Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

Heavy Metal Havoc: Deciphering the Cellular Mechanisms of Cadmium Toxicity

[1] Hindol Chakraborty, [2] Sonjit Das*, [3] Abhijit Ghosh, [4] Koushik Jana, [5] Suman Sahu, [6] Biplab Debnath

[1] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, West Bengal, India.
[2] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, West Bengal, India.
[3] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, West Bengal, India.
[4] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, West Bengal, India.
[5] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, West Bengal, India.
[6] Department of Pharmaceutical Chemistry, Bharat Technology, Uluberia, Howrah, West Bengal, India.

(Received: 02 September 2023 Revised: 14 October Accepted: 07 November)

KEYWORDS

Cadmium, DMTs, ER, Oxidative stress:

ABSTRACT:

Cadmium (Cd), a ubiquitous heavy metal pollutant, poses a significant threat to human health and the environment. The primary contributors to Cd pollution include drinking water, tainted food products, cigarette smoking, mineral extraction and processing, industrial applications, and the widespread utilization of Cd batteries. Cd enters cells primarily through passive diffusion and active transport mechanisms involving divalent metal transporters (DMTs). Once inside the cell, Cd accumulates in various sub-cellular compartments, including the cytoplasm, endoplasmic reticulum (ER), mitochondria, and nucleus. The way Cd is distributed within cells holds significant importance in influencing the harmful effects of Cd exposure. Cd-triggered toxicity primarily stems from oxidative stress, due to the formation of oxygen and nitrogen derived free radicals such H2O2, HO•, O2•−, RO•, ROO•, NO•, NO2• and ROO•. This oxidative stress can result in lipid peroxidation, damage to proteins, and fragmentations and alterations in DNA strands, thereby contributing to cellular dysfunction and the process of apoptosis. Cd can also modulate various signalling pathways, including MAPKs, NF-κB, JNK and p53, further exacerbating cellular damage.

1. Introduction

Chemically, Cadmium (Cd) is an element of atomic number 48, having a silvery-white appearance. According to Flora et al. [1]., industrial pollution increases the consumption and production of heavy metals like Cd as well as global metal pollution. Globally, approximately 13,000 tons of Cd is produced each year. The primary contributors to Cd pollution are diverse and include sources such as drinking water, tainted food products, cigarette smoking, mineral extraction and processing, industrial applications, and the widespread utilization of Cd batteries. **(Figure 1**) [2].

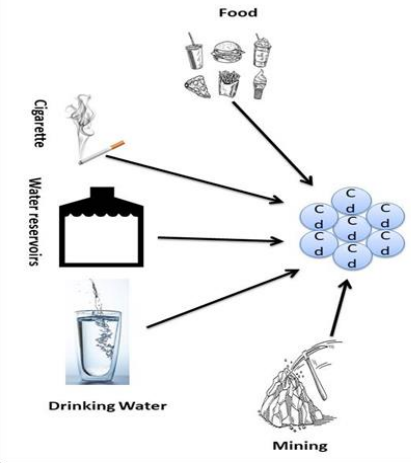

Fig 1: Source of cadmium

While environmental discharges have notably reduced in leading-most developed states, Cd remains a health concern for industrial workers and inhabitants residing in regions marked by high pollution levels [3,4,5]. On

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

account of its lengthy biological half-life, Cd accumulation throughout a lifetime is its most hazardous feature [6]. In 1858, for the first time, an author named Sovet reported instances of acute gastrointestinal symptoms and delayed respiratory effects in individuals who utilized Cd carbonate powder as a polishing agent [7]. Furthermore, Cd toxicity was confirmed by Stephens [8]. Likewise, distinct clinical indications and structural alterations in the organs of various vertebrates, encompassing birds and dogs, were noted in various experimental investigations [9]; [10]. In a separate experiment, cats exposed to Cd oxide fumes exhibited significant lung impairment and observed histological alterations in the liver and kidneys [11, 12]. reported lungs injury in Cd-exposed workers [12]. In the year 1940, another research investigation documented immediate gastrointestinal impacts like vomiting, and diarrhoea in individuals who had consumed food and beverages contaminated with Cd. Various pathological disorders, including osteomalacia, proteinuria, and emphysema, were identified among individuals exposed to Cd in occupational settings [13,14]. In the 1960s, the itaiitai illness in Japanese women, caused by Cd-contaminated rice and water, highlighted its toxicity [15]. Valko et al. reported Cd induced toxicological effect like osteoporosis, anemia, non-hypertrophic emphysema, irreversible renal tubular injury, eosinophilia, anosmia and chronic rhinitis. Cd has been reported to induce cancers like lung, prostate, pancreas, and kidney [16]. Current research on Cd has been primarily focused on understanding its toxic impact on various organs and unravelling the molecular mechanisms underlying this toxicity. This review predominantly examines Cd's toxicity in diverse organs and its role in inducing apoptosis, autophagy, genotoxicity, and other processes through oxidative stress.

2. Toxicity Induced by Cd in Various Tissues

Cd is a pollutant that has drawn a lot of attention because it has been shown to have harmful effects on a variety of tissues, including the liver, respiratory tract, testes, urinary tract, prostate, skeletal system, cardiovascular tract, gastrointestinal (GI) tract, and central nervous system (CNS) [17,18]. This toxicity affects cells across numerous systems and tissues, as depicted in **Figure 2**.

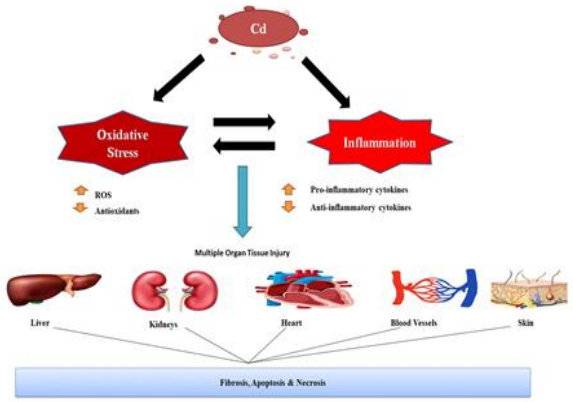

Fig 2: Graph illustrating the multi-organ tissue injury caused by cadmium poisoning

2.1. Cd induced Kidney damage

Cd exposure induces significant kidney damage by primarily affecting the proximal tubules responsible for nutrient reabsorption and waste filtration [19]. Cd disrupts mineral reabsorption, particularly calcium, magnesium, and phosphate, leading to electrolyte imbalances. Additionally, glomerular impairment causes proteinuria, with leaked proteins in the urine. Prolonged exposure results in degeneration, atrophy, and fibrosis of renal tubular cells [19]. This cumulative impact leads to Cd-induced nephropathy characterized by renal tissue accumulation [20]. Efforts to limit Cd exposure are crucial to prevent these detrimental kidney effects and associated disorders.

2.2. Effects of Cd in reproductive health

Cd is known to have detrimental effects on reproductive health, affecting both males and females. Cd exposure has been linked to decreased sperm quality, including reduced sperm count, motility, and viability. It can also disrupt the hormonal balance in males, affecting testosterone production and leading to hormonal imbalances [21]. In females, Cd exposure can lead to disruptions in the menstrual cycle and impairments in ovarian function. It may also increase the risk of adverse pregnancy outcomes, such as preterm birth and low birth weight [21]. Prenatal exposure to Cd is associated with developmental abnormalities, impaired growth, and compromised cognitive function in children [22].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

2.3. Effects of Cd in liver

The liver plays a crucial role in detoxification and metabolic processes, making it susceptible to the harmful impacts of Cd. Chronic exposure to Cd has been associated with hepatotoxicity. Cd can induce inflammation, oxidative stress, and cellular damage in the liver tissue, leading to impaired liver function [23]. Prolonged Cd exposure can result in the accumulation of scar tissue in the liver, a condition known as fibrosis. This can progress to cirrhosis [23]. Chronic exposure to high levels of Cd has been linked to an increased risk of liver cancer in certain occupational groups (IARC, 2012). Cd disrupts liver metabolism, impacting energy production, lipid processing, and detoxification. These disturbances compromise liver function and overall well-being [23].

2.4. Effects of Cd on bone

Cd, a highly toxic heavy metal, can have profound effects on bone health due to its ability to accumulate in bone tissue. Chronic exposure to Cd, often through contaminated food, water, and inhaled air, can lead to detrimental impacts on bones. Prolonged exposure can lead to a decrease in bone density, weakening the bone structure and increasing the risk of fractures. This condition is often referred to as Cd-induced osteoporosis [24]. Itai-itai disease arises from extended high-dose Cd exposure, predominantly affecting women. It manifests as significant tubular and glomerular dysfunction, accompanied by widespread osteomalacia and osteoporosis, resulting in frequent bone fracture [25]. Cd exposure in growth phases like childhood and adolescence can hinder bone development, causing reduced length. It interferes with calcium absorption and mineralization, impairing bone growth [24]. Cd's harm to kidneys indirectly affects bones via renal osteodystrophy. Kidney damage by Cd disrupts mineral balance, causing bone abnormalities. [21] Long-term Cd exposure, leading to diminished bone density and compromised structure, heightens the fracture risk, particularly in affected individuals [26].

