Int J Clin Exp Med 2016;9(8):15764-15771
www.ijcem.com /ISSN:1940-5901/IJCEM0007321

*Original Article*

# L-2-Oxothiazolidine-4-carboxylic acid mitigates the thromboembolic effects and systemic toxicity induced by sub-acute exposure to cadmium in mice

Mohamed Abdelmonem Fahim[1], Abderrahim Nemmar[2], Sarabjit Singh[2], Mohamed Shafiullah[3], Javed Yasin[4], Mohamed Yousif Hasan[3]

*[1]Educational Neuroscience Research Centre, Emirates College for Advanced Education, Abu Dhabi PO Box 126662, United Arab Emirates; [2]Department of Physiology, [3]Pharmacology, [4]Internal Medicine, Faculty of Medicine, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates*

Received February 25, 2015; Accepted July 9, 2016; Epub August 15, 2016; Published August 30, 2016

**Abstract:** Exposure to cadmium (Cd) as a result of its environmental pervasiveness poses deleterious health effects, which has been attributed to oxidative stress. Therefore, this study aims to examine the sub-acute (1 mg Cd/kg/day, i.p., for 3 weeks) systemic and thrombotic influence of Cd exposure in vivo, and to assess the protective effects of the antioxidant L-2-Oxothiazolidine-4-Carboxylic acid (OTC, 80 mg/kg/day, i.p.). Cd compared with control group significantly reduced both the time for the first platelet aggregate and until blood flow stopped in pial microvessels. OTC significantly increased both the time for the first aggregate and until flow stopped. Cd induced a significant increase in total WBC, CK, AST, and LDH. The antioxidants SOD and catalase activities significantly increased in mice treated with Cd. OTC, through its antioxidant actions, appeared to effectively protect Cd induced thrombosis in mice. Hence, OTC represents a potential protective candidate from the detrimental effect of Cd toxicity.

**Keywords:** Cadmium, thrombosis, liver, kidney, OTC, toxicology

## Introduction

With the expansion of the industrial revolution, humans can be inadvertently exposed to cadmium (Cd), which is a ubiquitous heavy metal widely used in many industries. As a result of its emissions to the air, water and soil, Cd is often present in individuals, particularly in urban areas. Cd is one of the key components abundantly present in nickel cadmium (Ni-Cd) battery wastes. Other sources of Cd exposure however, include cigarette smoke, ingestion of polluted vegetables, and ambient air in urban-industrialized areas [1-5]. Chronic exposure to Cd through the aforementioned contaminated sources have increased and become a universal concern. Once it has been absorbed by the human body, the biological half-life of cadmium is beyond 10 years [6]. It has been reported that Cd exposure in the population is associated with inducing toxicity in lungs, skeletal muscles by causing edematous emphysema, osteoporosis and osteomalacia, diabetes, cancer, blood pressure, reproduction, brain edema and hemorrhage and blood-brain barrier disruption [7-9].

As a consequence of environmental and industrial pollution, on inhalation or ingestion, Cd has been found to pose a potential threat and affects many systems in human and animals. Carcinogenic damage was observed in the lungs in Cd exposed workers [5].

Cd may also contribute towards endothelial damage either directly by interacting with the endothelium or by inducing the generation of reactive oxygen species in endothelial and inflammatory cells [5]. Cd can inhibit protein synthesis completely to facilitate apoptotic cell death [10-12]. Moreover, Cd induces cell death *in vivo* and *in vitro* at varied concentrations from 1 to 300 μM [13]. Cd has been described as a pro-necrotic metal ion [14, 15].

Cd is known to increase oxidative stress by being a catalyst in the formation of reactive oxygen species, increasing lipid peroxidation, and depleting glutathione and protein-bound sulfhydryl groups [16]. Cd has a high affinity for sulfhydryl (-SH) groups, inactivating numerous enzymatic reactions, amino acids, and sulfur-containing antioxidants including N-acetylcysteine, alpha-lipoic acid and glutathione with subsequent decreased oxidant defense and increased oxidative stress [17]. Long-term exposure to Cd increases lipid peroxidation and causes inhibition of SOD activity indicating oxidative damage in the liver, kidney and testes [9, 17]. Studies on Cd induced intoxication which caused severe platelet aggregation (PA) and thrombosis in testes and epididymis [18] have been demonstrated. The tendency to increase the leukocyte adhesion in male subjects has also been reported [19]. We have recently demonstrated that acute (1 h) exposure to Cd cause systemic and thromboembolic events in mice [20]. However, the sub-acute effects of Cd on cerebral microvessels thrombosis and systemic toxicity, and the effect of cysteine pro-drug L-2-Oxothiazolidine-4-Carboxylic acid (OTC) thereon has not been reported so far.

