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Review Article

A Review on Toxic Potential of Cadmium: Cellular to Organ Level

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ABSTRACT

Heavy metals pose a serious threat if they go beyond permissible limits in our bodies. Cadmium is a heavy metal that occurs as a natural constituent in the earth's crust along with Copper, Lead, Nickel and Zinc. It is naturally occurring in the environment as a pollutant that is derived from agricultural and industrial sources. The rapid industrial development has led to serious cadmium (Cd) pollution. Cd can enter the body through the atmosphere, water, soil and food, and has a long half-life (10–30 years), it largely accumulates in kidneys, liver, bone and other organs and causes irreversible damage to the target organs. Epidemiological evidence indicates a potential association between occupational and environmental cadmium exposure and the development of multiple cancer types such as breast, lung, prostate, nasopharynx, pancreas, and kidney cancers. Additionally, cadmium has been linked to the development of *Itai-Itai* disease, a condition characterized by severe osteoporosis. The exposure to Cd has been associated with epigenetic modifications, characterized by apoptosis, caspase activation, and structural changes in the hepatocytes, kidneys, lungs, and reproductive organs. Several liver and kidney diseases may be attributed to the oxidative stress induced by this xenobiotic. The involvement of mitochondria in the formation of reactive oxygen species (ROS) and their vulnerability to cadmium make them prime targets. Upon exposure to Cd, mitochondria may experience dysfunction, resulting in diminished ATP production and increased ROS generation. Recently, investigations of the capability of sunflower (*Helianthus annuus* L.), Indian mustard (*Brassica juncea*), and river red gum (*Eucalyptus camaldulensis*) to remove cadmium from polluted soil and water have been carried out. Moreover, nanoparticles of TiO_2 and Al_2O_3 have been used to remove cadmium from wastewater and soil efficiently. Finally, microbial fermentation has been studied as a promising method for removing cadmium from food. This review provides an update on the effects of Cd exposure on human health, focusing on the cellular and molecular alterations involved.

Keywords: Cadmium; Toxicity; Metallothionein; Apoptosis; Remediation

1 INTRODUCTION

Heavy metals are metallic elements with a density greater than 4.5 g/cm^3. Cadmium (Cd) is a toxic heavy metal with high mobility and no known biological advantage to the human body and environment. It is found in soil (0.53mg/kg), the lithosphere (0.2mg/kg), and sedimentary rocks (0.3mg/kg). According to the Safe Drinking Water Act by the EPA, an allowable maximum concentration of Cd in drinking water is 0.005mg/L. Agricultural and industrial activities are the main cause of its' occurrence in the environment as a pollutant. Progressive industrial expansion and modernization in developing countries is indisputable. Cd is released from industrial production to the environment mainly through mining, smelting, coal burning, Cd electroplating industry, chemical industry, fertilizer manufacturing and waste incineration. Environmental smoking is the main source of Cd pollution in indoor air and a serious threat to human health. Since, the emergence of *Itai-Itai* disease in Japan in 1912, the toxicity of Cd has generated wide attention from the public, governments and scientists.

Industrial Cd consumption in the world has increased steadily from 18,400 tons in 2003 to 20,400 tons in 2007 (World Bureau of Metal Statistics, Ware, United Kingdom). As a chemical element, Cd cannot be degraded. Cadmium bound to air particles can travel long distances, dissolve to some extent in water, and bind strongly to soil. Atmospheric deposition of cadmium results in contamination of the

topsoil. Cadmium can easily be taken up by some plants (leafy vegetables) and contaminate the food chain. Exposure to Cd takes place mainly through oral ingestion, dermal absorption and inhalation of contaminated dust, food or water [1]. Outdoor air concentrations of Cd are generally below 10 ng/m^3 but near zinc/lead smelters cadmium concentrations up to 1.16 mg/m^3 air have been reported [2]. Daily human intakes are from 10 μg Cd/kg body weight (humans exposed to high Cd concentrations) to 0.1 μg /kg b.w. [3]. Inhalation absorption of Cd is generally higher than gastrointestinal absorption. It ranges 10–50%, however, the absorption of Cd from cigarette smoke is between 25 and 50% wind can carry Cd-contaminated soil, resulting in the creation of contaminated dust particles. The majority of Cd-containing particles are larger than 10 μm. Since they are too big to fit through the lung alveoli, the nasopharynx, bronchi, and mucociliary clearance will take them into the gastrointestinal system. Once absorbed, Cd binds to metallothionein. Cd is stored mainly in the kidneys and the liver, and also in testes. The half-life in the body is 10–30 years.

