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THE INTERACTION BETWEEN ZINC AND CADMIUM IN TERMS OF ANTIOXIDANT AND ANTI-INFLAMMATORY PERSPECTIVES. IS ZINC A NATURAL PROTECTOR?

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ABSTRACT

Cadmium is known as a toxicant for animals and human beings. Despite of its toxic properties it is used in many industrial branches. Thus, people are likely to be exposed to cadmium due to professional and environmental reasons. The underlying mechanisms of cadmium toxication are oxidative stress, oxidative stress-related inflammation and interaction with bio-elements. Many studies have reported a protective role of zinc against cadmium toxication in animals and at cellular levels. Thus, this review focuses on the protective effect of zinc due to its antioxidant and anti-inflammatory effects. In this study, documents analyzing the interaction between Zn and Cd in metabolism were examined.

1 INTRODUCTION

Environmental metal pollution is important because it causes toxic effects in biological systems [1]. Although metals are essential for physiological functions, non-essential metals are harmful to animals and human beings [2,3]. Being one of the non-essential metals, cadmium (Cd) is a highly common metal with high toxicity [4]. Cd is a soft silver-white metal element in group of IIB in periodic table with 112.41 atomic weight. Cd may be present in the pure form or in compounds with oxygen, chlorine and sulfur in the environment [5]. Being a heavy metal, Cd was discovered as an impurity of zinc (Zn) carbonate for the first time. Besides, Cd is a rare element having concentrations of 0.15 mg/kg and 1.1 × 10−4 mg/L in the earth's crust and seas, respectively [6]. Cd is released into the environment naturally or from industrial, agricultural, and other sources [7].

Cd is used in numerous industrial applications including electroplating, pigments, paint additives, welding, and Ni-Cd batteries [8]. It is stated that Cd may be associated with toxic effects in some tissues and organs including kidneys, liver, lungs, bones, endocrine and reproductive systems [9-11]. Moreover, Cd causes diabetes mellitus [12], cardiovascular diseases [13], and neurodegeneration [14]. It is also identified by International Agency for Research on Cancer (IARC) as a human carcinogen causing development of tumor in the lung, injection site, prostate, and other tissues [15]. In addition, Cd may cause oxidative damage in some tissues that leads to defects in membrane functions [16]. Moreover, heavy metals cause inflammation [17], and thus Cd can induce inflammation in various animals [18,19]. Although human beings are exposed to Cd regularly through foods, there is no identified method for inhibiting or minimizing Cd contamination in foods [20]. However, studies have been still ongoing to reduce the absorption of metals or to reduce Cd toxicity by increasing the antioxidant capacity of metabolism. Remarkably, medical plants and natural antioxidant substances have been found to be beneficial [21]. Furthermore, antioxidant molecules have been suggested to inhibit Cd-induced oxidative damage due to their upregulation features in cellular antioxidant system [22].

Zn, a trace element, has important beneficial functions including cell proliferation, and antioxidant and anti-inflammatory defense and immune system [23,24]. Zn exhibits antioxidant properties because it has a role in cell membrane stabilization, Cu/Zn SOD structure, and metallothionein (MT) induction [25]. Zn treatment may prevent absorption and accumulation of Cd and inhibit adverse actions [26].

The aim of this review is to explain the interactions between Zn and Cd and evaluate possible protective effects of Zn against oxidative damage and inflammation induced by Cd. This study is limited to evaluate the interactions between Zn and Cd in rats.

2 MATERIAL AND METHODS

A systemic review was performed using Science Direct by combining the terms of zinc and cadmium, antioxidant, anti-inflammatory and toxicity terms. The literature review was limited with studies published in English between 2010 and 2023 years. This study focused only on rat-based experimental studies that investigated only Zn supplementation (not in combination with any other metals or agents) as a potential antioxidant/antidote (including MDA, GSH, GPX, SOD, and CAT) and anti-inflammatory (including TNF-α, NF-κB, Interleukin-6, and IL-1β) effects against Cd-induced oxidative damage. This is because there were only a few in vivo experimental studies except for rat models. At the end of the literature review, approximately 30 studies including experimental studies between 2010–2023 were found. The number of studies on both antioxidant and anti-inflammatory effects is limited. Moreover, according to our knowledge there is no report that shows negative effect of Zn on Cd toxication. Appendix 1 shows the detailed results of the studies used in this work.

