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Protective Effects of Zinc and Vitamin C on Antioxidant Status Against Cadmium Toxicity – A Review

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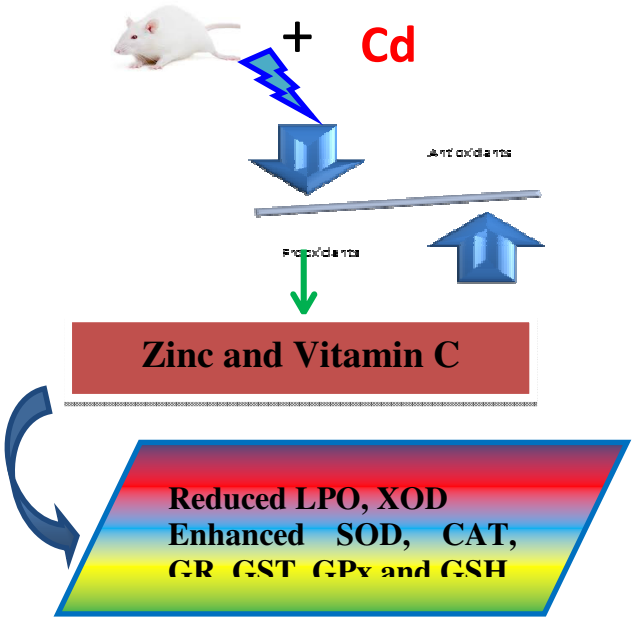
Abstract:

Cadmium is an Internationally recognized one of the toxic, non-biodegradable, non-essential heavy metal, with no biological role in human body. Cd induced bioaccumulation promotes the development of oxidative stress in organism by enhanced production of Malondialdehyde (MDA). Oxidative stress induces the generation of free radicals with subsequent changes in the Antioxidant status of SOD, CAT, XOD, GST, GPx, GR and GSH. Zinc and Vitamin C are the powerful chain breaking antioxidants with protective effects that neutralizes free radicals like hydrogen peroxide, superoxide, nitric oxide, hydroxyl, singlet oxygen and hypochlorous acid radicals. Hence treating Cd induced rats with Zinc and Vitamin C showed many beneficial effects in preventing organ damage. The present study clearly indicates that Zinc and Vitamin C showed positive impact on organs (liver, kidney and testis) that are damaged under Cd toxic insult.

Key Words: Cadmium, Albino rat, Zinc, Vitamin C and Antioxidants



INTRODUCTION

Industrialization is a worldwide problem faced by the organisms in both the developed and developing countries posing severe threat for survival of humanity. The metallic toxins are delivered into the environment, soil and water by various anthropogenic activities, industrial processes and occupational exposure. Arsenic, lead, plutonium, cadmium, mercury and chromium are the most poisonous heavy metals delivered into the ecosystem by different sources like leaded petroleum, mines, pesticides, colors, electroplating, volcanoes, vehicular discharges, storage batteries and fertilizers.

Heavy metals have no biological role in the organism, but get gathered in different organs of human body and cause many undesirable side effects, thus needs more attention on this. Heavy metals bioaccumulate in different organs and tissues of living organisms and biotransforms from producers to consumers in a food chain ultimately affecting the human health.

Cadmium (Cd):

Among the toxic metals, Cadmium (Cd) is well known most deleterious, highly toxic, non-essential and non-biodegradable systemic toxicant in the environment, both in terrestrial and aquatic ecosystems with no physiological function in the living organisms including humans. Cd promote oxidative insult and disturb the essential metal homeostasis in the tissues by its characteristic features-bioaccumulation and biomagnification. Minimum quantity of heavy metals may not pose any adverse effects, but increased concentrations are harmful to biota.

Cadmium shows influence on the enzymatic systems of the cells, causing oxidative stress [1]. It is ubiquitous in nature and is harmless in small amounts, and released into environment by weathering, river transport, volcanic eruptions and various anthropogenic activities include mining, smelting, tobacco smoking and manufacture of fertilizers [2]. Industrial usage of Cadmium has intensified exposures to high levels that can alter biochemical functions in the organs by disrupting the prooxidant and antioxidant balance and causing organ damage.