Consequently, the aim of the present study is to investigate the effect of Cd on cerebral microvessels thrombosis, systemic inflammation and oxidative stress, and its effect on liver. Also, to evaluate the ability of antioxidants OTC to ameliorate the detrimental effect of Cd toxicity.

## Methods

### *Animals and treatment*

This project was reviewed and approved by the Institutional Review Board of the United Arab Emirates University, College of Medicine and Health Sciences, and experiments were performed in accordance with protocols approved by the Institutional Animal Care and Research Advisory Committee. Adult male mice, of TO strain, were selected. The mice weighed 30-35 g. Each group consisted of six to ten animals from a colony maintained at our animal house facility. Animals were group-housed in a temperature maintained (22±2°C) and a light/dark cycle (12/12 h) environment. They had access to standard pelleted diet and water ad libidum. Except for their intended treatment all animals were handled in the same manner. All animal treatment procedures met both the NIH and Institutional Animal Ethics Committee guidelines.

Cd, in the form of cadmium chloride hemipentahydrate (Sigma Chemicals) was dissolved in normal saline. Daily dose of 1 mg/kg body weight injection was administered intraperitoneally (ip), for 3 weeks. OTC pretreatment (80 mg/kg/day, i.p.) or saline was started one hour before Cd administration. Control mice received normal saline only.

### *Experimental cerebral thrombosis model*

*In vivo* cerebral microvessel thrombogenesis was assessed as previously described [20, 21]. Mice were anaesthetized with urethane (25%, 0.1 ml/10 g b.w., ip) and the trachea was intubated. Cerebral microvessels were exposed after performing craniotomy on the anaesthetized mice on the left side of the head, with the aid of a microdrill and the dura was carefully removed. Average body temperature fell to 33.2±0.6°C after anesthesia and surgery. The body temperature was stabilized at 37°C with the help of an infra-red lamp and monitored with a rectal thermoprobe (Physitemp Model RET-3). The preparation was kept moist with artificial cerebrospinal fluid (ACSF). Composition of the ACSF used was (mM): NaCl 124, KCl 5, $NaH_2PO_4$ 3, CaCl 2.5, $MgSO_4$, 2.4, $NaHCO_3$ 23, and glucose 10; pH 7.3. Only untraumatized preparations were used. Those mice showing trauma to either microvessels or underlying brain tissue (10%) were discarded. The closed circuit set up used consisted of: an fluorescent microscope (Olympus, BH-2), a color video camera (JVC, TK-890E), a VHS-VCR (JVC, BR-S600E) and a television monitor (JVC, TM-1500PS). All microscopic observations utilized a fiber-optic light source and were made using a 4× objective lens and a 10× eye piece. Total magnification of the observed field, from the microscope stage to the television monitor was ×250. Sodium fluorescein (2%, 0.1 ml/10 g, iv.) was injected *via* the tail vein. Sodium fluorescein was allowed to circulate in the body for 30 seconds before high intensity mercury light was switched on. The combination of light and fluorescent dye produced a free radical which injured the endothelium of the microvessel's