3 Cd EXPOSURE

The most important sources of Cd exposure in the community are food and smoking. Seafood, kidney, liver, flaxseed, cocoa powder, wild mushrooms, potatoes, cereals, and vegetables grown on contaminated soil contain high levels of Cd [27]. Tobacco is one of the Cd-accumulating plants and it has been reported that one

cigarette contains approximately 1-2 µg Cd. Besides it has been observed that children are exposed to Cd through cigarette smoke [28, 29]. Furthermore, air is another source of Cd exposure but Cd concentration in the air is low [30].

It has been reported that inhalation of cadmium oxide particles may cause lung and acute pneumonia. In case of occupational or environmental exposure, Cd can damage the lungs and cause obstructive pulmonary disease (COPD), heart failure, and heart attack [31,32]. Moreover, studies provide evidence showing that Cd exposure is positively associated with different liver diseases such as non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hyperglycemia, necroinflammation, etc. [33,34].

FAO/WHO has reported that the tolerable weekly intake of Cd is 400-500 µg per person or 140-260 µg/day for over 50 years and 2000 mg for life-time [35]. A recent report of FAO/WHO (2010) states that Cd is 0.83 µg/kg body weight per day or 58 µg/day for a 70 kg person [36]. In addition, European Food Safety Authority reported 25 µg/day Cd for a 70 kg person [37,38]. The absorbed Cd amount can change based on its exposure and entry route. Cd is absorbed by the gastrointestinal system at the rate of nearly 3-10% and 50% of inhaled Cd is absorbed [39]. Cd is transferred to other organs including liver, kidney, pancreas, heart, spleen, testicles, lungs and bones via albumin and alpha -2- macroglobulin. Cd binds glutathione (GSH) and metallothionein (MT) and these compounds are slowly secreted from bile or released to blood stream. [40,41]. In general population, Cd blood levels were determined as 3.5–8.9 nM for non-smokers and 12.4–35.5 nM for smokers. But IARC detected Cd blood levels much higher for environmental and occupational exposure (above 89 nM and up to 445 nM) respectively [42]. Blood Cd levels are examined in whole blood generally. The half-life of Cd may be in 3- 4 months to 10 years in blood [43]. In another study, it has been reported that the effect of Cd can last for about 10 years due to its long biological half-life [44].

3.1 Mechanism of Cd Action

In the bloodstream, Cd binds to alpha-2-macroglobulin and albumin, and by this way it is transferred to organs. Cd binds to GSH or MT in the liver. These complexes have significant storage and transport roles because of their long life time. They are slowly secreted into the bile or bloodstream [40,41].

Cd exhibits its toxic effects via the Cd^{+2} ion's physical and chemical properties which are similar to those of Ca and Zn. For this reason, it is possible that Cd replaces Ca and Zn in important physiological processes in which a number of signaling pathways might be incorrectly activated or repressed. And in this case various signaling pathways can be activated or inhibited [45]. Cd has been addressed with some structural and biochemical changes. It causes apoptosis at low doses and necrosis at higher doses in cell cultures [46].

Besides, Cd affects plasma membranes and damages mitochondrial and nuclear membranes and DNA [47,48]. Joseph et al. (2004) have stated that four group mechanisms have an effective role in Cd carcinogenesis including inhibition of DNA damage repair, inhibition of apoptosis, inhibition of aberrant gene expression, and induction of oxidative stress [49]. Furthermore, previous studies have revealed that the mechanisms underlying Cd toxicity are both oxidative stress and inflammation [50,51,52].

3.2 Cd and Inflammation

Inflammation is a protective response of metabolism to injury caused by microorganisms, and physical and chemical agents to prevent tissue damage [53]. Chronic Cd exposure, through the downstream effects of Cd-induced oxidative stress or through various mechanisms, induces systemic levels of inflammation. [54]. Previous reports documented systemic inflammation and oxidative stress as main reasons of some chronic diseases including diabetes mellitus (type 2) and cancer [55,56]. In another study, Kayama et al. [48] revealed that high levels of pro-inflammatory cytokines associated with Cd exposure cause pathological conditions in biologic systems.