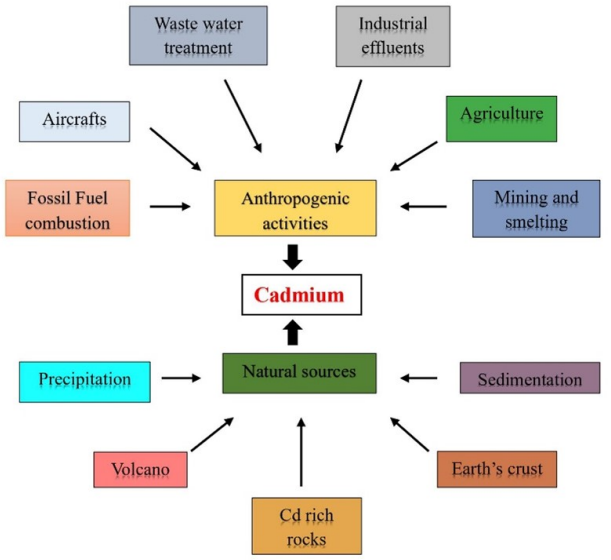

Figure 1: Sources of Cadmium in the environment

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) has permanently listed Cd as No. 7 (out of 275) in its priority list of hazardous materials [4]. In 1993 the International Agency for Research on Cancer [5], which is part of the World Health Organization, classified Cd and Cd-containing compounds as group-1 human carcinogens based on data obtained from human occupational exposure.

Cadmium exposure has been documented through various means over the course of the last century. Human exposure to Cd compounds may create a serious health problem even in a low concentration. Incidence of lung impairment was observed in workers exposed to Cd. After absorption, Cd is carried throughout the body, typically attached to a protein called metallothionein that contains sulfhydryl groups. Approximately 30% of the deposits reside within the liver and 30% are localized in the kidneys, while the remaining proportion is distributed throughout the body [6].

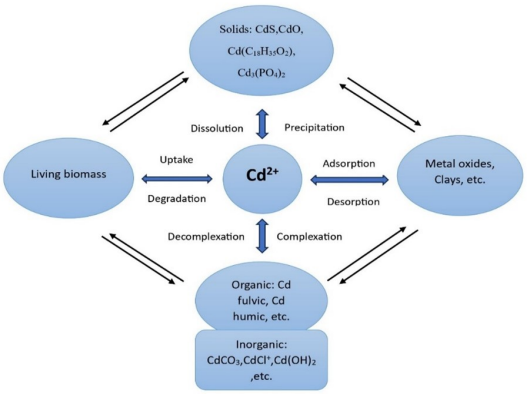

Figure 2: Cadmium cycle in the environment

The estimated half-life of cadmium in the blood ranges from 75 to 128 days; however, it predominantly signifies the accumulation of cadmium in organs rather than its elimination from the body [7]. The liver plays a vital role as a substantial reservoir and metabolic hub for the *in vivo* management of Cd. The liver exhibits a remarkable capability to trigger antioxidant mechanisms and possesses an extensive reserve potential. The liver is responsible for the production of metallothionein, which is subsequently secreted into the bloodstream and transported to the kidneys and various other target organs. The kidney serves as the primary organ responsible for toxic impact in the human body. The renal function of Vitamin D metabolism may also be adversely affected by the presence of cadmium [8] with the detrimental effects on bone. In conjunction with this particular effect, the compromised absorption of calcium in the gastrointestinal tract coupled with the disrupted metabolism of collagen can lead to the development of osteomalacia or osteoporosis. One of the most remarkable instances showcasing this phenomenon is the prevalence of *Itai - Itai* disease in Japan. The cardiovascular system is influenced by cadmium through multiple mechanisms, inducing hypertension [9] and diabetes [10]. Cd has been epidemiologically linked to sudden cardiac death [11], peripheral arterial disease [12], elevated vascular intima, media thickness [13], and myocardial infarction [14]. It also Provokes oxidative stress, elevates lipid peroxidation, and exhausts glutathione levels [15]. The process of haematopoiesis is negatively impacted, particularly in cases of *Itai - Itai* disease, which is characterized by the presence of severe anaemia and significant suppression of

erythropoietin production [16]. Cd-induced suppression of lymphocyte proliferation and natural killer cell activity has been observed [17].