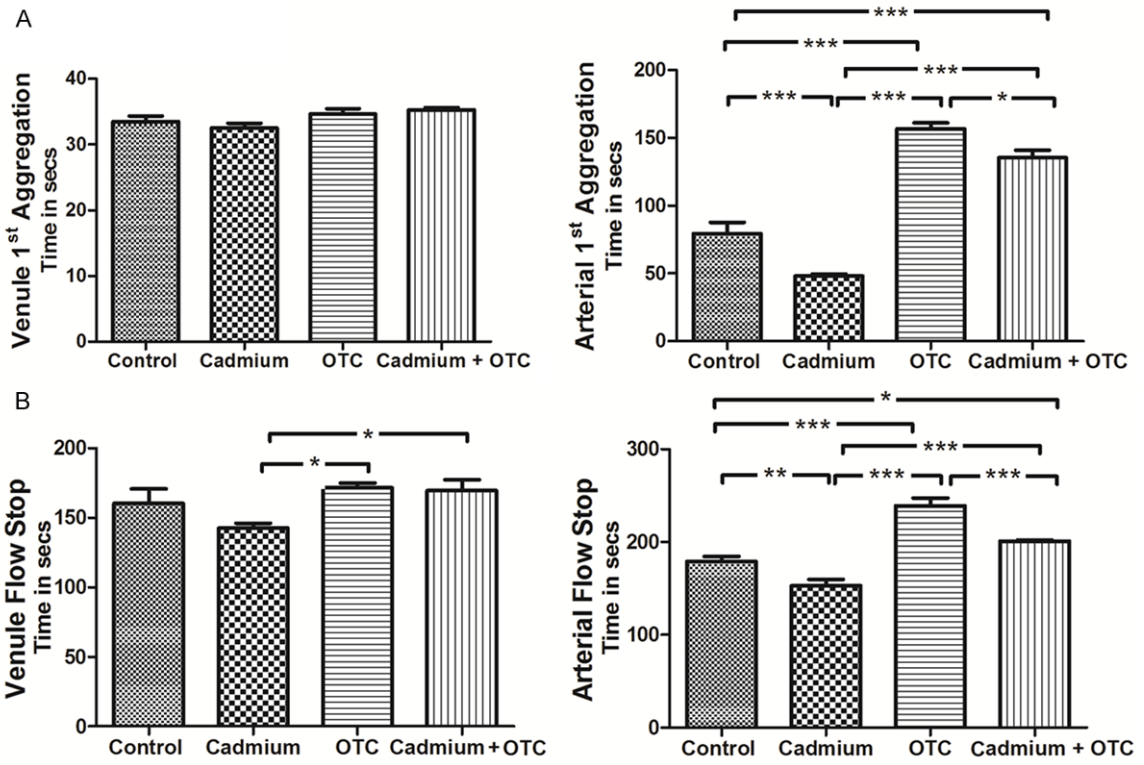


**Figure 1.** Effect of control, cadmium (Cd), L-2-Oxothiazolidine-4-Carboxylic acid (OTC) and concurrent Cd with OTC exposure on cerebro vascular thrombosis in which the start of the aggregation in the venule and arteriole (A) and the complete flow stop after adequate aggregation in venule and arteriole (B) in saline treated control, Cd, OTC and concurrent Cd with OTC treated animals. Data in bar graph shown are mean ± SEM, number of samples (n=10); ***P<0.001, **P<0.01, *P<0.05.

lumen. This in turn, caused platelets to adhere at the sites of endothelial damage and then aggregate. The aggregated fluoresced and were readily visible as they adhered to the damaged endothelium. Platelet aggregates grow in size until complete vascular occlusion. All events were videotaped for analysis. The time when the first observable aggregate appeared (time to first aggregate) and until full vascular occlusion (time to flow stop) in both venules and arterioles were measured in seconds with four stop watches. The time to aggregate growth was calculated as the difference between the time to first aggregate and the time to flow stop.

*Blood collection and complete blood count analysis*

Another group of animals was subjected to Cd, OTC, Cd + OTC or saline treatment at the dose mentioned earlier. One hour after the treatment, the animals were anesthetized i.p. with sodium pentobarbital (45 mg/kg), and then blood was drawn from the inferior vena cava in EDTA (4%). Part of the blood was used for a white blood cell (WBC) counts using an ABX VET ABC Hematology Analyzer with a mouse card (ABX Diagnostics, Montpellier, France). The remaining blood was centrifuged for 15 min at 4°C at 900× g, and the plasma obtained was stored at -80°C pending analysis.

*Liver function and lactate dehydrogenase (LDH) and creatine kinase (CK) estimation*

Liver function tests included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) estimation in plasma. The ALT and AST were measured using standard laboratory methods using L×20 multiple automated analyzer (Beckman Coulter, CA, USA) with their estimation kit. The LDH was measured using commercial kits (Sigma Chemical, St. Louis, MO, USA) which determined the conversion of lactate to pyruvate in the presence of LDH with equivalent lessening of NAD. The formation of NADH from the above reaction can show a dif-

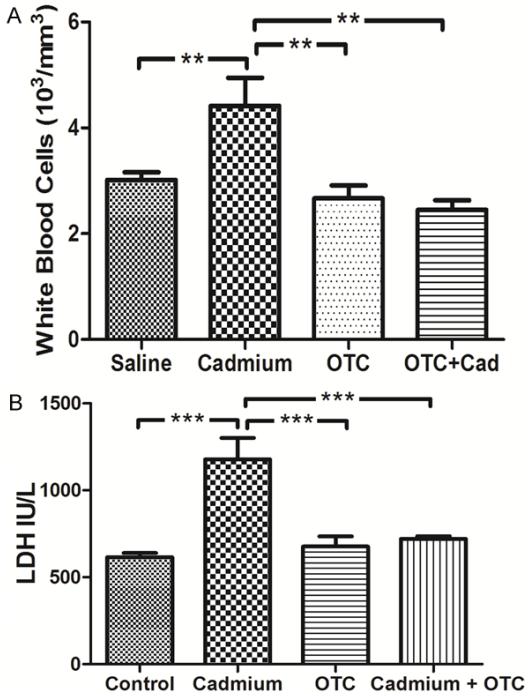


**Figure 2.** Effect of control, Cd, OTC and concurrent Cd with OTC exposure on white blood cell counts (A), LDH (B) and in saline treated control Cd, OTC and concurrent Cd with OTC treated animals. (n=6); ***P<0.001, **P<0.01.