2.5. Effects of Cd on lung

Cd can have adverse effects on the respiratory tract when individuals are exposed to it through inhalation of contaminated air or particulate matter. Inhalation of Cd-containing particles can lead to lung damage including inflammation, irritation, and the development of respiratory diseases. Chronic exposure can contribute to the development of conditions such as chronic obstructive pulmonary disease (COPD) and pneumoconiosis [27]. Prolonged Cd exposure heightens lung cancer risk by accumulating the metal through inhalation, promoting malignancy [28]. Long-term exposure also induces fibrosis, scarring lung tissue and impairing bronchial function [27]. Immune suppression in the respiratory tract due to Cd raises vulnerability to respiratory infections and diseases [29].

2.6. Effects of Cd on gastrointestinal tract

Cd poses risks to the gastrointestinal tract (GI) tract through food and water contamination. Cd leads to GI irritation, causing symptoms like nausea and abdominal pain [19]. Chronic exposure disrupts vital nutrient absorption (calcium, iron, zinc) in the intestines [30]. Cd induces GI inflammation, potentially causing long-term health issues [31]. Prolonged exposure links to higher gastrointestinal cancer risks, like stomach and colorectal cancers [28].

2.7. Effects of Cd on central nervous system

Cd can have adverse effects on the central nervous system (CNS) when individuals are exposed to it over time. The CNS, which includes the brain and spinal cord, is sensitive to the harmful impacts of Cd due to its ability to accumulate in neural tissues. Chronic Cd exposure has been associated with neurotoxic effects, including cognitive impairments, memory deficits, and behavioural changes [32]. Cd can disrupt the balance of neurotransmitters, which are essential for proper communication between nerve cells. This disruption can lead to changes in mood, behaviour, and cognitive function [33]. Cd induces oxidative stress in neural tissues, leading to damage to neurons and other components of the CNS. This oxidative stress can contribute to neurodegenerative processes [34]. Prolonged Cd exposure has been associated with an increased risk of neurological disorders, including Parkinson's disease and Alzheimer's disease [35].

3. Cd-Induced Oxidative Stress

Oxidative stress is the imbalance between the production of reactive oxygen species (ROS) and nitrogen species (RNS) and the ability of the body's

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

antioxidant defences to neutralize them. Oxidative stress is reported to cause significant cellular disturbances [36,37]. ROS include hydrogen peroxide (H2O2), hydroxyl radical (HO•), superoxide anions (O2•−), peroxyl (RO•), and alkoxyl radicals (ROO•), while RNS consist of nitric oxide radical (NO•), nitrogen dioxide radical (NO2•), and peroxynitrite (ONOO) [38.39]. Oxidative free radicals have been documented as initiators of various redox-specific pathological signal transduction processes, thus playing a role in multiple pathological occurrences [40]. Conversely, the body possesses an intrinsic redox defence mechanism that manages cellular oxygen metabolism and counteracts oxidative stress by transferring electrons to ROS and RNS [40]. Antioxidant enzymes, namely superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GR), glutathione S-transferase (GST), glutathione (GSH) etc. act as counteract oxidative stress as shown in Figure 4 [40]. SOD converts superoxide anions into H2O2 and oxygen molecule [41,42,43,44]. CAT is a crucial enzyme that plays a central role in neutralizing H2O2 by converting it into water (H2O) and oxygen. One of the key functions of GSTs is to catalyze the conjugation of GSH with various electrophilic compounds

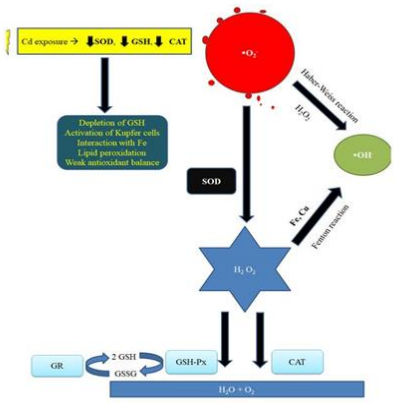

Figure 3

Fig 3: The image illustrates the biological procedures required for the preservation of redox balance. Superoxide dismutase (SOD) transforms superoxide anions into hydrogen peroxide, regardless of whether they originate internally or externally. By catalase (CAT) or glutathione peroxidase (GSH-Px), hydrogen peroxide is then converted into water and molecule oxygen. Glutathione reductase (GR) and GSH-Px collaborate to uphold the balance between glutathione (GSH) and its reduced counterpart (GSSG). The presence of cadmium, however, interferes with these processes, lowering levels of SOD, GSH, and CAT. This causes the production and accumulation of dangerous OH radicals through the Haber-Weiss and Fenton reactions, which ultimately results in oxidative stress.

[40]. GPx reduces peroxides and in turn converts GSH to glutathione disulphide (GSSG), while GR promotes the reduction of GSSG into GSH [45]. GPx is responsible for reducing H2O2 and other peroxides using GSH as a cofactor. During this process, GSH is oxidized to form GSSG, and GR is responsible for the reduction of GSSG back to its active form, GSH. NADPH plays significant role in these reduction phenomena [45] In normal conditions GSH is present and counteracts oxidative free radicals. It undergoes conversion to GSSG while maintaining a balance. The GSH/GSSG ratio signifies cellular redox status. GR uses NADPH to efficiently reduce GSSG back to GSH [45,46]. Cd stands out as one of the most highly toxic heavy metals, and its detrimental effects on organisms are diverse and multifaceted. It has high affinity toward biological structure containing –SH groups and disulfide –S–S– groups, causing disturbance of their functions [47]. Upon exposure, Cd enters the bloodstream either via erythrocytes or albumin, undergoes hepatic conjugation, and binds with metallothionein (MT) to form Cd-MT. This compound is subsequently filtered by the glomerulus, reabsorbed in proximal and distal tubules, and disintegrated within lysosomes to release Cd into tubular cells. This released Cd detrimentally affects the kidneys and contributes to oxidative stress build-up. Additionally, Cd can displace metals like iron and copper from MT or deplete GSH, resulting in the generation of ROS [43]. The abundant intracellular molecule GSH is vulnerable to binding with free Cd ions, disrupting the redox equilibrium by depleting the pool of reduced GSH and establishing a pro-oxidative environment. This disruption weakens antioxidant mechanisms, significantly amplifying the toxicity of Cd across different organs. Although Cd doesn't directly trigger ROS production, it indirectly induces the formation of free radicals [43,48]. The response to oxidative stress following Cd exposure

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

varies based on its duration. Acute exposure leads to the generation of free radicals such as superoxide anions, H2O2, hydroxyl radicals, and lipid radicals. The creation of these Cd-induced radicals is influenced by factors like GSH depletion, activation of Kupffer cells, inflammation, and the involvement of iron in Fenton reactions [49,50,51]. In chronic exposure scenarios with environmentally relevant low doses, there's a hypothesis that adaptive mechanisms come into play to counter Cd-induced ROS and oxidative stress. These mechanisms aim to mitigate oxidative damage, but when ROS production overwhelms the antioxidant defense system, lipid peroxidation and oxidative injury become more pronounced [46]. Several studies reported production of nitric oxide (NO), superoxide radicals, H2O2, and hydroxyl radicals upon exposure of Cd. Additionally, downregulation of GSH, SOD, CAT, GPx, GST, GR were also reported upon exposure of cadmium in different in experimental models [52,53].

4. Cd-Induced Inflammation

Inflammation and oxidative stress are correlated [54]. Increased generation of oxidative free radicals initiates inflammation by triggering NF-κB activation, thereby supporting subsequent expression of inflammatory genes, activation of inflammasomes, and release of cytokines [54]. Mitochondrial ROS play a key role in promoting inflammation by initiating the release of cytokines, activating NF-κB through the inositol 1,4,5-trisphosphate receptor Ca2+signaling pathway, triggering activator protein 1 (AP-1) activation, and influencing subsequent endothelial mechanisms [53,55,56,57]. The activation of NF-κB can support the initiation, differentiation, viability, and functional capabilities of both inflammatory T cells and innate immune cells. NF-κB-driven activation of macrophages leads to the release of diverse cytokines and chemokines [58]. NF-κB directly activated M1 macrophages, leading to the triggering of numerous inflammatory genes, including tumour necrosis factor α (TNF-α), IL-1β, IL-6, IL-12p40, and cyclooxygenase-2 [58]. NF-κB facilitates the differentiation of CD4+ T-helper cells by regulating TCR signaling, and it also operates within innate immune cells to facilitate the initiation of cytokines like IL-12 and IL-21 [58]. Inside the nucleus, NF-κB supports NLR3, pro-IL-1β, and pro-IL-18, pivotal elements in triggering the inflammasome's activation [58]. As a whole, oxidative free radicals play a substantial role in inflammation through their involvement in NF-κB signalling. The link between Cd exposure and inflammation is well-established, shedding light on the intricate interplay between toxic metal exposure and immune responses. Cd exposure activates proinflammatory cytokine IL-8 and main mitogen-activated protein kinases (MAPKs) (i.e., p38, JNK, and Erk1/2) in lung epithelial cells [59]. Studies have shown that Cd at micro-molar levels triggers the activation of multiple intracellular signaling pathways, particularly NF-κB and AP-1, within immune cells [60]. This activation leads to the upregulation of inflammation-related markers and agents. Cd has the potential to initiate both immediate and prolonged inflammatory reactions in organs such as the heart, liver, kidneys, lungs, and reproductive system. These responses could potentially result in tissue harm or even a systemic inflammatory reaction [60].