Cadmium is extensively used in batteries, paints, metal coatings, plastics and electroplating. Due to its non-degradable nature it gets bioaccumulated in different organs like kidney, testis and liver of vertebrates and invertebrates. The half-life of cadmium in human tissue is more (upto years) and varies with different tissues due to the ineffective pathways to excrete cadmium. Due to its long biological half-life in humans of about 10-30 years cadmium gets accumulated in the body [3] and excess accumulation is observed in the liver and kidney.

Prooxidants – Antioxidants status:

Lipid peroxidation (LPO) induces malondialdehyde (MDA) production under heavy metal intoxication. Lipid peroxidation, plays a prominent role in the toxicity of many xenobiotics causing oxidative damage of lipids, proteins leading to progressive loss of membrane fluidity, disturbs cell integrity thus reducing membrane potential and increases permeability Ca^{2+}ions. Hence oxidative stress is generated in the organism and promotes organ damage by imbalancing antioxidant status

Antioxidants are the first line of defense for cell protection also called “free-radical scavengers” that can prevent or slow down cell damage caused by free radicals, unstable molecules that are produced in body in response to environmental stress. Increased intake of antioxidants in the diet will help maintain cell

integrity and also maintain the normal physiological and biochemical functions of living system, thereby neutralizes the free radicals and protects cells [4].

Depending upon enzymes antioxidants are broadly classified into two types namely enzymatic antioxidants and non- enzymatic antioxidants. Enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT), Xanthine oxidase (XOD), glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione-*S*-transferase (GST). Non- enzymatic antioxidants includes Vitamin derivatives like Vitamin C, Vitamin E and Vitamin A; Mineral derived antioxidants like Zinc, Manganese and selenium; Carotenoid derived antioxidants like Beta carotene, lycopene, lutein, zeaxanthin; Thiol antioxidants like Glutathione (GSH), thioredoxin and lipoic acid; Organo sulfur compounds like Allium, allyl sulfide and indoles; Antioxidants cofactors like Coenzyme Q_{10}; Phytochemical derivatives like Flavonoids and polyphenols [4].

Superoxide dismutase (SOD)

Superoxide dismutase (EC 1.15.1.1) maintains normal physiological conditions in all living cells, speeds up chemical reactions in body and protects the biological integrity of tissues against toxic effects of superoxide radicals. SOD catalyzes the conversion of superoxide radicals into oxygen and hydrogen peroxides and neutralizes free radicals by detoxifying the excess of O2.– radicals [5]. Dismutation of superoxide radicals helps in the protecting cells from oxidation of lipids, proteins and DNA. SOD levels decline with increase in age where, its deficiency promotes the formation of free radicals.

Catalase (CAT)

Catalase (EC 1.11.1.6) is a prominent antioxidant enzyme and hemoprotein with four heme groups in its structure that neutralizes the toxic effects of H_2O_2, a non radical ROS. CAT, an enzyme found nearly all living organisms like plants, animals and aerobic bacteria, is found mostly in peroxisomes in the cell and shows high activity in erythrocytes, kidney and liver [6]. Decomposition of H_2O_2, helps in maintaining optimum levels in cell that is essential for cellular signaling.

Xanthine Oxidase (XOD)

Xanthine oxidase (EC 1.17.3.2) is the key enzyme responsible for purines catabolism that catalyzes hypoxanthine to xanthine oxidation to uric acid. Xanthine dehydrogenase (XDH) form can be easily converted into xanthine oxidase form by formation of 2 cysteine disulfide bonds. Xanthine oxidase pathway is important site for generating free radicals like superoxide radicals, nitric oxide radicals and hydrogen peroxide molecules that promote oxidative damage [7]. Hence superoxide radicals are the index molecules to determine the activity of xanthine oxidase and xanthine dehydrogenase [8] XOD acts as a dehydrogenase enzyme (Xanthine dehydrogenase-XDH) during ordinary physiological conditions. But under hypoxic and ischemic conditions it responsible for conversion of the dehydrogenase form (XDH) of xanthine oxido reductase to an oxidase form (XOD). Under nutrients supplementation, superoxide anion formation is decreased by XO and declined uric acid content and scavenges free radicals.