ference when measured in absorbance at 340 nm. The CK activity was measured using standard laboratory method using L×20 multiple automated analyzer with estimation kit.

*Superoxide dismutase (SOD) and catalase (CAT) estimation*

The SOD and CAT, free radical scavenging enzymes, were performed by the photo oxidation method and measured using a commercial kit (Cayman Chemicals, Michigan, USA) [22].

*Statistical analysis*

Data were statistically analyzed using the ANOVA 1 followed by Neuman-Keuls post-hoc test (Graphpad Prism®). Tests were carried out to detect differences among the means of the each groups and a *P*-value of<0.05 was considered significant.

## Results

*Effect of cadmium on cerebral thrombosis*

The effects of Cd treatment on the time required for platelet aggregation (PA) and for full occlusion in *cerebral* microvessels are shown in **Figure 1**. In our results on the animals treated with Cd, the onset time for PA in both venules and arteriole showed very significant quickening (*P*<0.001) when compared to control group. The onset time of aggregation in arteriole was found to be 60% whereas in venule a 20% quicker response was observed when compared to control group (**Figure 1**). This indicates an increased susceptibility to thrombosis in cadmium exposed animals.

Subsequently, the total occlusion in the arterioles but not the venules showed a significant shortening in time (*P*<0.001) when compared to the control group (**Figure 1**). OTC treatments significantly increased the time for the first aggregate and the time for full occlusion either by itself or in conjunction with Cd treatment (**Figure 1**).

*Haematological and biochemical findings*

Acute exposure of mice with Cd significantly increased WBC level (**Figure 2**). Treatment of OTC in combination with Cd alleviated the harmful effects of Cd on WBC which reached the control value. There was a significant increase in LDH activity following Cd exposure. The pretreatment with OTC reversed the effects of Cd (**Figure 2**). **Figure 3** depicts the significant increase in serum AST, and the insignificant increase in ALT. Treatment of OTC alone or in combination with Cd alleviated the harmful effects of Cd (**Figure 3**).

There were significant increases in the values and CK (**Figure 3**) in mice treated with Cd. These values returned to nearly normal values with OTC treatment alone or in combination with Cd.

*CAT and SOD estimation*

Our estimation of SOD and CAT in the plasma in Cd treated animals showed significant increase at the dose tested (**Figure 4**). Treatment of OTC in combination with Cd alleviated the effects of Cd on SOD, and CAT levels that were returned to normal levels (**Figure 4**).

## Discussion

In our present study, we have showed that acute intraperitoneal daily injection of Cd for 3 weeks, compared to control group, in mice showed significant quickening of platelet agg-