5. Genotoxicity Effect of Cd

Genotoxicity refers to the ability of certain agents to cause damage to the genetic material within a cell, leading to mutations or other genetic alterations. These agents, known as genotoxic agents, can include various chemicals, radiation, and some types of pharmaceuticals. Genotoxicity is a crucial concern in toxicology and risk assessment, as it can lead to long-term health implications, including cancer [61]. Cd exposure led to the induction of DNA single-strand damage in cultured liver cells, as demonstrated by [62]. Similarly, the exposure of peripheral blood lymphocytes to Cd resulted in an increased frequency of chromosomal aberrations, formation of micronuclei, and occurrences of sister chromatid exchanges, as observed in the study conducted by Rozgaj et al. & Ünyayar et al. [63,64] found that elevated levels of Cd can lead to increased lipid peroxidation, which in turn triggers oxidative stress. This oxidative stress is believed to play a role in the genetic and cellular damage caused by Cd ions. Another research study documented that exposure to Cd results in foetal deformities, such as exencephaly, micrognathia, ablephary, microphthalmia, and clubfoot. Additionally, there was a notable rise in the levels of micronucleated polychromatic erythrocytes (MNPE) and micronucleated normochromatic erythrocytes (MNNE) within the blood cells of both pregnant mice and their foetuses [65]. Chromosomal anomalies, including

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

disruptions (PM 2), end associations (PM 3), centric fusions (PM 4), early centromere separation (PM 5), and C-mitosis (PM), were witnessed in the group of fish exposed to Cd treatment. Moreover, variations in the protein composition were identified within the Cd-exposed group [66]. Cd has been documented to trigger chromosomal damage in both Chinese hamster cells and cultured human lymphocytes, in addition to being observed in in vivo experiments [63]. In 2010, Schwerdtle et al.,[67] documented the capability of Cd to generally inhibit nucleotide excision repair in A549 cells. According to Aimola et al. [68], Cd is known to have an impact on cellular functions like DNA synthesis, apoptosis, cell division, and proliferation. Another effect of Cd may be the prevention of DNA repair [69,70], which would make it a co-genotoxic chemical and a contributor to genomic instability (a condition known to cause cancer). Additionally, some indirect explanations for Cd carcinogenesis are being put forth. These include DNA methylation changes, oxidative stress, dysregulated gene expression, and proto-oncogene activation [71,72,73]. In another experiment, Cd-oxide nanoparticles revealed downregulation of endotoxin levels and concentration-dependent cytotoxicity in lymphoblast cell line (TK6) and liver cell line (HepG2) [74].

6. Cd and Apoptosis

Numerous morphological and biochemical studies have confirmed that cell death resulting from Cd intoxication occurs through apoptosis [75,76,77,78,79] Cd induces apoptosis through various pathways, covering all phases from the initiation to the removal of apoptotic cell fragments. This toxic heavy metal affects both intrinsic & extrinsic apoptotic regulatory mechanisms.When specific signaling molecules like Fas-ligand (FasL) and tumor TNF-α attach to death receptors such as CD95/APO-1 (Fas) and TNF receptors, they initiate what is known as the extrinsic pathway. In particular, Cd has been observed to modify the CD95/APO-1 (Fas)/FasLsignaling pathway, particularly in nerve cells, leading to an increase in inflammatory indicators like TNF-α and NF-kB in cells related to kidney function [77, 80]. This sequence of events triggers the activation of caspase-8, which subsequently triggers caspase-3, initiating the process of apoptosis [77]. The intrinsic pathway, often referred to as the mitochondrial apoptotic pathway, involves the B-cell lymphoma-2 (Bcl-2) protein family [53,57,77]. According to Ghajari et al. [81]., Cd suppresses the production of the anti-apoptotic protein Bcl-2 while elevating the production of the pro-apoptotic protein Bax. When there is an alteration in the Bcl-2/Bax ratio, it results in the release of cytochrome-c from the mitochondria and calcium from the endoplasmic reticulum into the cytoplasm [75,77,81] This, in turn, triggers the activation of caspase-9, which subsequently activates caspase-3. Number of research reported the Cd impact on both the intrinsic and extrinsic apoptotic pathways [57,75,79], reported upregulation in the expressions of proteins involved in death receptor-mediated apoptosis, such as FAS, t-Bid, and cleaved caspase 8 in Cd treated mouse proximal tubular epithelial cells. Furthermore, the release of cytochrome C into the cytosol from mitochondria, upregulation of Apaf-1, and cleavages of caspases 9 and 3 were observed in the Cd exposed mice [57]. Cd has been reported to activate Bad expression in mitochondria, suppress Bcl-2 expression, and activate caspases caspases3 and 9 in both in vitro and in vivo studies [53]. The initiation of caspase activity is seen as a principal mechanism through which Cd triggers apoptosis [53,75,79,80,82] Research indicates that the reduction in the permeability of the mitochondrial membrane and the heightened activity of caspase-3 and caspase-9 play a direct role in programmed cell death within hepatic cells as a consequence of exposure to Cd. This has been highlighted in studies conducted by Das et al and Wallace et al. [53,83] Furthermore, Cd's induction of apoptosis is linked to its impact on protein kinases, specifically those belonging to the MAPK family. This includes the amplification of p38 MAPK by Cd, a process that triggers the expression of genes associated with inflammation and apoptosis. Ultimately, these changes contribute to the development of conditions like tubular necrosis and nephrotoxicity in rat models [80]. An investigation focusing on TM3 Leydig cells have revealed that Cd's apoptotic effects are mediated through the generation of ROS and an escalated level of phosphorylation, primarily via the JNK pathway. This sequence of events leads to the decrease of the anti-apoptotic protein Bcl-2, setting off a downstream cascade that activates caspase-3 and ultimately leads to cellular demise [78].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

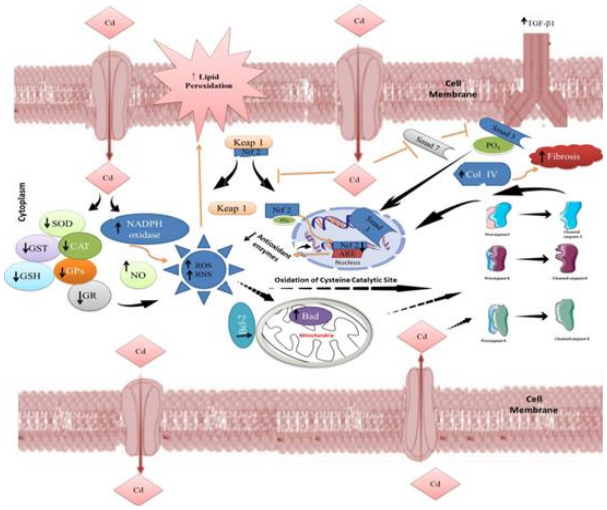

Figure 4

Fig4. Schematic overview of probable mechanism of cadmium-mediated renal toxicity. The black arrows (→) indicate down-steam cellular events. The red lines (⊥) indicate the activities restricted