Cadmium is acknowledged as a metalloestrogen; however, the substantiation favouring this assertion is more robust in *in vitro* and *in vivo* animal investigations compared to population-based human studies. The mechanism underlying the oestrogen-like effects of Cd is distinct from that of steroidal oestrogens [18]. Cd exposure in rats causes male infertility by inducing damage to the blood-testis barrier, resulting in a decline in germ cell adhesion. This impairment ultimately leads to the loss of germ cells, a decrease in sperm count, and subsequently, subfertility or infertility [19]. Cadmium exposure has been identified as a well-established risk factor that contributes to the development of insulin resistance [20]. Ultimately, it is crucial to acknowledge the presence of numerous heavy metals in the environment. Consequently, the assessment of health risks associated with Cd should be undertaken in tandem with the cumulative impacts of other metallic elements.

Zinc possesses notable antioxidant properties, thereby exhibiting remarkable free radical scavenging potential [21]. The upregulation of antioxidant pathways, particularly, the Nrf2 pathway, and the activation of target genes such as SOD1, CAT, MT2 are among the beneficial effects of zinc [22]. Zinc also safeguards hepatic stellate cells against Cd induced cytotoxicity by maintaining the normal activities of GSH, Catalase, and Glutathione peroxidase.

The application of nanotechnology in the detection and removal of hazardous metals like cadmium can effectively address the issue of cadmium poisoning and enhance environmental protection. Nanosized TiO_2 particles have the capacity to effectively eliminate cadmium from wastewater [23]. Al_2O_3 nanoparticles featuring low levels of citrate can serve as an efficient means of extracting Cd and Zn from contaminated solutions [24]. In order to effectively mitigate the harm caused by cadmium poisoning, acquiring essential knowledge and formulating an educational and preventive approach are important. A thorough examination of this topic has the potential to offer valuable insights and support toward the goal of effectively managing all aspects related to toxicities caused by cadmium compounds.

2 PHYSICOCHEMICAL PROPERTIES OF CADMIUM

Cadmium (Cd) is a chemical element with atomic number 48 and atomic mass number 112. This element is characterized by its soft, ductile, silvery-white appearance with a bluish color, lustrous surface, and electropositive properties. Despite its lack of odour or taste, cadmium is highly toxic. It has eight stable isotopes, namely ^{106}Cd, ^{108}Cd, ^{110}Cd, ^{111}Cd, ^{112}Cd, ^{113}Cd, ^{114}Cd, and ^{116}Cd. ^{112}Cd and ^{114}Cd are the most prevalent isotopes of Cadmium [25]. Cadmium is insoluble in water and not flammable. In its powdered form, it may burn and release toxic fumes. Cadmium possesses an electronegativity of 1.5 and a crystal ionic radius of 0.97 in its principal valence state. Its ionization potential is 8.993, and its electron configuration is $Kr4d_1,5S_2$. The density of cadmium is 8.64g/cm3, and it has a melting point of 320.9^{o}C and a boiling point of 765 ^{o}C at 100kPa. Cadmium is commonly found as a mineral combined with other elements, such as oxygen (cadmium oxide), chlorine (cadmium chloride), and sulfur (cadmium sulfate, cadmium sulfide). The marine diatom unicellular micro aglae *Thalassiosira weissflogiii*, which reside in a zinc-limited environment, have been found to possess a cd-dependent carbonic anhydrase (CDCA1), inspite of the fact that cadmium has no known biological function in higher organisms. Cadmium acts as a catalytic metallic ion, replacing zinc in the enzyme's active site [26].

3 SOURCE OF EXPOSURE

In recent years, the heavy metal industry has witnessed remarkable progress, but this has come at a cost. The surge in environmental contamination caused by Cadmium has become a pressing issue. The consequences of Cd pollution extend beyond the environment, posing significant health risks to humans. Cd can infiltrate various mediums, including air, water, soil, and food sources, thereby exacerbating the severity of the problem.