Glutathione reductase (GR)

Glutathione reductase (EC 1.8.1.7) catalyzes glutathione disulfide (GSSG) reduction to form the reduced glutathione (GSH). Glutathione plays prominence in preventing oxidative stress by scavenging free

radicals like hydroxyl radicals ($^{\cdot}OH$) and singlet oxygen ($^1O_2$). Glutathione reductase maintains the depleted reduced glutathione levels and further converts it into oxidized glutathione disulfide in presence of glutathione peroxidase enzyme. Glutathione peroxidase (GPx) catalyzes hydrogen peroxide radicals conversion into water molecules which are toxic to the cell. Inhibition of glutathione reductase enzymes occurs due to depletion of GSH content in the cell that converts GSSG to GSH by utilizing NADPH [9].

Glutathione-S-transferase (GST)

GST belongs to a family of multi gene products that catalyse the conjugation of reduced GSH—via a sulfhydryl group to electrophilic centers on a wide variety of substrates in order to make the compounds more water-soluble. It is involved in the detoxification of a number of electrophilic molecules of exogenous as well as endogenous origin, including ROS. The glutathione transferases are phase II detoxification enzymes found mainly in the cytosol. These isoenzymes are present in organisms ubiquitously and widely distributed in nature. Glutathione S-transferases (GSTs) reduce upon glutathione (GSH) addition and prevents cell from bursting by oxidative insult. GST efficiently detoxifies exogenous (Xenobiotics and their metabolites) and endogenous (primary products of oxidative stress), toxic compounds in the classical detoxification phase II system.

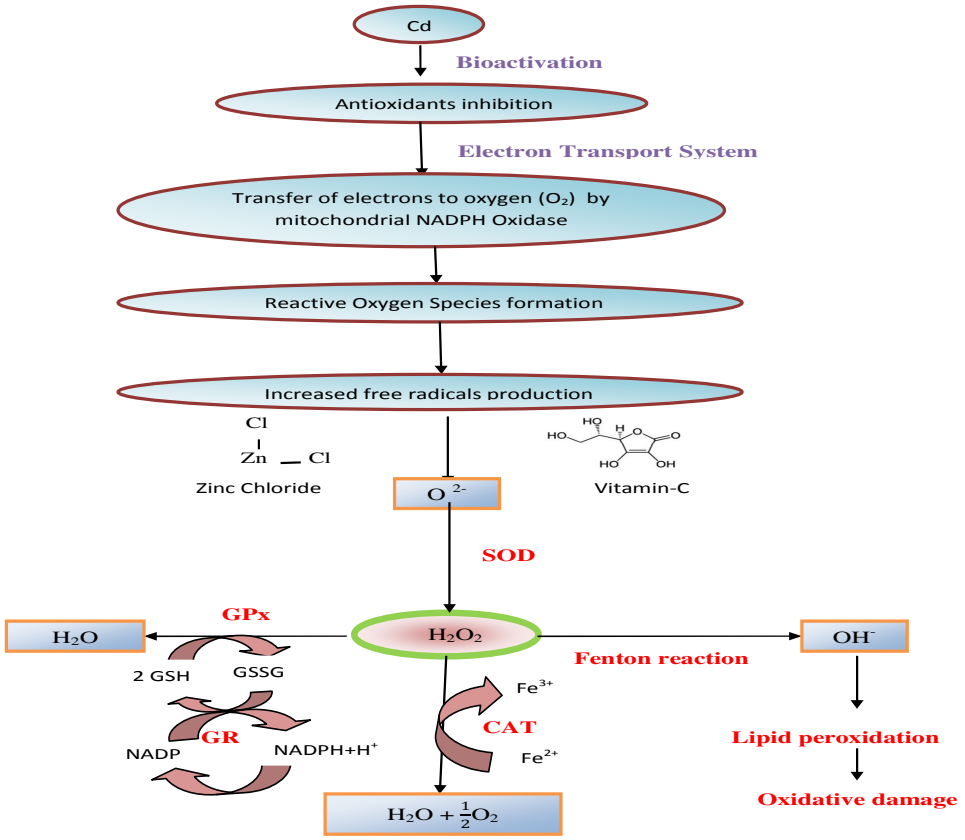
Glutathione peroxidase (GPx)

Glutathione peroxidase (EC: 1.11.1.9) belongs to cytosolic enzymes family that catalyzes glutathione oxidation in order to detoxify peroxides. The GPx catalyze H_2O_2 reduction into water and oxygen molecules and catalyzing the reduction of organic peroxide radicals (R-O-O-H) to the corresponding stable alcohols and oxygen (R-OH) using glutathione (GSH). GPx reduces lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water. GPx catalyzes the reaction of hydroperoxide and form glutathione disulfide (GSSG) by reducing glutathione (GSH) [10]. The GPx eliminates lipid peroxidation levels by reducing MDA content. GPx is found in all mammalian cells and helps to prevent lipid peroxidation of cell membranes by consuming free peroxide in the cell.

