was shown to be elevated in cadmium-treated rats. GABA release is boosted due to inhibition of the voltage-dependent calcium channels with cadmium [85] and as a result, the degree and balance of excitation–inhibition in synaptic neurotransmission was altered by the metal toxicity [86]. Meanwhile, we observed reduction in cerebral monoamines levels by cadmium administration, in consistent with [23,87]. The impairment in the catecholaminergic and serotoninergic transmission by cadmium administration is mediated by alterations in the intracellular calcium metabolism and impairment in calcium function as a second messenger in the CNS [88]. The calcium overload, mediated by cadmium, also inhibits the calcium ATPase activity in cell membrane and eventually potentiates irreversible cell destruction [89]. The activities of these ATPase enzymes are affected by the exposure of cadmium leading to the alterations in membrane and neurotransmitter functions [23,90,91]**.** Another suggested mechanism is MAO activity increase by cadmium exposure, an indicator of impaired neuronal functions leading to brain damage [57]. Disorders in behavior of both humans and animals were previously reported by chronic exposure to low doses of cadmium [16,17]. Herein, both the ambulation and rearing frequencies were decreased in cadmium- received rats, while the latency was increased indicating lesser exploratory and locomotor activity. In cerebrum, ChE content was elevated by cadmium treatment reflecting cholinergic hypo-activity due to low level of acetyl choline. Administration of cinnamon extract in cadmium-treated rats improved both latency and ambulation frequencies in open field test, thus locomotor activity was enhanced. Effect of cinnamon in low and high doses was extended to normalize GABA as well as DA content in cerebrum. Furthermore, both doses restored cerebral ChE activity. Likewise, cognition perfection by cinnamon extract through anticholinergic activity was discussed in Alzheimer's disease animal model and scopolamine-treated rats [92,93]. Ngoc et al. [94] also reported that a methanol extract of cinnamon exhibited a strong tyrosinase-inhibitory activity. Tyrosinase inhibitors offer a possible treatment for Parkinson's disease [95]. Hence, lending a plausible explanation to the current normalization of DA and consequently, the observed improvement in locomotor activity in cinnamon treated rats.

In conclusion, our data indicate that cinnamon extract in low dose possess neuro and hepato-protective effect against cadmium-mediated toxicity in brain and liver via inhibiting MPO, LPO and subsequently restoring the ChE, DA, GABA along with better locomotor activity, as well as histological appearance. Therefore, populations of high risk to cadmium should be advised to use frequent low dose of cinnamon to reduce risk factors associated with its toxicity.

Acknowledgements

The authors would like to thank Professor Kawkab A. Ahmed, Pathology Department, Faculty of Veterinary Medicine, Cairo University (Giza, Egypt) for her assistance in the histopathological examination.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest

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