3.1 Occupational exposure

Occupational exposure encompasses the engagement with a potentially hazardous physical, chemical, or biological agent arising from one's professional activities. Occupational exposure to Cd primarily arises from contaminated air, as indicated by the findings of the International Agency for Research on Cancer working group. Nevertheless, the chemical composition of Cd may vary across different industrial settings. Throughout the years 1990 to 1993, the European Union observed a substantial expanse of 207,350 workers who encountered exposure to Cd and its related compounds [5]. The findings of de Queiroz and Waissmann's investigation reveal that more than 1,500,000 industrial employees in the United States were exposed to Cd every year before 2006. Workers in the electroplating, battery production, and pigment industries are commonly exposed to Cd hydroxide oxide [5]. Blood and urine levels can serve as indicators of elevated Cd levels among Cd workers. It has been observed that Cd levels exceeding the occupational safety and health administration level category C limit of 10μg/L have been detected to be twice as high [27].

3.2 Environmental exposure

Besides occupational exposure to Cd, the general population can be exposed environmentally through anthropogenic activities. Cd compounds possess the ability to manifest in multiple phases within the realm of nature, and their presence can be observed in the air, water, and sediment. These phases undergo interchanges through chemical reactions such as chelation, adsorption/desorption, and precip-

itation/dissolution. Cd is extracted from deep reservoirs in the earth either by volcanic eruption or mining processes. Subsequently, it undergoes transportation between various environmental compartments such as the atmosphere, surface water, ground water, and surface soil layer. The interchanges between these phases play a crucial role in the movement of Cd [28]. While Cd exists in insignificant levels within the air, water, and soil, it has the ability to bioaccumulate. This characteristic allows the metal to potentially accumulate in various biological organisms [29]. Atmospheric cadmium can arise from natural occurrences, such as spontaneous biomass combustion and volcanic eruptions. However, the primary origin of Cd aerosols in the atmosphere is currently attributed to human activities, with industrial emissions being the predominant contributor. Cadmium exposure through respiratory pathways can be attributed to smoking habits. Smokers exhibited a mean urine Cd value that was twice as high as individuals who had never smoked. The presence of Cd in the hydrosphere occurs naturally through the deposition of atmospheric Cd, the dissolution of solid Cd found in minerals, and the weathering of bedrock in watersheds, soils, and sediments. According to a national survey China has released about 30 tons of Cd from wastewater. The primary cause of an increase in Cd concentration in water is the direct discharge of industrial and agriculture runoff into the natural water system. Cd, which exists as water-soluble inorganic compounds like Cd halides and Cd chloride ($CdCl_2$) can dissolve in water to form Cd^{2+}, $CdCl^{+}$, $CdCl^{3-}$, and CdOHCl, and it also complexes with water to form $CdCl_2.H_2O$ and $CdCl_2.5H_2O$. Cd free ions (Cd^{2+}) in the water will form complexes such as $CdOH^{+}$, $Cd(OH)_2$, $Cd(OH)^{3-}$, $Cd(OH)_4^{2-}$, and Cd_2OH^{3+} [28].

4 ABSORPTION AND DISTRIBUTION

Cd is distributed throughout the body following absorption, typically binding to a protein that contains a sulfhydry1 group, such as metallothionein. Approximately 30% of the Cd is stored in the liver, while another 30% is deposited in the kidneys. The remaining Cd is distributed throughout the rest of the body. It is worth noting that the clearance half-life of Cd is twenty-five years [6]. The estimated half-life of cadmium in the blood is reported to be between 75 and 128 days. However, it is crucial to acknowledge that this particular duration primarily signifies the process of cadmium deposition in the organs, rather than the elimination of the element from the body [7]. Hence, relying on the levels of Cd found in blood, hair, and urine as indicators of the body's Cd burden is not reliable. These measurements mainly reflect recent exposure to cadmium, similar to other heavy metals. To obtain a precise estimation of the body burden of Cd, it is essential to conduct urine provocation testing. Following absorption into the body, this substance irreversibly accumulates, with a significant presence found in both the liver and kidney. Dietary Cd is absorbed and transported to the liver, where it induces synthesis of MT, and CdMT is formed. CdMT is released when hepatocytes are injured or die. Similarly, inhaled Cd induces MT synthesis with the formation of CdMT in the lungs. Cd not absorbed by hepatocytes in the first pass reaches the systemic circulation and is taken up by tissues and organs throughout the body, including pancreas, bone, thyroid gland, heart, and adipose tissue. In the kidney, CdMT undergoes glomerular filtration and is reabsorbed by tubular epithelial cells through receptor-mediated endocytosis. CdMT is degraded in lysosomes with the release of free Cd2+ ions that induce the synthesis of nascent MT. New CdMT complexes are formed and retained until their release by injured or dying cells. Excreted Cd is bound to MT along with zinc (Zn) and copper (Cu) in complexes, such as Cd3Cu3ZnMT, Cd4CuZn2MT, and Cd6CuMT. The non-MT forms of Cd in the primary filtrate are retrieved by transporters for the essential metal ions calcium (Ca), iron (Fe), Cu, Zn, and manganese (Mn).