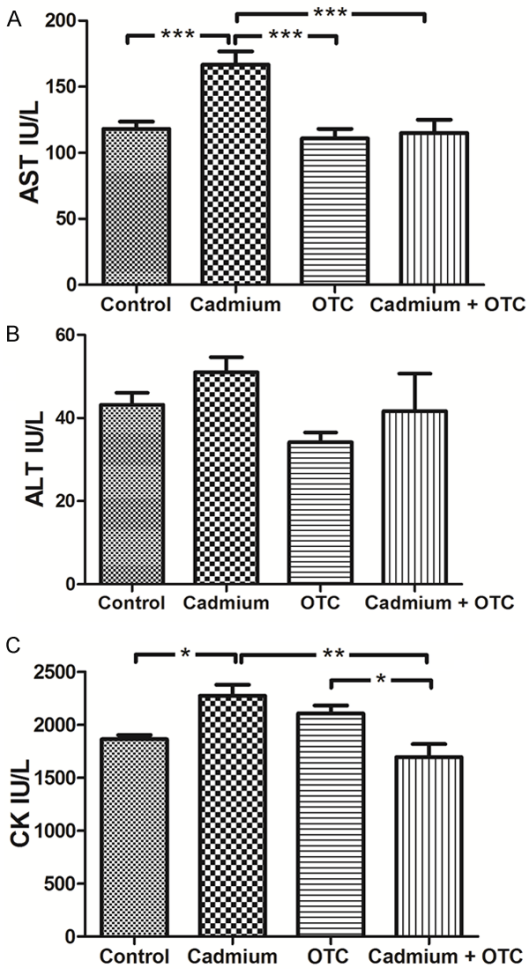


**Figure 3.** Effect of control, Cd, OTC and concurrent Cd with OTC treatment on the liver enzyme levels. A. Shows AST, B. ALT - and C. CK in saline control Cd, OTC and concurrent Cd with OTC treated animals. Data in bar graph shown are mean ± SEM, number of samples (n=6). ***P<0.001, **P<0.01, *P<0.05.

regation leading to pial cerebral thrombosis. Likewise, Cd exposure caused a significant increase in white blood cell numbers indicating the occurrence of systemic inflammation. The activities of ALT and AST in serum were measured as indicators of liver function. Interestingly, the SOD and CAT activities were significantly increased in the Cd treated group compared to control group, suggesting the occurrence of oxidative stress. The effect of OTC, a potent antioxidant, was found to ameliorate the decremental impact of cadmium on the microcirculation and liver toxicity.

The 1 mg/kg dose we have used in the present experiments were well below the LD50 and the minimum toxic dose for Cd [23]. The intraperitoneal route of Cd exposure was selected for its effectiveness [24]. The toxic level of Cd affects haemopoietic system and liver [25]. There is still much to dicover about the mechanisms of action, the biomarkers of critical effects and strategies to protect the health risks induced by Cd. In our thromboembolic studies, the Cd treatment reduced the time required for both the appearance of the first aggregate and the time for full occlusion in pial arterioles. *In-vitro* study on Cd stimulates adenylate cyclase and inhibits phosphodiesterase (PDE) activity with a decrease in the rate of PA [26]. Circulating platelets do not normally adhere to the endothelial cells of the vascular wall or aggregate, except when activated or when damage to the endothelium is attained. When such damage occurs, the aggregates are induced which will lead to formation of thrombosis. The development of thrombi in the circulatory system would result in reduced blood delivery and consequently, in tissue hypoxia/ischemia [27]. Francavilla *et al.* [18] reported the quickening of the thrombosis induced by Cd in testes and epididymis in rats. In concurrence with this previous study, our revealed a quickening of PA activity in pial cerebral vasculature during *in-vivo* treatment of Cd in mice. The same authors also demonstrated the variability of *in-vitro* and *in-vivo* treated Cd on PA activity to induce thrombosis. Likewise, our results also support the previous report by Järup *et al.* [5] who found a correlation between the endothelial damage that was either directly induced by Cd on endothelium or was indirectly induced by releasing the reactive oxygen species in endothelial and inflammatory cells. Wolf and Baynes [28] reported that 3-5 uM of Cd exposure caused endothelial dysfunction and increased LDH leakage leading to profound cytotoxicity. They also reported that lower level of Cd caused glutathione (an important cytoplasmic antioxidant), [29, 30] induction, a compensatory protective response, which may explain the increase in the level of SOD and CAT antioxidants enzymes that were observed in the current study. Furthermore, Fagerberg *et al*. [31] have reported that Cd exposure was associated with prevalence and growth of atherosclerotic plaques in the carotid arteries in old women. These direct or indirect effects are mediating the quickening of thrombosis, as found in our studies. This was well supported

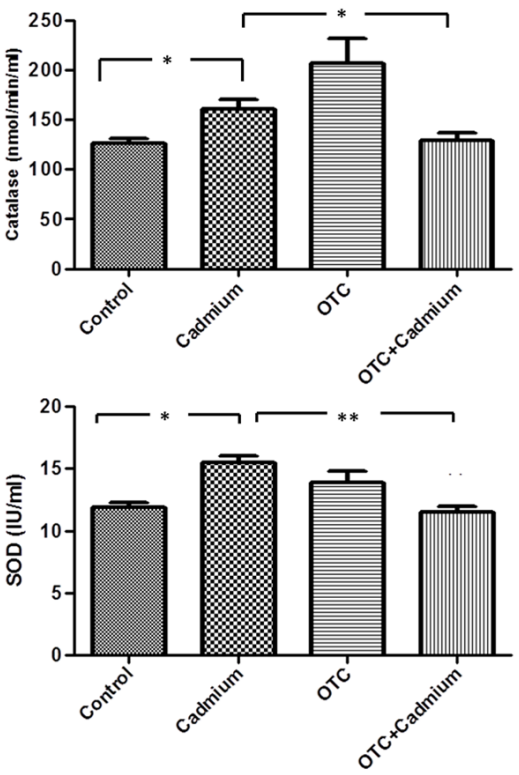


**Figure 4.** Effect of control, Cd, OTC and concurrent Cd with OTC treatment on SOD and CAT levels in the control, Cd, OTC and concurrent Cd with OTC treated animals. Data in bar graph shown are mean ± SEM, number of samples (n=6). **P<0.01, *P<0.05.