7. Cd and Autophagy

Autophagy is a damaged organelles and macromolecules cleansing natural phenomena [84]. In this pathway, phagophores are formed first, followed by the formation of autophagosomes through the internalization of damaged components [84]. The fusion of autophagosomes with lysosomes forms a structure called an autolysosome. Within the autolysosome, the enzymes from the lysosome break down the sequestered material into smaller molecules that can be transported back into the cell for reuse. This process is crucial for maintaining cellular homeostasis, eliminating damaged organelles, and providing the cell with a source of nutrients during periods of stress or nutrient scarcity [84]. Several studies reported the importance of autophagy in protecting the kidneys against kidney diseases in AKI models [85]. Kaushal and Shah reported that the loss of a key autophagy protein resulted in decreased renal function, elevated levels of p62, and increased oxidative stress [85]. Liu et al.reported cytosolic Ca2+-dependent autophagy inhibition in rat proximal tubular cells. Exposure to cadmium inhibited autophagosome-lysosome fusion and thus blocked the degradation of autophagosom [58]. In a different study, rat proximal tubular cells exposed to Cd showed accumulation of the autophagosome, lysosomalalkalinization, and impairment of lysosomal degradation, as well as lysosomal membrane permeabilization [78]. Additionally, it was reported that Cd stimulates Nrf2 nuclear translocation and subsequently elevates the expression of Nrf2 downstream targets in the proximal tubular cells [78,86]. found that BRD4 functions as a transcriptional repressor during Cd exposure, mediating lysosomal dysfunction, autophagy blockade, and oxidative stress [86]. Ferroptosis, an emerging form of regulated cell death, is defined by the generation of reactive oxygen species resulting from the accumulation of iron and lipid peroxidation [87]. Moreover, a research investigation indicated that the presence of autophagy is essential for the occurrence of Cd-triggered ferroptosis due to autophagy suppression. Additionally, it was noted that the disruption of iron homeostasis through ferritinophagy played a role in facilitating Cd-induced ferroptosis [88]. An experiment showed that the upregulation of HO-1 due to Cd exposure is governed by PKC-δ, p-Ser GSK3αβ, and PKB/Akt. These elements curb autophagic cell death while inducing apoptosis to a limited extent in NRK52E cells [89]. Numerous studies have shown that osteoblasts, osteocytes, and osteoclasts in bone tissue depend on autophagy for their survival, differentiation, and activity [90]. Liu et al. reported an increase in the Bax/Bcl-2 ratio, activation of poly (ADP-ribose) polymerase (PARP), and nuclear condensation in cells exposed to cadmium. Furthermore, the cells treated with cadmium demonstrated the induction of beclin 1, autophagy gene 5 (Atg5), and the expression of microtubule-associated protein 1 light chain 3 (LC3). Furthermore, an increase in the Bax/Bcl-2 ratio, activation of poly (ADP-ribose) polymerase (PARP), and nuclear condensation were noted in cells exposed to cadmium. These findings suggested that cadmium's stimulation of apoptotic cell death coincided with the initiation of autophagy in primary rat osteoblasts [91]. Ran et al. reported the formation of autophagosomes, LC3-II lipidation, and p62 downregulation, and increased autophagic flux in the osteoblast. According to reports, Cd increases AMPK phosphorylation through TAK1 activation, which in turn encourages ULK1 phosphorylation at S317 to promote autophagy. He observed decrease in the phosphorylation of mTORC1, S6K1, 4E-BP1, S6, ULK1S555, and ULK1S757 indicates a suppression of

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

mTORC1 activity. When mTORC1 is inactive, it inhibits the activation of ULK1 by modifying ULK1 at SerS555 and Ser757 through phosphorylation [92]. Cadmium has been reported to induce neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) in various experimental models [93,94,95] Exposure to cadmium led to an elevated level of senescence in neuronal cells, and this effect was further exacerbated by the use of 3-MA or the suppression of Atg5. Cadmium has been documented to increase the expression of ER stress regulatory proteins like Bip, chop, eIf2α, and ATF4, consequently activating autophagy, as indicated by the heightened expression of LC3. Moreover, the exposure to cadmium resulted in the augmentation of GATA4 expression within PC12 cells [42]. In a study, Tang and his colleagues reported a decrease in the total antioxidant capacity (T-AOC) and an increase in methane dicarboxylic aldehyde (MDA) levels upon exposure to cadmium in brain tissues. Additionally, cadmium has been shown to enhance the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), the expression of light chain 3II (LC-3II), and the levels of sequestosome 1 (SQSTM-1/p62) in rat brains [96]. Upon exposure to Cd, cellular LC3-II protein levels exhibited an increase, accompanied by a distinct punctate pattern in the distribution of endogenous LC3-II, and a noticeable rise in the presence of numerous autophagosomes. These observations collectively indicate a substantial induction of autophagy due to the influence of Cd [97]. Exposure to cadmium (Cd) disrupts the process of autophagy in nerve cells, which eventually leads to programmed cell death known as apoptosis. This harmful effect is brought about by the activation of a signaling pathway called JNK, which is triggered by an increase in calcium ions (Ca2+) within the cells and thus it can be concluded that by controlling the levels of intracellular calcium and modulating the activity of the JNK pathway, it might be possible to improve autophagy and counteract the neurotoxic effects of Cd exposure [98]. Zhang et al., documented that exposure to cadmium (Cd) caused a rise in autophagosomes along with higher levels of LC3-II and p62 in both PC12 cells and primary neurons. The accumulation of autophagosomes was linked to apoptosis and occurred due to Cd-induced impairment of the autophagic process, which was connected to the Aktsignaling pathway. This study emphasizes that targeting Akt to enhance the flow of autophagy holds potential as a viable approach to mitigate the neurotoxic effects of Cd and the subsequent development of neurodegenerative disorders [99].

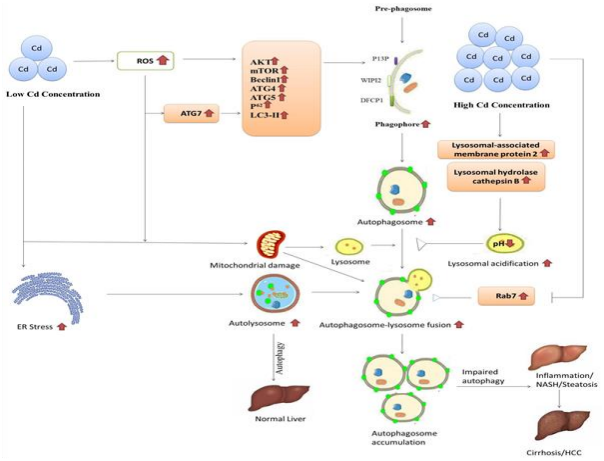

Figure 5

Fig5. A schematic model represents a dual role of Cd in autophagy regulation in the liver. Low concentrations of Cd exposure increase ER and oxidative stress in the liver and the expression of autophagy regulatory components such as ATG7, ATG4, p62, LC3B, and Beclin-1, leading to increased function autophagy and reduced Cd-mediated liver toxicity. In contrast, at higher concentrations, there is Cd-induced defective autophagy by increasing lysosomal acidification and by blocking autophagosome-lysosome fusion, leading to increased liver steatosis, NAFLD, and HCC

8. Cd Influencing Bioelements

A pivotal mechanism underlying Cd toxicity involves its interaction with bioelements at sites where these elements fulfil their physiological roles. Cd competes with bioelements such as zinc in CuZnSOD and Zn finger proteins, manganese in MnSOD, iron in CAT, and selenium in GSH-Px. This competition displaces the bioelement and renders the corresponding enzyme non-functional [100]. However, studies have demonstrated that a heightened intake of zinc, selenium, or magnesium during Cd exposure can enhance the bioelement status and improve the performance of antioxidant enzymes like CuZnSOD, total SOD, and GSH-Px, as observed in work by [101,102].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

Additionally, the intake of magnesium, a cofactor for GSH synthase, significantly mitigates Cd's impact on GSH, as outlined by [103]. Exposure to Cd can disrupt the equilibrium of crucial bioelements including iron, calcium, copper, magnesium, manganese, selenium, zinc and others. Conversely, an increased intake of specific bioelements can impact the fate of Cd within the body and mitigate its harmful consequences [103,104,105 ,106,107,108]. Cd interacts with bio elements that share similar chemical and physical attributes during various stages of its toxicokinetic, including absorption, distribution, elimination, and sites where essential elements carry out their physiological functions. This interaction arises due to a competition for binding sites on transport proteins that facilitate their entry into cells [109]. While certain bio elements might experience deficiencies, while Cd's absorption and accumulation increase, leading to distinct toxic impacts. An instance is Cd's competition with calcium for hepatocyte transport proteins and its competition with bioelements like zinc and manganese at the level of ZIP family transport proteins in the gastrointestinal tract and kidneys [110]. Research has indicated that elevated consumption of bioelements can curtail Cd absorption and alleviate its detrimental consequences [106,108,111]

9. Conclusion

Cd-induced toxicity involves a complex interplay of molecular mechanisms. Exposure to Cd has been reported to lead to the generation of ROS, which in turn has led to the downregulation of endogenous antioxidants enzymes such as SOD, catalase, GSH-Px, GST, and GR [53,57]. This reduction in the scavenging activity of antioxidant enzymes results altered mitochondrial functions by interacting with mitochondrial and cellular components such as DNA, proteins, and lipids [112]. It is evident from this studies that Cd, a prevalent environmental pollutant, disrupts vital cellular processes, ultimately leading to detrimental health outcomes. The elucidation of these mechanisms is pivotal for understanding how Cd-induced toxicity impacts various organ systems and contributes to diseases such as cancer, kidney dysfunction, liver, lung, GI tract, and bone disorders. Cd-induced elevation of intracellular calcium contributes to ROS production, initiating cell apoptosis through the intricate crosstalk between calcium signaling and ROS in physiological and pathophysiological contexts [113]. The impact of Cd on autophagy can either lead to its induction or disruption, likely influenced by gene expression. Autophagy, in response to Cd exposure, can neither suppress nor activate apoptosis, while both processes could be triggered by the accumulation of ROS. It is challenging, if it is not impossible, to make a general assumption about the dominant pathway responsible for a specific toxic effect caused by Cd. It is conceivable that various factors dictate which mechanisms are involved and hold prominence in the development of particular toxic effects induced by Cd. Given the widespread presence of Cd in the environment and its intricate toxicity, further research is needed in the future. Attention should be paid to factors such as dosage, exposure route, and duration, as well as the specific cell and tissue types in which Cd's toxic effects manifest. These investigations will contribute to a deeper understanding of the molecular mechanisms underlying Cd toxicity.Continued efforts in this field will not only deepen our understanding of heavy metal havoc at the cellular level but also pave the way for innovative solutions to minimize the devastating consequences of Cd exposure.