5 MECHANISM OF TOXICITY

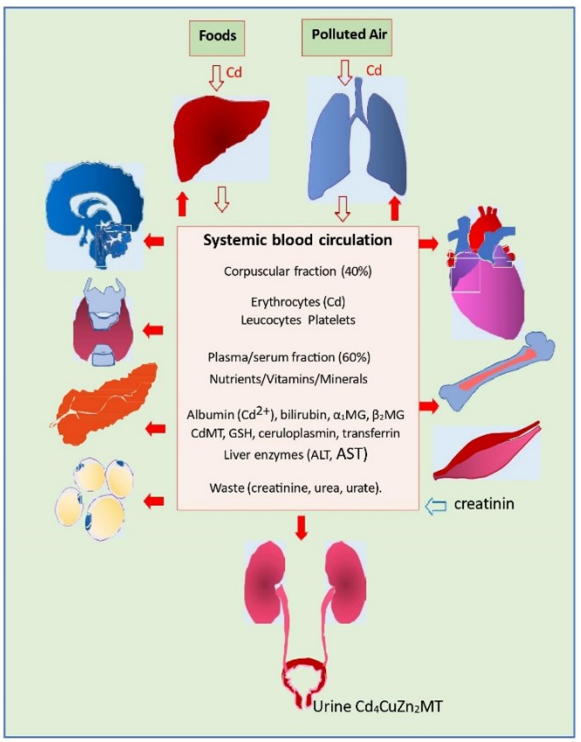

Figure 3: Cadmium intoxication in body (Cd, cadmium; MT, metallothionein; CdMT, cadmium-metallothionein complex; CdPC, cadmium-phytochelatin complex; CdO, cadmium oxide; α1MG, α1-microglobulin; β2MG, β2-microglobulin; GSH, glutathione; ALT, alanine aminotransferase; AST, aspartate aminotransferase).

The harmful effects of cadmium on several organs have been substantiated in subsequent sections. Cell prolifera-

tion, differentiation, and apoptosis are all affected by the presence of cadmium. These cellular activities are intricately connected to the DNA repair mechanism, the production of reactive oxygen species (ROS), and the induction of apoptosis.

In low concentrations, cadmium can effectively attach itself to the mitochondria, resulting in the suppression of both cellular respiration and oxidative phosphorylation. The induction of oxidative stress by cadmium leads to tissue injury [30]. Cell lines experience various genetic alterations as a consequence of this phenomenon, including chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA-protein crosslinks. Modifications in the expression of DNA due to epigenetic changes [31]. The modulation of transport pathways, specifically in the proximal S1 segment of the kidney tubule, can result in either inhibition or upregulation. This regulatory mechanism plays a crucial role in the overall functioning of the kidney [32, 33]. Various pathogenic mechanisms include hindering the physiological action of Zn or Mg through competitive interface. For instance, inhibition of the activity of antioxidant enzymes, such as catalase, manganese superoxide dismutase, and copper/zinc dismutase [34], and suppression of heme production [35]. The toxicity of this substance is characterized by the reduction of glutathione (GSH), the binding of sulfhydryl groups with proteins, and the stimulation of reactive oxygen species (ROS) production, including superoxide ion, hydrogen peroxide, and hydroxyl radicals. Cadmium toxicity is typically resisted by cells that contain metallothionein. Metallothionein, a protein with a high affinity for zinc, is composed of 33% cysteine residues. Specifically, it scavenges hydroxyl and superoxide radicals, thereby mitigating their potential harmful effects. Alternatively, cadmium intoxication affects cells that are unable to synthesize metallothionein [36]. Cadmium has the ability to regulate the intracellular concentration of Ca^{2+} as well as influence the functions of caspases and nitrogen-activated protein kinases (MRPKs) within cells. These cellular processes, in turn indirectly lead to apoptosis [37]. These effects are intensified by interaction with other toxic metals such as Pb and As [38].