NF-κB is a transcription factor of genes including cell survival, inflammation, differentiation and growth [57]. Different studies have revealed that Cd exposure may increase activity of NF-κB in various systems. Go et al. (2012) indicated that low dose Cd treatment caused to increase NF-κB activity in HeLa cells [58]. In a mice study, it was determined that cadmium chloride (CdCl2) led to an important increase in the expression of NF-κB [59]. However, in their study, Souza et al. (2004) reported that the NF-κB activity did not increase after Cd treatment (1.5 or 10 μM CdCl2) of human liver hepatoma HepG2 cells [60].

Interleukin-6 (IL-6) is an important pro-inflammatory cytokine that promotes the induction of acute phase proteins [61]. In a previous study, it was determined that Cd treatment increased IL-6 status at doses of 0.5 mg and 1 mg Cd/kg body weight [62]. When an important increase was determined in the levels of IL-6 in M1 fibroblasts and type 2 epithelial cell cultures, there was no increase in alveolar macrophages [61].

Tumor-necrosis factor (TNF) is a sufficient mediator which reflects systemic or local inflammation [63]. Lag et al. [61] stated that Cd caused an important increase in the TNF-α release (from 3 to 10 μM) in rat alveolar macrophages after exposure for 20 hours. Freitas and Fernandez [64] showed that Cd treatment induced the release of TNF-α in THP-1 human monocytic leukemia cells. However, in their study, Cormet-Boyaka et al. [65] revealed that Cd administration did not increase the levels of TNF-α in human SAEC and Calu-3 cells.

IL-1β and TNF-α are important players in the onset of inflammatory processes as well as regulation and expression of the other chemokines and cytokines [61]. Cormet-Boyaka et al. (2012) reported that Cd treatment did not change IL-1β status in human SAEC and Calu-3 cell lines [65].

3.3 Cd and Oxidative Stress

Cd may cause oxidative stress via different pathways. It shows high affinity to sulfhydryl (SH) groups and thus it reduces glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (Gpx) activities of the tissues [66,67]. Besides, the intracellular release of Cd affects the structure of the cellular membrane via lipid peroxidation (LPO) [68]. There is more evidence that support Cd induced oxidative stress and increased LPO [69], decreasing of GSH [70], and activity of some stress response genes [71]. Many studies have reported that Cd increases LPO and causes an increase in malondialdehyde (MDA) levels, which is the most important biomarker of LPO [72]. In a recent study, Taşdemir et al. (2020) reported that MDA levels statistically significantly increased in rats exposed to Cd [73]. Athmounia et al. [74] stated that MDA levels showed an important increase in liver tissue of CdCl2-induced group compared to the control. In another study, Ahmada et al. [75]. reported that Cd caused decreasing of CAT activity in the liver,

kidneys, and red blood cells. Moreover, Cd-induced oxidative stress has a major role in inhibiting DNA damage repair mechanisms and inducing apoptosis [76].

3.4 Zinc (Zn)

Zn is one of the most abundant metals and an essential trace element. It has an important role in maintaining physiological and cellular functions of body. It is absorbed from small bowel and stored in liver and kidney. It binds to metalloproteins in intracellular conditions. It has a key role for many enzymes and supports the immunity of the body [77-79]. Zn deficiency causes failure of immunity and growth, hypogonadism, diarrhea and alopecia, impaired taste and smell, dermatitis and respiratory tract infections [79]. However, the increased amount of Zn in the cell has a neurotoxic effect [80].

Intracellular Zn binds to proteins in cellular physiology. Between 30 and 40 per cent of cellular zinc is found in the nucleus, 50 per cent in the cytosol and organelles, and the remainder is associated with the membranes. Moreover, it has many roles in phosphorylation/ dephosphorylation cascades and in the signaling system [81,82]. Zn homeostasis is provided via zinc transporters (ZnT). Totally 25 zinc transporters have been identified as 10 zinc exporters (ZnT) and 15 zinc importers (Zip). ZnT proteins exports intracellular Zn through organelles or across the membrane. Zn is transported across plasma membrane only via ZnT-1. The other ZnT transporters provide Zn sequestration into zincosomes [83,84]. Zip proteins allow Zn to enter the cell and release Zn from the zincosomes [83]. Zip proteins are divided into four groups: I, II, gufA, and LIV-1 subfamilies of Zip transporters. In addition, both ZnT and Zip proteins need energy and their production is regulated based on Zn status [85].