Acknowledgements

We acknowledge Mr. Hiranmoy Bhattacharya, Assistant Professor, Bharat Technology for his contribution in formulating the manuscript. We acknowledge Bharat Technology, West Bengal, India for providing us with necessary means to formulate the review.

References:

1. Flora, S. J. S.; Mittal, M.; Mehta, A. Heavy Metal Induced Oxidative Stress & Its Possible Reversal by Chelation Therapy. Indian J. Med. Res. 2008, 128 (4), 501–523.
2. Niture, S.; Lin, M.; Qi, Q.; Moore, J. T.; Levine, K. E.; Fernando, R. A.; Kumar, D. Role of Autophagy in Cadmium-Induced Hepatotoxicity and Liver Diseases. J. Toxicol. 2021, 2021, 9564297. https://doi.org/10.1155/2021/9564297.
3. Govil, P. K.; Sorlie, J. E.; Murthy, N. N.; Sujatha, D.; Reddy, G. L. N.; Rudolph-Lund, K.; Krishna, A. K.; Rama Mohan, K. Soil Contamination of Heavy Metals in the Katedan Industrial

Development Area, Hyderabad, India. Environ. Monit. Assess. 2008, 140 (1–3), 313–323. https://doi.org/10.1007/s10661-007-9869-x.

4. Sun, L.-N.; Zhang, Y.-H.; Sun, T.-H.; Gong, Z.-Q.; Lin, X.; Li, H.-B. Temporal-Spatial Distribution and Variability of Cadmium Contamination in Soils in Shenyang Zhangshi Irrigation Area, China. J. Environ. Sci. (China) 2006, 18 (6), 1241–1246. https://doi.org/10.1016/s1001-0742(06)60069-7.
5. Bernard, A. Cadmium & Its Adverse Effects on Human Health. Indian J. Med. Res. 2008, 128 (4), 557–564.
6. Shimada, H.; Yasutake, A.; Hirashima, T.; Takamure, Y.; Kitano, T.; Waalkes, M. P.; Imamura, Y. Strain Difference of Cadmium Accumulation by Liver Slices of Inbred Wistar-Imamichi and Fischer 344 Rats. Toxicol. In Vitro 2008, 22 (2), 338–343. https://doi.org/10.1016/j.tiv.2007.09.013.
7. Sovet, U. Poisoning Caused by Powder Used in the Cleaning of Silver. PresseMedicale 1958, 10 (9), 69–70.
8. Stephens, GA. Cadmium Poisoning. Public Health Rep. 1942, 57 (17), 601–612.
9. Alsberg, C. L.; Schwartze, E. W. Pharmacological Action of Cadmium. Journal of Pharmacology and Experimental Therapeutics 1919, 13, 504–505.
10. Schwartze, E. W.; Alsberg, C. L. Studies on the pharmacology of cadmium and zinc with particular reference to emesis1. The Journal of Pharmacology and Experimental Therapeutics 1923, 21.
11. Prodan, L. Cadmium Poisoning: II. Experimental Cadmium Poisoning. Journal of Industrial Hygiene 1932, 14, 174–196.
12. Bulmer, F. M.; Rothwell, H. E.; Frankish, E. R. Industrial Cd Poisoning: A Report of Fifteen Gases, Including Two Deaths. Canadian Public Health Journal 1938, 29 (1), 19–26.
13. Nicaud, P. Les Troubles de l'intoxication chronique Par Le Cd. Arch Mal Prof 1942, 4, 192–202.
14. Friberg, L. Proteinuria and Kidney Injury among; Workmen Exposed to Cadmium and Nickel Pust-Preliminary Report. Journal of Industrial Hygiene and Toxicology 1948, 30 (1), 32–36.
15. Nishijo, M.; Nakagawa, H.; Suwazono, Y.; Nogawa, K.; Kido, T. Causes of Death in Patients with Itai-Itai Disease Suffering from Severe Chronic Cadmium Poisoning: A Nested Case–Control Analysis of a Follow-up Study in Japan. BMJ Open 2017, 7 (7), e015694. https://doi.org/10.1136/bmjopen-2016-015694.
16. Valko, M.; Morris, H.; Cronin, M. T. D. Metals, Toxicity and Oxidative Stress. Curr. Med. Chem. 2005, 12 (10), 1161–1208. https://doi.org/ 10.2174/ 0929867053764635.
17. Morselt, A. F. Environmental Pollutants and Diseases. A Cell Biological Approach Using Chronic Cadmium Exposure in the Animal Model as a Paradigm Case. Toxicology 1991, 70 (1), 1–132. https://doi.org/10.1016/0300-483x(91)90102-7.
18. Zarros, A.; Skandali, N.; Al-Humadi, H.; Liapi, C. Cadmium (Cd) as a Carcinogenetic Factor and Its Participation in the Induction of Lung Cancer. Pneumon 2008, 21 (2), 172–177.
19. Satarug, S.; Moore, M. R. Adverse Health Effects of Chronic Exposure to Low-Level Cadmium in Foodstuffs and Cigarette Smoke. Environ. Health Perspect.2004,112(10),1099–1103. https://doi.org/10.1289/ehp.6751.
20. Bernard, A. Cadmium & Its Adverse Effects on Human Health. Indian J. Med. Res. 2008, 128 (4), 557–564.
21. Järup, L.; Akesson, A. Current Status of Cadmium as an Environmental Health Problem. Toxicol. Appl. Pharmacol. 2009, 238 (3), 201–208. https://doi.org/10.1016/j.taap.2009.04.020.
22. Tchounwou, P. B.; Yedjou, C. G.; Patlolla, A. K.; Sutton, D. J. Heavy Metal Toxicity and the Environment. Molecular, Clinical and Environmental Toxicology. environmental toxicology 3, 133–164.
23. Waalkes, M. P. Cadmium Carcinogenesis.Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2003, 533, 107–120.
24. Ahlborg, G.; Bodin, L.; Hogstedt, C. Heavy Metals and Musculoskeletal Conditions in Former Cadmium Alloy Workers. Scandinavian journal of work environment& health 1992, 18, 327–332.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

25. Inaba, T.; Kobayashi, E.; Suwazono, Y.; Uetani, M.; Oishi, M.; Nakagawa, H.; Nogawa, K. Estimation of Cumulative Cadmium Intake Causing Itai-Itai Disease. Toxicology Letters. 2005, 159, 192–201.
26. Nordberg, G. F. Historical Perspectives on Cadmium Toxicology. Toxicol. Appl. Pharmacol. 2009, 238 (3), 192–200. https://doi.org /10.1016/j.taap. 2009.03.015.
27. Antonini, J. M.; Roberts, J. R.; Schwegler-Berry, D. Environmental Cadmium and Lead Exposures and Immunological Outcomes in Adults: A Systematic Review of the Epidemiologic Evidence. Critical Reviews in Toxicology 2016, 46 (4), 336–362.
28. Cadmium and Cadmium Compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer 2012, 100, 121–145.
29. Thurston, S. W.; Ryan, L.; Christiani, D. C.; Snow, R. Cadmium Exposure and Acute Respiratory Infections in Ghanaian Children. Environmental Health Perspectives 2017, 125 (12).
30. Staessen, J. A. Cadmium and Blood Pressure. The Lancet 1991, 337, 1616–1618.
31. Nishijo, M.; Nakagawa, H.; Morikawa, Y.; Tabata, M.; Senma, M.; Miura, K. Relationship between Urinary Cadmium Levels and Dietary Habits in Endemic Areas of "Itai-Itai" Disease. Environmental Health Perspectives 2004, 112 (6), 622–626.
32. Takeda, A. Movement of Metals in the Brain. Environmental Health and Preventive Medicine 2003, 8 (1), 1–9.
33. Lopez, E.; Figueroa, S.; Oset-Gasque, M. J. Neurotoxicity and Oxidative Damage of Cadmium Alone or Combined with Aluminum or Zinc in Brain Cortex of Wistar Rats. Toxicology 2003, 186 (1–2), 112–127.
34. Friberg, L.; Nordberg, G. F.; Vouk, V. B. Handbook on the Toxicology of Metals. Elsevier/North-Holland Biomedical Press, 335 Jan van Galenstraat, 1061 AZ; Elsevier/North-Holland Biomedical Press: AZ Amsterdam, The Netherlands, 1061.
35. González-Reyes, R. E.; Nava-Ruíz, C.; Nuñez-Álvarez, C. A. Cadmium Exposure and Cognitive Function: An Updated Systematic Review and Meta-Analysis. Environmental Research 2018, 166, 334–346.
36. Sies, H. Oxidative Stress: Oxidants and Antioxidants. Exp. Physiol. 1997, 82 (2), 291–295. https://doi.org/10.1113/expphysiol.1997.sp004024 .
37. Liu, J.; Qu, W.; Kadiiska, M. B. Role of Oxidative Stress in Cadmium Toxicity and Carcinogenesis. Toxicol. Appl. Pharmacol. 2009, 238 (3), 209–214. https://doi.org/ 10.1016/j.taap.2009.01.029.
38. Collin, F. Chemical Basis of Reactive Oxygen Species Reactivity and Involvement in Neurodegenerative Diseases. Int. J. Mol. Sci. 2019, 20 (10), 2407. https://doi.org /10.3390/ijms20102407.
39. Ozcan, A.; Ogun, M. Basic Principles and Clinical Significance of Oxidative Stress. 2015, 3, 37–58.
40. Bhattacharyya, A.; Chattopadhyay, R.; Mitra, S.; Crowe, S. E. Oxidative Stress: An Essential Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. Physiol. Rev. 2014, 94 (2), 329–354.https://doi.org/10.1152/physrev. 00040.2012.
41. Nozik-Grayck, E.; Suliman, H. B.; Piantadosi, C. A. Extracellular Superoxide Dismutase. Int. J. Biochem. Cell Biol. 2005, 37 (12), 2466–2471. https://doi.org/10.1016/j.biocel.2005.06.012.
42. Wang, L.; Wang, X.; Yin, S. Effects of Salinity Change on Two Superoxide Dismutases (SODs) in Juvenile Marbled Eel Anguilla Marmorata. PeerJ 2016, 4 (e2149), e2149. https://doi.org /10.7717/peerj.2149.
43. Cuypers, A.; Plusquin, M.; Remans, T.; Jozefczak, M.; Keunen, E.; Gielen, H.; Opdenakker, K.; Nair, A. R.; Munters, E.; Artois, T. J.; Nawrot, T.; Vangronsveld, J.; Smeets, K. Cadmium Stress: An Oxidative Challenge. Biometals 2010, 23 (5), 927–940. https://doi.org/10.1007/s10534-010-9329-x.
44. Burton, G. J.; Jauniaux, E. Oxidative Stress. Best Pract. Res. Clin. Obstet. Gynaecol. 2011, 25 (3),287–299.https://doi.org/10.1016/ j.bpobgyn.2010.10.016.
45. Birben, E.; Sahiner, U. M.; Sackesen, C.; Erzurum, S.; Kalayci, O. Oxidative Stress and