by our other estimations of SOD, WBC, and LDH and discussed in this paper which shows significant change in all their levels. Clearly these parameters are the indicators of oxidative stress and/or systemic inflammatory responses by tissues. As Cd primarily accumulates in the liver, it becomes more important target organ for damage [32]. Reliability of the hepatocellular function can be attained by quantifying the enzymes ALT and AST. Changes in the levels of these enzymes reveal the variations in the cell membrane functions including the alteration in the permeability which leads to cell damage [13]. Among these two enzymes, measurement of AST is considered as a good marker to indicate the liver damage particularly in animal species [33]. In our experiments we have demonstrated the acute administration of Cd significantly elevate the levels of AST indicating the severe damage to liver. Recently, rats were treated with 10 mg/kg subcutaneouse for 20 days, liver depicted mulifocal leukocytic infiltrate, and cellular vacuolization in the centerlobular zone [34]. Emerging evidence indicates that oxidative stress is related to regulation of multiple signaling pathways including transcription factors [35]. An imbalance between reactive oxygen species (ROS) and the antioxidant defense system leads to oxidative stress, which is closely linked to the pathogenesis. Increased levels of ROS cause direct tissue injury and promote inflammatory responses. The response of a cell to excessive ROS involves activation of multiple signaling pathways, which can cause transcriptional changes and consequently exhibit a variety of activities [35]. Antioxidant enzymes and proteins are crucial for maintaining the reducing environment of the cell and preventing the oxidative damage. Because glutathione (GSH) synthesized from cysteine is a vital protective antioxidant against oxidative stress. A thiazolidine derivative, L-2-oxothiazolidine-4-carboxylic acid (OTC) is a pro drug of cysteine that raises the concentrations of cysteine and GSH [36]. OTC raises the plasma concentrations of cysteine, which is the rate-limiting amino acid for intracellular GSH synthesis [37]. GSH is synthesized from cysteine and is a vital intra- and extracellular protective antioxidant against oxidative stress [37] subsequently potentiate the natural antioxidative cellular defense mechanisms. OTC is reported to be more effective than N-acetylcysteine in replenishing intracellular glutathione stores when GSH is depleted [38]. Recently, it has been demonstrated that OTC which can reduce the increased ROS generation is able to reduce inflammation and hyper-reactivity in animal models of hepatotoxicity [38]. Moreover, it has been shown that OTC prevents the pulmonary inflammation and thrombotic complication induced by diesel exhaust particle in mice [21] and cisplatin induced nephrotoxicity in rats [39]. Our present results have revealed that sub-acute Cd treatment has led to ROS generation which subsequently triggered an increase in CAT and SOD activities as a compensatory protection. The increased levels of these molecules are significantly reduced by administration of OTC. The administration of OTC resulted in significant Increase in the time of arterial 1$^{st}$ aggregate and the time of arterial flow stop demonstrating a protective effect against thrombosis. OTC treatment significantly reduced the level of WBC and LDH compared with the Cd treated group. Additionally, OTC reduced the increase of AST, ALT and CK enzymes activity

after Cd exposure. These results indicate that the antioxidant OTC is able to mitigate the systemic toxicity induced by Cd. Moreover, OTC exposure has significantly reduced the effect of Cd on CAT and SOD activities which lend support to its capacity as a potent antioxidant.

In conclusion, Cd induced acceleration in thromboembolic formation leading to quick occlusion of the vascular tissues are in concurrence with the changes in the levels of liver enzymes, increase in the leucocyte levels. The results summarized above show the high implication of Cd against the PA and liver dysfunction and the protective effects of OTC thereon. Further studies are essential to determine the mechanisms behind these observations.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Mohamed Abdelmonem Fahim, Educational Neuroscience Research Centre, Emirates College for Advanced Education, Abu Dhabi PO Box 126662, United Arab Emirates. E-mail: mfahim@ecae.ac.ae

## References

[1] Thomas LD, Hodgson S, Nieuwenhuijsen M, Jarup L. Early kidney damage in a population exposed to cadmium and other heavy metals. Environ Health Perspect 2009; 117: 181-4.