Zn has a role in the structure of enzymes as a cofactor and metabolic pathways. For instance, it is required for phosphatases, glutamate dehydrogenase or SOD and many other enzymes [86]. Valle and Auld [87] reported that approximately 200 enzymes were related with Zn. It may inhibit some enzymes including caspase-3 and protein tyrosine phosphatase [88], NAD+-dependent isocitrate dehydrogenase, succinate dehydrogenase, α-ketoglutarate dehydrogenase, aconitase, and cytochrome C oxidase [89]. These findings are supported by the data showing that

treatment of 30 mol/L Zn causes inhibition of the GSH and the increase of oxidized glutathione (GSSG) in liver cells [90,91].

Zn is a trace element which has an antioxidant capacity to neutralize free radical generation [92]. Zn shows an antioxidant ability with different properties as shown in Figure 1. Zn^{2+} inhibits reactive oxygen species (ROS) and supports a cellular membrane stability [93]. Besides, it acts as an antagonist of Cd, prevents Cd toxicity and supports the antioxidant system [94]. Zn may have different antioxidant features. It keeps intracellular levels of GSH by preventing oxidation of sulfhydryl groups [95]. It also reduces oxidant promoting enzymes such as iNOS and supports activities of antioxidant enzymes (CAT, SOD) [96].

SODs are metalloenzymes and four SOD types have been identified; Cu-Zn SOD, Mn SOD, Fe SOD, and Ni SOD. The most important type is Cu-Zn SOD due to importance of its physiological and therapeutic properties in eukaryotic cells [97]. In addition, Zn induces synthesis of MT, an important scavenger of free radicals [98] and regulates metabolism of other antioxidant vitamins such as vitamin E and vitamin C [99-101]. Zn can also inhibit ROS production through competition with Fe^{2+} and Cu^{+} ions which have prooxidative action [102].

On the other hand, MT is a metal-binding protein rich in cysteine [103]. It has antioxidant features and it is induced via Zn [92,104,105]. It has been reported that MT neutralizes hydroxyl radicals and inhibits oxidative stress [106]. MTs are also thought to have an efficient role in the homeostasis of cellular Zn metabolism [107]. Zn and Cd are good inducers of MT transcription and protein synthesis. Cd toxicity can be improved by Zn through the induction of MTs [108,109].