Antioxidant Biswas SK. Does the Interdependence between Oxidative Stress and Inflammation Explain the Antioxidant Paradox. In Oxidative medicine and cellular longevity; 2016.

46. Patra, R. C.; Rautray, A. K.; Swarup, D. Oxidative Stress in Lead and Cadmium Toxicity and Its Amelioration. Veterinary Medicine International; 2011.
47. Genchi, G.; Sinicropi, M. S.; Lauria, G.; Carocci, A.; Catalano, A. The Effects of Cadmium Toxicity. Int. J. Environ. Res. Public Health 2020, 17 (11), 3782. https://doi.org /10.3390/ijerph17113782.
48. Rani, A.; Kumar, A.; Lal, A.; Pant, M. Cellular Mechanisms of Cadmium-Induced Toxicity: A Review. Int. J. Environ. Health Res. 2014, 24 (4), 378–399.https://doi.org/10. 1080/ 09603123.2013.835032.
49. Liu, J.; Qu, W.; Kadiiska, M. B. Role of Oxidative Stress in Cadmium Toxicity and Carcinogenesis. Toxicol. Appl. Pharmacol. 2009, 238 (3), 209–214. https://doi.org/n 10.1016/j.taap.2009.01.029.
50. Nair, A. R.; Degheselle, O.; Smeets, K.; Van Kerkhove, E.; Cuypers, A. Cadmium-Induced Pathologies: Where Is the Oxidative Balance Lost (or Not)? Int. J. Mol. Sci. 2013, 14 (3), 6116–6143. https://doi.org/10.3390/ijms14036116.
51. Rikans, L. E.; Yamano, T. Mechanisms of Cadmium-Mediated Acute Hepatotoxicity. J. Biochem. Mol. Toxicol. 2000, 14 (2), 110–117. https://doi.org/10.1002/(sici)10990461(2000)14:2 <110: aid-jbt7>3.0.co;2-j.
52. Hassoun, E. A.; Stohs, S. J. Cadmium-Induced Production of Superoxide Anion and Nitric Oxide, DNA Single Strand Breaks and Lactate Dehydrogenase Leakage in J774A.1 Cell Cultures. Toxicology 1996, 112 (3), 219–226. https://doi.org/10.1016/0300-483x(96)03404-x.
53. Das, S.; Dewanjee, S.; Dua, T. K.; Joardar, S.; Chakraborty, P.; Bhowmick, S.; Saha, A.; Bhattacharjee, S.; De Feo, V. Carnosic Acid Attenuates Cadmium Induced Nephrotoxicity by Inhibiting Oxidative Stress, Promoting Nrf2/HO-1 Signalling and Impairing TGF-B1/Smad/Collagen IV Signalling. Molecules 2019, 24 (22), 4176. https://doi.org/10.3390/molecules24224176.
54. Shi, X.; Li, D.; Deng, Q.; Li, Y.; Sun, G.; Yuan, X.; Song, Y.; Wang, Z.; Li, X.; Li, X.; Liu, G. NEFAs Activate the Oxidative Stress-Mediated NF-KB Signaling Pathway to Induce Inflammatory Response in Calf Hepatocytes. J. Steroid Biochem. Mol. Biol. 2015, 145, 103–112. https://doi.org/ 10.1016 /j.jsbmb.2014.10.014.
55. Walsh, M. C.; Lee, J.; Choi, Y. Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF 6) Regulation of Development, Function, and Homeostasis of the Immune System. Immunological reviews 2015, 266 (1), 72–92.
56. Alevriadou, B. R.; Shanmughapriya, S.; Patel, A.; Stathopulos, P. B.; Madesh, M. Mitochondrial Ca2+ Transport in the Endothelium: Regulation by Ions, Redox Signalling and Mechanical Forces. J. R. Soc. Interface 2017, 14 (137). https://doi.org /10.1098/rsif.2017.0672.
57. Joardar, S.; Dewanjee, S.; Bhowmick, S.; Dua, T. K.; Das, S.; Saha, A.; De Feo, V. Rosmarinic Acid Attenuates Cadmium-Induced Nephrotoxicity via Inhibition of Oxidative Stress, Apoptosis, Inflammation and Fibrosis. Int. J. Mol. Sci. 2019, 20 (8), 2027. https://doi.org/10.3390/ijms20082027.
58. Liu, F.; Wang, X.-Y.; Zhou, X.-P.; Liu, Z.-P.; Song, X.-B.; Wang, Z.-Y.; Wang, L. Cadmium Disrupts Autophagic Flux by Inhibiting Cytosolic Ca2+-Dependent Autophagosome-Lysosome Fusion in Primary Rat Proximal Tubular Cells. Toxicology 2017, 383, 13–23. https://doi.org/10.1016/j.tox.2017.03.016.
59. Cormet-Boyaka, E.; Jolivette, K.; Bonnegarde-Bernard, A.; Rennolds, J.; Hassan, F.; Mehta, P.; Tridandapani, S.; Webster-Marketon, J.; Boyaka, P. N. An NF-KB-Independent and Erk1/2-Dependent Mechanism Controls CXCL8/IL-8 Responses of Airway Epithelial Cells to Cadmium. Toxicol. Sci. 2012, 125 (2), 418–429. https://doi.org/10.1093/toxsci/kfr310.
60. Hossein-Khannazer, N.; Azizi, G.; Eslami, S.; Alhassan Mohammed, H.; Fayyaz, F.; Hosseinzadeh, R.; Usman, A. B.; Kamali, A. N.; Mohammadi, H.; Jadidi-Niaragh, F.; Dehghanifard, E.; Noorisepehr, M. The Effects of Cadmium Exposure in the Induction of Inflammation. Immunopharmacol.

Immunotoxicol. 2020, 42 (1), 1–8. https://doi.org/10.1080 /08923973.2019.1697284.