6 CLINICAL MANIFESTATIONS

The clinical manifestations of cadmium toxicity vary depending on the route, quantity, and rate of exposure. Cd is renowned for its prolonged half-life and its irreversible accumulation in the body upon absorption, particularly in the liver and kidneys. However, it is important to acknowledge that these organs, which play a crucial role in eliminating Cd, are also highly sensitive to its toxicity. The highest concentrations are observed in the kidney, which is considered the major target for cadmium-related toxicity. Different clinical manifestations and toxic effects of Cd were explained in the detail below.

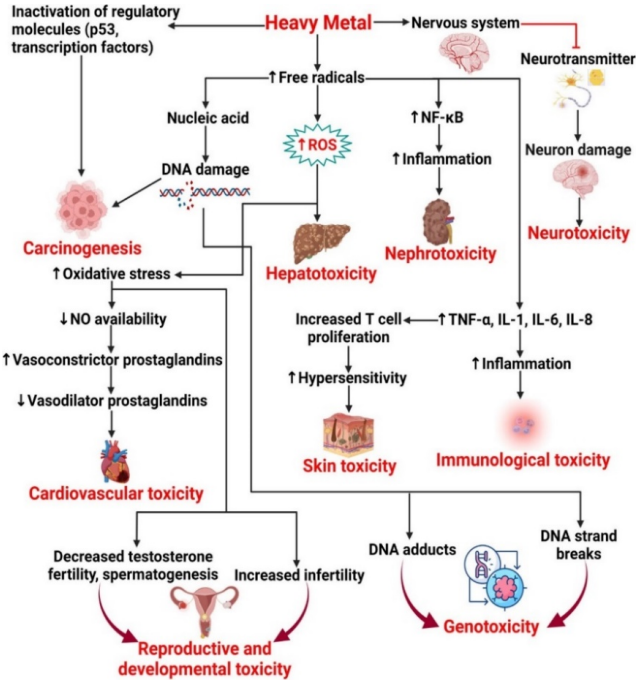

Figure 4: General mechanism of heavy metal toxicity. Mitra et al., 2022 [39]

6.1 *Gut*

The gastrointestinal tract (GIT) serves as the entry point for cadmium absorption into the body. Cd absorption in the gastrointestinal tract is projected to be roughly 5–8%, although this rate may rise under conditions of insufficient iron levels. The solubility and absorption of this element can be influenced by the pH levels present in the stomach and intestines. Notably, cadmium undergoes a reaction with hydrochloric acid (HCl), resulting in the formation of cadmium chloride. It can induce the inflammation of GIT. By raising the gastric pH, the H_2 blockers can effectively decrease the solubility of cadmium and hinder its absorption into the body [40] Furthermore, the chronic phase is characterized by the development of *Itai-Itai* disease due to the prolonged oral ingestion of cadmium [41]. The previous studies have provided evidence supporting the presence of enterohepatic circulation of Cd in the body [42]. Briefy, Cd which enters the digestive tract, is frstly absorbed by the intestinal tract, then into the liver, inducing the production of metallothionein (MT) and then forming Cd-MT complex; Cd in liver can be excreted in bile as a glutathione (GSH) and cysteine binding compound into the intestine, where it is reabsorbed by intestinal epithelial cells. The level of Cd absorbed in the intestines is directly proportional to the concentration of Cd found in the food. However, there are various factors that can influence the rate at which Cd is absorbed in the intestines. If the nutritional status of calcium, iron, or zinc is low, the absorption rate of Cd is increased. for instance, Iron deficiency leads to an upregulation of

the duodenal iron transporter, which in turn enhances the absorption of dietary Cd in the intestines. This is probably the main reason for the body burden of Cd, which is generally higher among women [11] whose prevalence of iron depletion is higher than that of men.