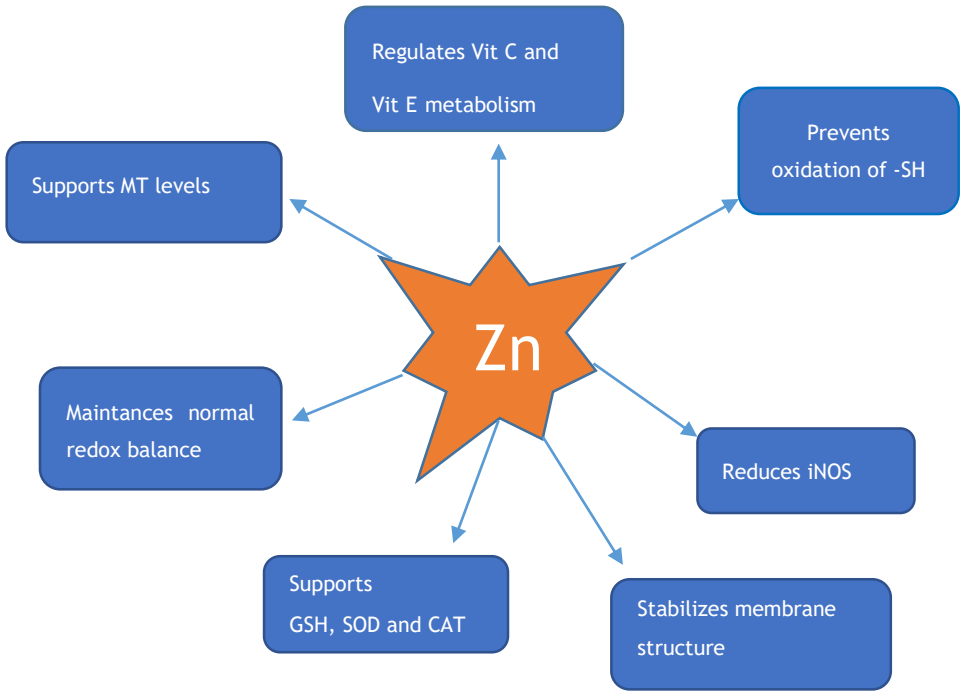

***Figure 1**. The summary of antioxidant properties of Zn.*

3.5 Preventive Effects of Zn Against Cd Toxicity

The preventive effect of Zn against Cd toxicity is known for many years. Zn has an ability to strongly reverse Cd intoxication in different organisms [110,111]. According to reports, Zn limits the gastrointestinal tract absorption of Cd and its accumulation, hence preventing its detrimental effects. [112]. Moreover, its preventive effect against Cd toxicity may be related to maintenance of redox balance in the cell [113].

Sidorczuk et al. [114] observed a decrease of 29% in LPO levels in 5 mg Cd/L + 30 mg Zn/L treated group only compared to Cd (5 mg Cd/L)-treated group in serum of rats. Accordingly, the detected decrease became 46% when Cd concentration increased to higher levels. In this study, the researchers showed increasing levels of GPx in serum, liver, and kidney samples only after Zn administration compared to Cd-treated groups.

Another study, Messaoudi et al. [115], determined that Zn administration decreased Cd- induced testicular MT-1 and MT-2 gene expression and an increasing antioxidant status in rats. Zn binds and detoxifies Cd by inducing MT synthesis. It also

reduces oxidative stress induced by Cd with its antioxidant properties [116]. In their study, Messaoudi et al. [117] stated that administration of Zn supported GSH, GSHPx (or GPX) and CAT levels of rat erythrocytes. Jemai et al. [118] revealed that pre-treatment with Zn played a preventive role against Cd intoxication and caused an important increase in GSH levels of rats.

Jihen et al. [119] revealed that Zn treatment may reverse Cd-induced oxidative stress in kidney of rats. Another study by the same group [120] reported that Zn has an indirect ameliorative effect in the liver of Cd-induced rats. In their study, they administrated 200 mg/L Cd of CdCl2 and 500 mg Zn of ZnCl2 to the subject animals. At the end of the study, they detected an increased CuZn SOD activity and GSH levels. Brzóska and Rogalska [121] evaluated GSH levels, GPX, SOD, and CAT activities of bones in Cd-induced rats. In their study, they administrated Cd (as CdCl2·2½H2O) of 5 or 50 mg for 6 months and Zn (as ZnCl2) of 30 and 60 mg for 6 months. At the end of the study, they did not notice any change in antioxidant parameters. Ebaid et al. [122] stated that Zn showed ameliorative effects on MDA status in Cd-treated rats. Moreover, they reported a positive effect of Zn on CAT, SOD, and GSH levels in the same study. Mimouna et al. [123] observed lower SOD activities after Zn treatment in rat fetal brain tissue compared to the Cd-induced groups. In addition, they found that MT levels of Cd+Zn induced group showed a decrease when compared to Cd-induced group.

Bashandy et al. [124] concluded that Zn administration showed a positive effect on Cd-induced oxidative stress, sex hormones, spermatogenesis, and inflammatory biomarkers. In the study, they administrated CdCl2 and ZnCl2 at dose level of 2.2 mg/kg. According to the study results, Cd exhibited significant increases in the level of testicular MDA, TNF-α and hydroperoxide of blood. And Zn treatment mitigated the toxic effect of Cd. Rogalska et al. [125] indicated that 30 mg Zn/L and 60 mg Zn/L treatment decreased TNF-α levels according to the Cd-induced group of rats.

Cd is an environmental pollutant that causes widespread oxidative stress and inflammation in metabolism, and its exposure leads to impairment of the innate immune system. Cd causes oxidative stress by triggering free radical production during metabolism. Free radicals have been reported to cause many diseases such as

diabetes mellitus, neurodegenerative diseases, DNA damage and cancer. Studies have shown that substances with antioxidant activity can counteract the oxidative stress-induced toxic effects of Cd. Strengthening antioxidant defense mechanisms may be a good option to counteract the harmful effects of free radicals. Because Zn is involved in the activity of many enzymes including antioxidant enzymes, and induces MT synthesis, it is a good option to strengthen the antioxidant defense system. Considering the side effects of synthetic antioxidants, the use of natural antioxidants will undoubtedly be more beneficial. Therefore, Zn may be an important candidate for the prevention and/or reversal of Cd-induced damage.