61. Kirkland, D.; Aardema, M.; Henderson, L.; Müller, L. Evaluation of the Ability of a Battery of Three in Vitro Genotoxicity Tests to Discriminate Rodent Carcinogens and Non-Carcinogens: I. Sensitivity, Specificity and Relative Predictivity. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 2005, 584 (1–2), 1–256.
62. Coogan, T. P.; Bare, R. M.; Waalkes, M. P. Cadmium-Induced DNA Strand Damage in Cultured Liver Cells: Reduction in Cadmium Genotoxicity Following Zinc Pretreatment. Toxicol. Appl. Pharmacol. 1992, 113 (2), 227–233. https://doi.org/10.1016/0041-008x(92)90118-c.
63. Rozgaj, R.; Kasuba, V.; Fucić, A. Genotoxicity of Cadmium Chloride in Human Lymphocytes Evaluated by the Comet Assay and Cytogenetic Tests. J. Trace Elem. Med. Biol. 2002, 16 (3), 187–192. https://doi.org/10.1016/S0946-672X(02)80024-4.
64. Ünyayar, S.; Celik, A.; Çekiç, F. Ö.; Gözel, A. Cadmium-Induced Genotoxicity, Cytotoxicity and Lipid Peroxidation in Allium Sativum and Viciafaba. Mutagenesis 2006, 21 (1), 77–81.
65. Argüelles-Velázquez, N.; Alvarez-González, I.; Madrigal-Bujaidar, E.; Chamorro-Cevallos, G. Amelioration of Cadmium-Produced Teratogenicity and Genotoxicity in Mice given Arthrospira Maxima (Spirulina) Treatment.Evidence-Based Complementary and Alternative Medicine; 2013.
66. Chandra, P.; Khuda-Bukhsh, A. R. Genotoxic Effects of Cadmium Chloride and Azadirachtin Treated Singly and in Combination in Fish. Ecotoxicol. Environ. Saf. 2004, 58 (2), 194–201. https://doi.org/10.1016/j.ecoenv.2004.01.010.
67. Schwerdtle, T.; Ebert, F.; Thuy, C.; Richter, C.; Mullenders, L. H. F.; Hartwig, A. Genotoxicity of Soluble and Particulate Cadmium Compounds: Impact on Oxidative DNA Damage and Nucleotide Excision Repair. Chem. Res. Toxicol. 2010, 23 (2), 432–442. https://doi.org/10.1021/tx900444w.
68. Aimola, P.; Carmignani, M.; Volpe, A. R.; Di Benedetto, A.; Claudio, L.; Waalkes, M. P.; van Bokhoven, A.; Tokar, E. J.; Claudio, P. P. Cadmium Induces P53-Dependent Apoptosis in Human Prostate Epithelial Cells. PLoS One 2012, 7 (3), e33647. https://doi.org/10.1371/ journal.pone.0033647.
69. Giaginis, C.; Gatzidou, E.; Theocharis, S. DNA Repair Systems as Targets of Cadmium Toxicity. Toxicol. Appl. Pharmacol. 2006, 213 (3), 282–290. https://doi.org /10.1016/ j.taap.2006.03.008.
70. 70. Hartwig, A. Mechanisms in Cadmium-Induced Carcinogenicity: Recent Insights. Biometals 2010, 23 (5), 951–960. https://doi.org/10.1007/s10534-010-9330-4.
71. Beyersmann, D.; Hechtenberg, S. Cadmium, Gene Regulation, and Cellular Signalling in Mammalian Cells. Toxicol. Appl. Pharmacol. 1997, 144 (2), 247–261. https://doi.org/10.1006/taap.1997.8125.
72. Bertin, G.; Averbeck, D. Cadmium: Cellular Effects, Modifications of Biomolecules, Modulation of DNA Repair and Genotoxic Consequences (a Review) Biochimie. 2006, 88, 1549–1559.
73. Joseph, P. Mechanisms of Cadmium Carcinogenesis. Toxicol. Appl. Pharmacol. 2009, 238 (3), 272–279. https://doi.org /10.1016/j.taap.2009.01.011.
74. Demir, E.; Qin, T.; Li, Y.; Zhang, Y.; Guo, X.; Ingle, T.; Yan, J.; Orza, A. I.; Biris, A. S.; Ghorai, S.; Zhou, T.; Chen, T. Cytotoxicity and Genotoxicity of Cadmium Oxide Nanoparticles Evaluated Using In vitro Assays. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 2020, 850–851 (503149), 503149. https://doi.org/10.1016/j.mrgentox.2020.503149.
75. Moon, S. H.; Lee, C. M.; Nam, M. J. Cytoprotective Effects of Taxifolin against Cadmium-Induced Apoptosis in Human Keratinocytes. Hum. Exp. Toxicol. 2019, 38 (8), 992–1003.https://doi.org /10.1177 /0960 327119846941.
76. Djordjevic, V. R.; Wallace, D. R.; Schweitzer, A.; Boricic, N.; Knezevic, D.; Matic, S.; Grubor, N.; Kerkez, M.; Radenkovic, D.; Bulat, Z.; Antonijevic, B.; Matovic, V.; Buha, A. Environmental Cadmium Exposure and Pancreatic

Cancer: Evidence from Case Control, Animal and in Vitro Studies. Environ. Int. 2019, 128, 353–361. https://doi.org /10.1016/j.envint.2019.04.048.

77. Yuan, Y.; Zhang, Y.; Zhao, S.; Chen, J.; Yang, J.; Wang, T.; Zou, H.; Wang, Y.; Gu, J.; Liu, X.; Bian, J.; Liu, Z. Cadmium-Induced Apoptosis in Neuronal Cells Is Mediated by Fas/FasL-Mediated Mitochondrial Apoptotic Signaling Pathway. Sci. Rep. 2018, 8 (1). https://doi.org/10.1038/s41598-018-27106-9.
78. Wang, S.; Ren, X.; Hu, X.; Zhou, L.; Zhang, C.; Zhang, M. Cadmium-Induced Apoptosis through Reactive Oxygen Species-Mediated Mitochondrial Oxidative Stress and the JNK Signaling Pathway in TM3 Cells, a Model of Mouse Leydig Cells. Toxicol. Appl. Pharmacol. 2019,368,37–48.https://doi.org/10.10 16/ j. taap .2019.02.012.
79. Zhao, H.; Liu, W.; Wang, Y.; Dai, N.; Gu, J.; Yuan, Y.; Liu, X.; Bian, J.; Liu, Z.-P. Cadmium Induces Apoptosis in Primary Rat Osteoblasts through Caspase and Mitogen-Activated Protein Kinase Pathways. J. Vet. Sci. 2015, 16 (3), 297–306. https://doi.org/10.4142/jvs.2015.16.3.297.
80. Jiao, D.; Jiang, Q.; Liu, Y.; Ji, L. Nephroprotective Effect of Wogonin against Cadmium-Induced Nephrotoxicity via Inhibition of Oxidative Stress-Induced MAPK and NF-KB Pathway in Sprague Dawley Rats. Hum. Exp. Toxicol. 2019, 38 (9), 1082–1091. https://doi.org/10.1177/0960327119842635.
81. Ghajari, H.; Hosseini, S. A.; Farsi, S. The Effect of Endurance Training along with Cadmium Consumption on Bcl-2 and Bax Gene Expressions in Heart Tissue of Rats. Ann. Mil. Health Sci. Res. 2019, In Press (In Press). https://doi.org/10.5812/amh.86795.
82. Ansari, M. A.; Raish, M.; Ahmad, A.; Alkharfy, K. M.; Ahmad, S. F.; Attia, S. M.; Alsaad, A. M.; Bakheet, S. A. Sinapicacid Ameliorate Cadmium-Induced Nephrotoxicity: In Vivo Possible Involvement of Oxidative Stress, Apoptosis, and Inflammation via NF-KBdownregulation. Environmental Toxicology and Pharmacology 2017, 51, 100–107.
83. Wallace, D. R.; Spandidos, D. A.; Tsatsakis, A.; Schweitzer, A.; Djordjevic, V.; Djordjevic, A. B. Potential Interaction of Cadmium Chloride with Pancreatic Mitochondria: Implications for Pancreatic Cancer. Int. J. Mol. Med. 2019, 44 (1), 145–156. https://doi.org/10.3892/ijmm.2019.4204.
84. Dewanjee, S.; Das, S.; Das, A. K.; Bhattacharjee, N.; Dihingia, A.; Dua, T. K.; Kalita, J.; Manna, P. Molecular Mechanism of Diabetic Neuropathy and Its Pharmacotherapeutic Targets. Eur. J. Pharmacol. 2018, 833, 472–523. https://doi.org/10.1016/j.ejphar.2018.06.034.
85. Kaushal, G. P.; Shah, S. V. Autophagy in Acute Kidney Injury. Kidney Int. 2016, 89 (4), 779–791. https://doi.org/10.1016/j.kint.2015.11.021.
86. Gong, Z.-G.; Zhao, Y.; Wang, Z.-Y.; Fan, R.-F.; Liu, Z.-P.; Wang, L. Epigenetic Regulator BRD4 Is Involved in Cadmium-Induced Acute Kidney Injury via Contributing to Lysosomal Dysfunction, Autophagy Blockade and Oxidative Stress. J. Hazard. Mater. 2022, 423 (Pt A), 127110. https://doi.org/10.1016/j.jhazmat.2021.127110.
87. Hou, W.; Xie, Y.; Song, X.; Sun, X.; Lotze, M. T.; Zeh, H. J., 3rd; Kang, R.; Tang, D. Autophagy Promotes Ferroptosis by Degradation of Ferritin. Autophagy 2016, 12 (8), 1425–1428. https://doi.org/10.1080/15548627.2016.1187366.
88. Zhao, C.; Yu, D.; He, Z.; Bao, L.; Feng, L.; Chen, L.; Liu, Z.; Hu, X.; Zhang, N.; Wang, T.; Fu, Y. Endoplasmic Reticulum Stress-Mediated Autophagy Activation Is Involved in Cadmium-Induced Ferroptosis of Renal Tubular Epithelial Cells. Free Radic. Biol. Med. 2021, 175, 236–248. https://doi.org/10.1016/j.freeradbiomed.2021.09.008.
89. So, K.-Y.; Oh, S.-H. Cadmium-Induced Heme-Oxygenase-1 Expression Plays Dual Roles in Autophagy and Apoptosis and Is Regulated by Both PKC-δ and PKB/Akt Activation in NRK52E Kidney Cells. Toxicology 2016, 370, 49–59. https://doi.org/10.1016/j.tox.2016.09.010.
90. Trojani, M. C.; Santucci-Darmanin, S.; Breuil, V.; Carle, G. F.; Pierrefite-Carle, V. Joint Bone Spine. 2022, 89.
91. Liu, W.; Dai, N.; Wang, Y.; Xu, C.; Zhao, H.; Xia, P.; Gu, J.; Liu, X.; Bian, J.; Yuan, Y.; Zhu, J.; Liu, Z. Role of Autophagy in Cadmium-Induced Apoptosis of Primary Rat Osteoblasts. Sci. Rep.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 1875-1890 | ISSN:2251-6727

2016,6(1),20404.https://doi.org/10.1038/srep20404.