[2] Francavilla S, Moscardelli S, Francavilla F, Casasanta N, Properzi G, Martini M, Gallagher CM, Kovach JS, Meliker JR. Urinary cadmium and osteoporosis in U.S. Women ≥50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect 2008; 116: 1338-43.

[3] Svoboda L, Zimmermannová K, Kala P. Concentrations of mercury, cadmium, lead and copper in fruiting bodies of edible mushrooms in an emission area of a copper smelter and a mercury smelter. Sci Total Environ 2000; 246: 61-67.

[4] Kalao P, Ninanská M, Bevilaqua D, Staková I. Concentrations of mercury, copper, cadmium and lead in fruiting bodies of edible mushrooms in the vicinity of a mercury smelter and a copper smelter. Sci Total Environ 1996; 177: 251-258.

[5] Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure-a review of the literature and a risk estimate. Scand J Work Environ Health 1998; 24 Suppl 1: 1-51.

[6] Nawrot TS, Staessen JA, Roels HA, Munters E, Cuvpers A, Richart T, Ruttens A, Smeets K, Clijsters H, Vangronsveld J. Cadmium exposure in the population: from health risks to strategies of prevention. Biometals 2010; 23: 769-82.

[7] Shukla A, Shukla GS, Srimal R. Cadmium-induced alterations in blood-brain barrier permeability and its possible correlation with decreased microvessel antioxidant potential in rat. Hum Exp Toxicol 1996; 15: 400-405.

[8] Ding X, Zhang Q, Wei H, Zhang Z. Cadmium-induced renal tubular dysfunction in a group of welders. Occup Med (Lond) 2011; 61: 277-279.

[9] Patra RC, Rautray AK, Swarup D. Oxidative stress in lead and cadmium toxicity and its amelioration. Vet Med Int 2011; 2011: 457327.

[10] Jung YS, Jeong EM, Park EK, Kim YM, Sohn S, Lee SH, Baik EJ, Moon CH. Cadmium induces apoptotic cell death through p38 MAPK in brain microvessel endothelial cells. Eur J Pharmacol 2008; 578: 11-18.

[11] Ivanov L, Lesauskaite V, Sadauskiene I, Stapulionis R. Acute cadmium exposure changes protein synthesis in mice liver and activates apoptosis. Biomedicine 2002; 2: 41-45.

[12] Szuster-Ciesielska A, Lokaj I, Kandefer-Szerszeń M. The influence of cadmium and zinc ions on the interferon and tumor necrosis factor production in bovine aorta endothelial cells. Toxicology 2000; 145: 135-145.

[13] Shih CM, Ko WC, Wu JS, Wei YH, Wang LF, Chang EE, Lo TY, Cheng HH, Chen CT. Mediating of caspase-independent apoptosis by cadmium through the mitochondria-ROS pathway in MRC-5 fibroblasts. J Cell Biochem 2004; 91: 384-397.

[14] Kim SC, Cho MK, Kim SG. Cadmium-induced non-apoptotic cell death mediated by oxidative stress under the condition of sulfhydryl deficiency. Toxicol Lett 2003; 144: 325-336.

[15] López E, Figueroa S, Oset-Gasque MJ, González MP. Apoptosis and necrosis: two distinct events induced by cadmium in cortical neurons in culture. Br J Pharmacol 2003; 138: 901-911.

[16] Thevenod F. Cadmium and cellular signaling cascades: To be or not to be? Toxicol Appl Pharmacol 2009; 238: 221-239.

[17] Ognjanovic BI, Markovic SD, Djordjevic NZ, Trbojevic IS, Stajn AS, Saicic ZS. Cadmium-induced lipid peroxidation and changes in antioxidant defence system in the rat testes: Protective role of coenzyme Q(10) and Vitamin E. Reprod Toxicol 2010; 29: 191-197.

[18] Francavilla S, Moscardelli S, Francavilla F, Casasanta N, Properzi G, Martini M, Santiemma V. Acute cadmium intoxication: influence of