Glutathione (GSH)

GSH is intracellular thiol based antioxidant present in milli molar concentrations in all living aerobic cells, but there is a wide variability in GSH content among organs depending on production of free radicals. GSH serves as a sensitive marker of oxidative insult and maintain cell integrity [11]. The cells ability to tolerate toxic effects of chemical depends on GSH content in cell. GSH scavenges ROS, as non- enzymatic antioxidant. It functions as a GPx substrate and scavenges free radicals, oxy-radicals and singlet oxygen produced during stress conditions.

Cd alters the activity of various antioxidant enzymes activity like SOD, CAT, XOD, GR, GPx, GST and GSH. Inhibition of electron transport chain becomes highly reduced, that might be dangerous *due* to the risk of molecular oxygen reduction and electrons are transferred directly that results in free molecular oxygen production and lead to enhanced formation of ROS [12].



Cd bioaccumulation causing inhibition of Antioxidants production, Zn and Vit-C supplementation reducing free radicals by antioxidant activity

Cd – Essential micronutrients interactions:

Several essential micronutrients like Zn, Se, Cu and Vit-C participate in controlling various metabolic and signaling pathways. Several *in vitro* studies suggested that there is a competition for transport mechanism in between Cd and nutritive elements like Zn in Japanese quails, Ca in fish, Zn, Cu and Fe in rats. Cd interacts strongly with active site of proteins where high concentrations of dietary nutrient elements such as Zn, Se, Ca, and Fe are taken through various food sources and reduce the rate of Cd absorption. Zn and Vit C are the most essential nutrients to mitigate Cd toxic effects; hence we made a small attempt to check the dose of Zinc and Vitamin C essential to elicit prominent effects in neutralizing Cd toxicity.

Zinc:

Zinc (Zn) is ubiquitous essential trace element with numerous functions in biological systems and plays a catalytic, inhibitory or accessory role in the regulatory enzymes. Zn promotes intermediary metabolism of enzymes, synthesis of DNA and RNA and maintains hormones homeostasis. Zn is a component of numerous enzymes and activates antioxidant defense system by preventing toxic effects of Cd [13]. Zinc is an active immunomodulator, and much more potent anti-oxidant than vitamin C.

Zinc is a constituent of GPx and GSH, that promotes GSH metabolism to reduce toxicity of Cd in all living cells. Zinc antagonizes the Cd prooxidant effects in cultured cells in relation to cellular uptake. This shows the protective capability of Zn in altering the Cd distribution in tissues and induces binding of the Cd-Zn complex to proteins, and reduce Cd toxicity [14].

Vitamin C:

Ascorbic acid (Vit- C) is a dietary antioxidant with prominent role in ameliorating the oxidative insult and promotes metabolism and detoxification of heavy metals. Vit-C acts as a reducing agent by donating electrons to various enzymatic and non-enzymatic reactions and acts as a chain-breaking antioxidant in lipid peroxidation. Vitamin C have essential role in various enzymatic reactions and decreases Cd uptake in intestinal segments of rat. Vit-C exists in two oxidized forms- semidehydroascorbic acid and dehydroascorbic acid, respectively, that undergoes reduction in presence of glutathione and NADPH-dependent enzymatic mechanisms [15]. The amount of semi-dehydroascorbate radical produced during reaction, is an index of the extent of damage in biological system by oxidative stress. Vit-C and GSH are prominent reducing agents, where GSH deficiency occurred due to heavy metal toxicity declines under ascorbate administration.

Due to un-reactive nature of semi-dehydro ascorbate radical it interacts with free radicals and terminates free radicals chain reaction produced under toxic stress [16]. It scavenges free radicals and also donates electrons to free radicals (hydroxyl radicals and super oxide radicals, and thereby inhibits their chain termination. It also effectively inhibits lipid peroxidation by scavenging ROS via rapid electron transfer. Vitamin C has the ability to quench the free radicals reactivity by donation of electrons to these unstable radicals and declines the oxidative insult in organisms.