6.2 *Liver*

The liver is widely recognized for its significant immunologic role and its involvement in the detoxification process. It serves as the initial site where almost all substances absorbed in the small intestine are transported. Consequently, the liver plays a critical role in detecting any form of pollution, making it a vital organ in this regard. The "change in the diet/lifestyle" has gained significant attention. This alteration in dietary and lifestyle patterns has been linked to the development of disorders such as hepatotoxicity, which disrupts normal metabolic functions. The primary mechanism responsible for this occurrence involves oxidative stress reactions, a decline in antioxidant levels, and the enzymatic activity of nitric oxide synthase. These factors collectively result in the impairment of hepatocytes. These alterations include heightened levels of ROS, cholestasis, an excessive deposition of fat within the liver, liver necrosis, vascular lesions, and other related modifications [26]. The study conducted by Bagchi et al., 1996 [43] has demonstrated that following Cd induction, there is an observed increase in hepatic lipid peroxidation, mitochondrial lipid peroxidation, and microsomal lipid peroxidation. Additionally, the study found a depletion of glutathione levels. Oxidative damage induced by the metal Cd in the liver is primarily caused by the peroxidation of membrane lipids. This process involves the generation of free radicals, although Cd itself does not directly produce them. Instead, Cd generates superoxide, nitric oxide, and hydroxyl radicals, which contribute to oxidative stress-mediated damage. The cell membrane is a target for these free radicals, leading to both membrane instability and disintegration due to lipid peroxidation [44].

Cd toxicity effects on chicken showed that Cd exposure led to necrosis as well as sinusoidal dilation. A recent investigation demonstrated that exposure to Cd induces the suppression of Nrf2, along with its downstream target HO-1 (heme oxygenase 1), and a rise in the Keap1 protein. Furthermore, Cd intoxication leads to the activation of MAPKs, NLRP3, and NF-kB pathways. These molecular alterations are considered to be key contributors to the development of liver injury. TEM analysis conducted in another research on Cd hepatotoxicity revealed notable changes in the morphology of hepatocytes concerning their mitochondria and nuclei. Previous investigations have indicated that the sub-chronic administration of Cd could induce liver injury, potentially through the inhibition of UDGPT activity and cytochrome P450 activity. Additionally, a decline in Cytochrome-P450 levels may be attributed to an increase in heme oxygenase activity or an augmentation in LPO [45]. Cd is detected in conjunction with the chromatin within the nuclear membrane. Additionally, condensation occurring in the nucleolar region is recognized as an initial morphological alteration associated with Cd-induced hepatotoxicity. Animal studies have demonstrated that the accumulation of Cd in the liver leads to a significant increase in the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, and alkaline phosphatase. Additionally, various histopathological changes in the liver, such as parenchymal damage and infiltration of inflammatory cells, as well as the activation of Kupfer cells, have been observed [46]. Currently, the primary molecular mechanisms underlying Cd-induced liver toxicity involve sulfhydryl inactivation, oxidative stress, mitochondrial dysfunction, and cell apoptosis [47].

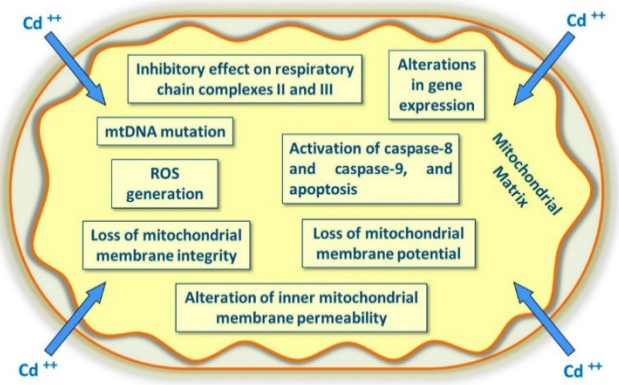

Figure 5: The mitochondrial alterations induced by cadmium. Genchi et al., 2020 [48]

Approximately 90% of the Cd present in the bloodstream is tightly bound to red blood cells, while the majority of Cd found in the plasma is bound to albumin, a protein [49]. It can be deduced that as senescent red blood cells are eliminated in the reticuloendothelial system, the Cd initially associated with these cells is released and subsequently binds to albumin. The Cd-albumin complexes are then repeatedly exposed to hepatocytes, that efficiently internalize Cd from these complexes. Upon entering hepatocytes, Cd forms complexes with metallothionein (MT), a protein, and these complexes contribute significantly to the accumulation of Cd in the kidneys [50].