cyproterone acetate on the testis and epididymis of the rat. Arch Androl 1981; 6: 1-11.
[19] Tubek S, Bunio A, Szyguła R, Tubek A. Frequency of hospitalization for angina pectoris, stroke, and peripheral venous thrombosis and its relationship to elements in rain water in Opole Voivodship, Poland, during 2000-2002. Biol Trace Elem Res 2010; 133: 243-250.
[20] Fahim MA, Nemmar A, Dhanasekaran S, Singh S, Shafiullah M, Yasin J, Zia S, Hasan MY. Acute cadmium exposure causes systemic and thromboembolic events in mice. Physiol Res 2012; 61: 73-80.
[21] Nemmar A, Al-Salam S, Dhanasekaran S, Sudhadevi M, Ali BH. Pulmonary exposure to diesel exhaust particles promotes cerebral microvessel thrombosis: protective effect of a cysteine prodrug l-2-oxothiazolidine-4-carboxylic acid. Toxicology 2009; 263: 84-92.
[22] Nemmar A, Al-Salam S, Zia S, Dhanasekaran S, Shudadevl M, Ali BH. Time-course effects of systemically administered diesel exhaust particles in rats. Toxicol Lett 2010; 194: 58-65.
[23] Liu Y, Liu J, Klaassen CD. Metallothionein-null and wild type mice show similar cadmium-absorption and tissue distribution following oral cadmium administration. Toxicol Appl Pharmacol 2001; 175: 253-259.
[24] Akesson A, Lundh T, Vahter M, Bjellerup P, Lidfeldt J, Nerbrand C, Samsioe G, Buha A, Bulat Z, Dkukic-Cosic D, Matovic V. Effects of oral and intraperitoneal magnesium treatment against cadmium induced oxidative stress in plasma of rats. Arh Hig Rada Toksikol 2012; 87: 247-254.
[25] Shim JY, Shin H, Han JG, Park HS, Lim BL, Chung KW, Om AS. Protective effects of Chlorella vulgaris on liver toxicity in cadmium-administered rats. J Med Food 2008; 11: 479-485.
[26] Kumar SV, Bhattacharya S. In vitro toxicity of mercury, cadmium, and arsenic to platelet aggregation: influence of adenylate cyclase and phosphodiesterase activity. In Vitr Mol Toxicol 2000; 13: 137-144.
[27] Geys J, Nemmar A, Verbeken E, Smolders E, Ratoi M, Hoylaerts MF, Nemery B, Hoet PH. Acute toxicity and prothrombotic effects of quantum dots: impact of surface charge. Environ Health Perspect 2008; 116: 1607-1613.
[28] Wolf MB, Baynes JW. Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction. Biometals 2007; 20: 73-81.
[29] Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem 2001; 1: 529-39.
[30] Pompella A, Visvikis A, Paolicchi A, De Tata V, Casini AF. The changing faces of glutathione, a cellular protagonist. Biochem Pharmacol 2003; 66: 1499-503.
[31] Fagerberg B, Bergstrom G, Boren J, Barregard L. Cadmium exposure is accompanied by increased prevalence and future growth of atherosclerotic plaques in 64-year-old women. J Internl Med 2012; 272: 601-610.
[32] Świergosz-Kowalewska R. Cadmium distribution and toxicity in tissues of small rodents. Microsc Res Tech 2001; 55: 208-222.
[33] Haschek W, Rousseaux C, Wallig M. Handbook of Toxicologic Pathology. San Diego, Academic Press; 2002.
[34] Diaz M, Quiroga MA, Landa R, Giordano A, Najle R. Effecto del cadmio en organos maternos de ratas y fetos en differentes tiempos de gestacion. Invet 14, Cludad Autonoma de Buenos Aires 2012.
[35] Comhair SA, Erzurum SC. Redox control of asthma. Molecular mechanisms and therapeutic opportunities. Antioxid Redox Signal 2010; 12: 93-124.
[36] Vita JA, Frei B, Holbrook M, Gokce N, Leaf C, Keaney JF. L-2-Oxothiazolidine-4-carboxylic acid reverses endothelial dysfunction in patients with coronary artery disease. J Clin Invest 1998; 101: 1408-1414.
[37] Promsote W, Veeranan-Karmegam R, Ananth S, Shen D, Chan CC, Lambert NA, Ganapathy V, Martin PM. L-2-oxothiazolidine-4-carboxylic acid attenuates oxidative stress and inflammation in retinal pigment epithelium. Mol Vis 2014; 20: 73-88.
[38] Choi J, Park KH, Kim SZ, Shin JH, Jang SI. The ameliorative effects of L-2-oxothiazolidine-4-carboxylate on acetaminophen-induced hepatotoxicity in mice. Molecules 2013; 18: 3467-3478.
[39] Ali BH, Al Moundhri MS, Tag Eldin M, Nemmar A, Tanira MO. The ameliorative effect of cysteine pro drug L-2-oxothiazolidine-4-carboxylic acid on cisplatin-induced nephrotoxicity in rats. Fundam Clin Pharmacol 2007; 21: 547-553.