Hence, an effort was made to study the Zinc and Vit- C interactions against Cd intoxication in the liver, kidney and testis of a mammalian model, rat.

Table. 1: Impact of Cadmium toxicity on Antioxidant enzyme status in Liver, Kidney and Testis

Animal model	Cadmium dosage	Antioxidant enzyme status	References
Male Rat Model	0.2 mg/kg $CdCl_2$	GR activity reduced in testis with increase in LPO	[17]
Male Albino Mice	0.35 mg/kg	GR and GST activities decreased in testis	[18]
Adult Male Wistar Rats	0.4 mg/kg BW	Decrease in GST, GPx and GR, vitamin C content in testis	[19]
Wistar Male Albino Rats	0.5mg/kg BW for 15 days	Decreased GSH with increase in LPO in testis	[20]
Male Rats	Cd 0.6 mg/kg for 30 days	Decreased Zinc content in liver and kidney of rat after cadmium intoxication	[21]
Adult Male Wistar Rats	1 or 5 mg Cd /kg water for 28 days	Caused increase in the Cd content and lipid peroxidation in liver and kidney	[22]

Female Wistar Rats	1 mg/kg Cd for 10 months	Zinc absorption decreased (unspecified tissue)	[23]
Male Sprague-Dawley Rats	1.67 mg/kg per day	Decreased CAT and GPx activity in testis	[24]
Male Kunming Mice	2 mg Cd/kg BW/day	Decreased GPx activity with increased MDA levels	[25]
Adult Male Wistar Rats	2 mg/kg $CdCl_2$	Elevated LPO and decreased GPx activity in testis	[26]
Wistar Albino Rats	2.5 mg/kg BW Cd	SOD, CAT and GPx declined in liver promoting liver damage	[27]
Female Wistar Rats	3 mg Cd/kg body weight for 13 consecutive days	Increased MDA in kidney Decreased GSH, GPx in kidney	[28]
Male Wistar Rats	4 mg/kg BW	Increased MDA, XOD with decrease in GPx, GR and GSH in Testis	[29]
Male Adult Swiss Albino Mice	5 mg/kg BW $CdCl_2$	Over production of MDA and XOD, with decline in glutathione and other glutathione dependent enzymes (GST, GPx, GR) in kidney.	[30]
Adult Male Albino Wistar Mice	5 mg/kg for 30 consecutive days (orally)	Liver GR, and GST were significantly reduced while XOD were increased significantly	[31]
Male Albino Rats	5 mg/kg $CdCl_2$	Increased MDA and Decreased SOD, CAT and GSH in liver and kidney	[32]
Swiss Male Mice	6.5 mg/kg for 7 days	Increase in LPO with decrease in GSH, GPx and GR in testis	[33]
Male Wistar Albino Rats	6.5mg/kg BW $CdCl_2$ for 5 days	Decrease in GPx, GR and GSH with increase in MDA in testis	[34]
Male Albino Wistar rats	20 mg/kg BW Cd	Decrease in SOD, CAT, GR, and GPx activity with concomitant increase in LPO in kidney	[35]
Wistar strain male albino rats	22.5 mg/kg BW $CdCl_2$ for 30 days	1. elevated LPO with GST and GPx activityin liver and kidney 2. LPO and XOD increased with concomitant decreased GST and GPx activity in liver, kidney and testis. 3. Significant increase in LPO levels, decreased activity GST and GPx in liver, kidney and testis. 4. Cd bioaccumulation increased with decrease in GR and GSH in liver, kidney and testis	1. [36] 2. [37] 3. [38] 4. [39]

Wistar Male Rats	$CdCl_2$ 50 mg/kg BW	Increase in LPO with decreased SOD, CAT, GSH and GPx activity in testis	[40]
Male Albino Rats	15ppm/day /30days	Increased MDA in the liver.	[41]
Wistar strain Female albino rats	50 ppm and 200 ppm	Reduces SOD, catalase, GPx and GST activity	[42]
Male Sprague-Dawley Rats	0.4 % w/v $CdCl_2$ in distilled water for 5 weeks	Lowered GSH with increase in LPO in testis	[43]
Adult Wistar Male Rats	$CdCl_2$ 40 mg/l, per os for 30 days	Decreased GPx activity in testis with increase in LPO	[44]
Wistar Albino Male Rats	200 mg/L $CdCl_2$	1. Increased LPO, reduction in GSH, CAT and GPx activities in liver 2. GSH levels and GSH/GSSG decreased, GSSG increased when compared to control animals in liver.	1. [45] 2. [46]

TABLE. 2: Protective effects of Zinc and Vitamin C supplementation in reducing Cd in toxicity.