92. Ran, D.; Ma, Y.; Liu, W.; Luo, T.; Zheng, J.; Wang, D.; Song, R.; Zhao, H.; Zou, H.; Gu, J.; Yuan, Y. TGF-β-Activated Kinase 1 (TAK1) Mediates Cadmium-Induced Autophagy in Osteoblasts via the AMPK/MTORC1/ULK1 Pathway. Toxicology 2020, 442.
93. Okuda, B.; Iwamoto, Y.; Tachibana, H.; Sugita, M. Parkinsonism after Acute Cadmium Poisoning. Clin. Neurol. Neurosurg. 1997, 99 (4), 263–265.https://doi.org/10.1016/s0303-8467(97)00090-5.
94. Panayi, A. E.; Spyrou, N. M.; Iversen, B. S.; White, M. A.; Part, P. Determination of Cadmium and Zinc in Alzheimer's Brain Tissue Using Inductively Coupled Plasma Mass Spectrometry. J. Neurol. Sci. 2002, 195 (1), 1–10. https://doi.org/10.1016/s0022-510x(01)00672-4.
95. Gonçalves, J. F.; Fiorenza, A. M.; Spanevello, R. M.; Mazzanti, C. M.; Bochi, G. V.; Antes, F. G.; Stefanello, N.; Rubin, M. A.; Dressler, V. L.; Morsch, V. M.; Schetinger, M. R. C. N-Acetylcysteine Prevents Memory Deficits, the Decrease in Acetylcholinesterase Activity and Oxidative Stress in Rats Exposed to Cadmium. Chem. Biol. Interact. 2010, 186 (1), 53–60. https://doi.org/10.1016/j.cbi.2010.04.011.
96. Tang, K.-K.; Liu, X.-Y.; Wang, Z.-Y.; Qu, K.-C.; Fan, R.-F. Trehalose Alleviates Cadmium-Induced Brain Damage by Ameliorating Oxidative Stress, Autophagy Inhibition, and Apoptosis. Metallomics 2019, 11 (12), 2043–2051. https://doi.org /10.1039/c9mt00227h.
97. Wang, J.; Zhang, P.; Shen, Q.; Wang, Q.; Liu, D.; Li, J.; Wang, L. The Effects of Cadmium Exposure on the Oxidative State and Cell Death in the Gill of Freshwater Crab Sinopotamonhenanense. PLoS One 2013, 8 (5).
98. Xu, C.; Chen, S.; Xu, M.; Chen, X.; Wang, X.; Zhang, H.; Dong, X.; Zhang, R.; Chen, X.; Gao, W.; Huang, S.; Chen, L. Cadmium Impairs Autophagy Leading to Apoptosis by Ca2+-Dependent Activation of JNK Signaling Pathway in Neuronal Cells. Neurochem. Res. 2021, 46 (8), 2033–2045. https://doi.org /10.1007/s11064-021-03341-x.
99. Zhang, H.; Dong, X.; Zhao, R.; Zhang, R.; Xu, C.; Wang, X.; Liu, C.; Hu, X.; Huang, S.; Chen, L. Cadmium Results in Accumulation of Autophagosomes-Dependent Apoptosis through Activating Akt-Impaired Autophagic Flux in Neuronal Cells. Cell. Signal. 2019, 55, 26–39. https://doi.org/10.1016/j.cellsig.2018.12.008.
100. Matović, V.; Buha, A.; Bulat, Z.; Đukić-Ćosić, D. Još o Toksičnostikadmija-s Posebnim osvrtom na nastanak oksidacijskoga stresa inainterakcije s cinkom i magnezijem. Arhiv za higijenu rada i toksikologiju 2011, 62, 65–75.
101. Bulat, Z.; Dukić-Ćosić, D.; Antonijević, B.; Bulat, P.; Vujanović, D.; Buha, A.; Matović, V. Effect of Magnesium Supplementation on the Distribution Patterns of Zinc, Copper, and Magnesium in Rabbits Exposed to Prolonged Cadmium Intoxication. ScientificWorldJournal 2012,2012,572514.https://doi.org /10.1100/2012/572514.
102. Jihen, E. H.; Imed, M.; Fatima, H.; Abdelhamid, K. Protective Effects of Selenium (Se) and Zinc (Zn) on Cadmium (Cd) Toxicity in the Liver of the Rat: Effects on the Oxidative Stress. Ecotoxicol. Environ. Saf. 2009, 72 (5), 1559–1564.https://doi.org/10.1016/j.ecoenv.2008.12.006.
103. Bulat, Z. P.; Djukić-Ćosić, D.; Maličević, Ž.; Bulat, P.; Matović, V. Zinc or Magnesium Supplementation Modulates Cadmium Intoxication in Blood, Kidney, Spleen, and Bone of Rabbits. Biological trace element research 2008, 124, 110–117.
104. Nordberg, G. F. Historical Perspectives on Cadmium Toxicology. Toxicol. Appl. Pharmacol. 2009, 238 (3), 192–200. https://doi.org/10.1016/j.taap.2009.03.015.
105. Matović, V.; Plamenac Bulat, Z.; Djukić-Cosić, D.; Soldatović, D. Antagonism between Cadmium and Magnesium: A Possible Role of Magnesium in Therapy of Cadmium Intoxication. Magnes. Res. 2010, 23 (1), 19–26. https://doi.org/10.1684/mrh.2010.0196.
106. Bulat, Z.; Đukić-Ćosić, D.; Antonijević, B.; Buha, A.; Bulat, P.; Pavlović, Z.; Matović, V. Can Zinc Supplementation Ameliorate Cadmium-Induced Alterations in the Bioelement Content in Rabbits?

Arh. Hig. Rada Toksikol. 2017, 68 (1), 38–45. https://doi.org/10.1515/aiht-2017-68-2919.

107. Andrulewicz-Botulińska, E.; Wiśniewska, R.; Brzóska, M. M.; Rogalska, J.; Galicka, A. Beneficial Impact of Zinc Supplementation on the Collagen in the Bone Tissue of Cadmium-Exposed Rats. J. Appl. Toxicol. 2018, 38 (7), 996–1007. https://doi.org/10.1002/jat.3608.
108. Bulat, Z. P.; Djukić-Ćosić, D.; Maličević, Ž.; Bulat, P.; Matović, V. Zinc or Magnesium Supplementation Modulates Cadmium Intoxication in Blood, Kidney, Spleen, and Bone of Rabbits. Biological trace element research 2008, 124, 110–117.
109. Matović, V.; Plamenac Bulat, Z.; Djukić-Cosić, D.; Soldatović, D. Antagonism between Cadmium and Magnesium: A Possible Role of Magnesium in Therapy of Cadmium Intoxication. Magnes. Res. 2010, 23 (1), 19–26. https://doi.org/10.1684/mrh.2010.0196.
110. Tang, L.; Qiu, R.; Tang, Y.; Wang, S. Cadmium-Zinc Exchange and Their Binary Relationship in the Structure of Zn-Related Proteins: A Mini Review. Metallomics 2014, 6 (8), 1313–1323. https://doi.org/10.1039/c4mt00080c.
111. Matović, V.; Buha, A.; Bulat, Z.; Đukić-Ćosić, D.; Miljković, M.; Ivanišević, J.; Kotur-Stevuljević, J. Route-Dependent Effects of Cadmium/Cadmium and Magnesium Acute Treatment on Parameters of Oxidative Stress in Rat Liver. Food Chem. Toxicol. 2012, 50 (3–4), 552–557. https://doi.org/10.1016/j.fct.2011.12.035.
112. Bhatti, J. S.; Bhatti, G. K.; Reddy, P. H. Mitochondrial Dysfunction and Oxidative Stress in Metabolic Disorders-A Step towards Mitochondria Based Therapeutic Strategies. Biochimica et Biophysica Acta 2017, 1863 (5), 1066–1077.
113. Yuan, Y.; Zhang, Y.; Zhao, S.; Chen, J.; Yang, J.; Wang, T.; Zou, H.; Wang, Y.; Gu, J.; Liu, X.; Bian, J.; Liu, Z. Cadmium-Induced Apoptosis in Neuronal Cells Is Mediated by Fas/FasL-Mediated Mitochondrial Apoptotic Signaling Pathway. Sci. Rep. 2018, 8 (1). https://doi.org/10.1038/s41598-018-27106-9.