4 CONCLUSION

Zn is a well-known natural antioxidant agent against Cd toxicity for many years. The preventive effect of Zn is manifested via the antioxidant and anti-inflammatory properties based on the used dose. Besides, oxidative stress is one of basic reasons of Cd toxication. It has been revealed that Zn may reverse Cd toxicity by supporting GSH, SOD, CAT, and MT levels and regulating Vit E and Vit C status. In addition, it stabilizes membrane structure, prevents LPO, and supports redox balance. However, zinc is not used as a detoxifying agent in clinical trails, yet. Zinc may be a good candidate for detoxifying Cd, but there is a need for further studies to be conducted at cellular levels, in animals, and in human beings. In addition, although an abundance of data available more research is required to fully understand the mechanisms underlying zinc's protection against Cd toxicity. Investigators may find new avenues to pursue in this field.

Statement of Research and Publication Ethics

The study is complied with research and publication ethics.

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APPENDIX

***Appendix 1**. Details of the studies evaluating Zn effects on Cd induced toxicity in rat models. This table shows that changing of MDA, GSH, GPx, SOD, CAT and TNF-a levels after Zn treatment (Zn+Cd) according to the only Cd induced groups of the studies. Statistical importance of the alterations reflected also. (**Note**: ↑ means increasing; ↓means decreasing; ● means no changing)*

Sample	Cd Source /Dose/ Administration type/ Duration time	Zn Source/Dose/Administration type / Duration time	MDA	GSH	GPx	SOD	CAT	TNF-α	Reference
Testis	CdCl2, 200 ppm, drinking water, 5 weeks	ZnCl2, 500 ppm, drinking water, 5 weeks	↓ p< 0.01	-	-	↑ p< 0.01	↓	-	[115]
Erythrocyte	CdCl2, 200 ppm, drinking water, 35 days	ZnCl2, 500 ppm, drinking water, 35 days, 5 weeks	-	↑	↑ p< 0.05	↓ p< 0.01	↑ p<0.0001	-	[117]
Kidney	CdCl2, 200ppm, drinking water, 35 days	ZnCl2, 500 ppm, drinking water, 35 days	-	↑ p<0.0001	↑ p<0.0001	↑ p<0.0001	-	-	[119]
Liver	CdCl2 200 mg, within drinking water 35 days	ZnCl2, 500 mg, drinking water. 35 days		↑ p<0.0001	↑ p<0.0001	↑ CuZn SOD p<0.0001 ↓ MnSOD			[120]
Liver	CdCl2, (5 and 50 mg/l), within drinking water, 6 months	ZnCl2 30 or 60 mg Zn/l, drinking water, 6 months						↓ p<0.0001 ↓ p< 0.05	[125]
Testis	CdCl2, 2.2mg/kg, subcutaneously,8 weeks	ZnCl2, 2.2mg/kg, subcutaneously, 8 weeks.	-	↑ p< 0.01	-	↑ p< 0.01	↑ p< 0.01	↓ p< 0.01	[124]
Blood	CdCl2, 2.2 mg/kg, subcutaneously, 60 days	ZnCl2, 2.2 mg/kg, subcutaneously, 60 days	↓ p< 0.05	↑ p< 0.05	-	↑ p< 0.05	↑ p< 0.05	-	[122]
Bone	CdCl2·2½H2O 5 or 50 mg, drinking water 6 months,	ZnCl2, 30 and 60 mg, drinking water 6 months	-	●	●	●	●	-	[121]
Brain	CdCl2, 50 mg/L, drinking water, during gestation	ZnCl2, 60 mg/L, drinking water, during gestation				↓ p < 0.05			[123]
Serum	5 or 50 mg Cd/L (as CdCl2 2 ½ H2O), drinking water, 6 months	ZnCl2, 30 mg Zn/L, drinking water, 6 months	↓		↑ P < 0.01				[114]
Liver					↑ p< 0.05				
Kidney					↑ p< 0.05				