Animal model	**Zinc / Vit C dosage**	**Changes in tissues**	**References**
Sprague-Dawley Rats	Vit-C 8.56 mg/kg for two weeks.	Improved GPx activity	[47]
Wistar Adult Male Albino Rats	Vit-C 30mg/kg BW orally for 30 days	Testis is prevented from Cd toxicity	[20]
Male Wistar Rats	Vit-C 40 mg/100 gm BW for 30 days	Glutathione activity improved in testis, sperm motility is improved.	[48]
Wistar Male Albino Rats	ZnCl2 20 ppm	SOD, CAT, GSH, GST and GPx activity improved in testis	[49]
Adult Albino Rats	Vit-C 100mg/kg-bw for 3 weeks	LPO reduced in liver tissue	[50]
Male Albino Rats	50 mg Zn/kg BW Vit-C 200 mg/kg of BW for 90 days	Liver, Kidney and Testis are protected upto some extent	[51]
Adult Male Wistar Rats	10 mg/L Vit-C in drinking water	Caused decrease in the Cd content, decreased lipid peroxidation in liver and kidney, showed protection cell death in testis	[22]

Wistar Albino Male Rats	Vit-C 1.5g/L of water for 30 days	Decreased LPO, with increased GSH, CAT and GPx activities in liver	[45]
Male Albino Rats	2.2 mg zinc/kg BW	Decreased LPO content in liver, kidney and testis. Prevented toxic effects on hepatic sinusoids in liver, cloudy swelling is reduced in kidney. Increased sperm count in testis	[52]
Wistar Male Rats	Zn 10 mg/kg	Prevented liver damage	[53]
Wistar Male Albino Rats	12 mg/kg BW Zinc for 30 days	1.Decrease in LPO content with increase in GST and GPx in liver and kidney 2.Decreased LPO content with increased activity levels of SOD, CAT, GPx, and GST in liver and kidney	1. [13] 2. [36]
Wistar Male Rats	Zn 2mg/kg BW	GSH, GPx, SOD, CAT, GR increased with decline in LPO levels in kidney	[54]
Male Kunming Mice	50 mg Zn/kg BW/day	Increased GPx activity with decrease in MDA levels	[25]
Male rats	Zinc (15 mg/kg) vitamin C (100 mg/kg BW)	LPO declined, SOD, CAT, GPx and GSH improved in Liver and kidney	[55]
Adult Wistar Male Rats	zinc 40 mg/l, per os for 30 days	Decreased GPx activity in testis is restored with reduction of LPO, DNA oxidation altered in gonads.	[44]
Male Wistar Albino Rats	500 mg/L ZnCl2	GSH and GSH/GSSG ratio increased and significant decrease in GSSG under Zn treated group of liver.	[46]
Wistar Male Albino Rats	12 mg/kg BW $ZnCl_2$ +200 mg/kg Vit-C for 30 days	1. LPO and XOD decreased with concomitant increase in GST and GPx in liver, kidney and testis. 2. Significant decrease in LPO levels, with increased activity GST and GPx in liver, kidney and testis. 3. increase in GR and GSH in liver, kidney and testis	1. [37] 2. [38] 3. [39]
Adult Male Mice	zinc and vitamin C (200 mg/kg and 300 mg/kg, respectively)	Improved antioxidant status by increasing zinc concentration in testis vitamin C supplementation and reduced oxidative stress in testis	[56]

Conclusion: Oxidative stress markers produced under cadmium induced toxic effects is noteworthy mechanism for monitoring negative impacts of Cadmium. Many studies have shown that mitigating LPO levels with nutrients supplementation preserved architecture of different tissues suggested that it is a justifiable mechanism for the conferment of the protective roles of Zinc and Vitamin-C against acute

cadmium induced toxicity. Therefore, the present observations may provide a scientifc justification for the increased usage of nutritive elements in our diets that have the ability to boost and elicit body response against toxic induced effects and improves anti-oxidant defense system.

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