6.3 *Kidney*

The kidney is a specific target of Cd. The deposition of Cadmium (Cd) primarily affects the S1 segment of the proximal tubule in the kidney, making it the chief organ of toxic impact. Exposure to cadmium can exhibit initial manifestations of renal damage, such as proteinuria, calcium loss, and tubular lesion. Conducting urine analysis can assist in confirming the early signs of renal damage [51]. The resulting oxidative damage to transport proteins and mitochondria causes notable impairments in the reabsorption function of protein, amino acids, glucose, bicarbonate,

and phosphate. Consequently, individuals may develop Fanconi syndrome, a condition characterized by defects in these essential substances' reabsorption. The glomerular filtration rate (GFR) and reserve filtration capacity are typically reduced, leading to nephrotoxicity accompanied by various complications including glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, polyuria, and decreased buffering capacity.

Earlier in the discussion, it was mentioned that approximately 30% of cadmium present in the body is accumulated in the kidney tubule region. It is important to note that the extent of damage to the tubules is directly related to the amount of cadmium that is not bound to metallothionein. As a consequence of Cd toxicity, hepatocyte death occurs, resulting in the transfer of the Cd-MT complex to the kidneys through the blood circulation. Subsequently, it undergoes filtration through the glomeruli in the kidneys and reabsorbed by the kidney tubules [52]. The intestinal mucosa has the ability to synthesize endogenous MT, which can combine with Cd to form a Cd-MT complex. This complex has a tendency to accumulate in the kidneys, resulting in an amplification of chronic toxicity. Following reabsorption, Cd undergoes separation into two distinct forms: free Cd and binding Cd. Among these two forms, free Cd is considered to be more toxic. The free Cd then combines with MT, which is produced by renal tubular epithelial cells. This combination leads to the decomposition of Cd, resulting in significant harm to renal tubular cells. As a consequence, the reabsorption function of epithelial cells is affected, and it also contributes to the development of proteinuria [53].

Cadmium-induced renal damage is characterized by dysfunction in the reabsorption of proximal tubules. The initial signs of tubular toxicity include an elevated excretion of low-molecular weight proteins, namely β2-microglobulin (β2-M), α1-microglobulin (α1-M), also known as protein HC, and retinol-binding protein (RBP). Additionally, there is an increase in the urinary excretion of markers indicating cytolysis, such as the lysosomal enzyme N-acetyl glucosaminidase (NAG). Moreover, prolonged exposure to Cd leads to an accumulation of Cd in the kidneys, resulting in elevated calcium excretion and an increased risk of kidney stones [54]. Additionally, it has been reported that if the exposure to Cd is both high and prolonged, or occurs in conjunction with certain triggers, it can progress to end-stage renal disease (ESRD) and ultimately lead to death. Currently, the molecular mechanisms underlying Cd toxicity on the kidneys primarily involve oxidative stress, mitochondrial stress, endoplasmic reticulum stress, apoptosis, autophagy, DNA methylation, and calcium ion imbalance. The Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) determined that the kidney is the primary organ affected by cadmium (Cd) toxicity (JECFA 2010).

6.4 Pancreas

The effects of cadmium on kidney function in individuals with diabetes have been found to be potentially intensified [55]. A major finding of the study conducted for the first time by Chang et al., 2013 [56] demonstrated that Cd induced oxidative stress-activates the JNK pathway, which plays a crucial role in the apoptosis of pancreatic b-cells. Cd exposure induced the production of reactive oxygen species (ROS) and triggered the activation of JNK-MAPK in RIN-m5F cells, ultimately resulting in the initiation of apoptotic-related signals that ultimately led to the death of pancreatic beta cells. It has been suggested that mitochondria display a high susceptibility to oxidative stress. Furthermore, it is well-established that the presence of mutated mitochondrial DNA can result in impaired mitochondrial function. This, in turn, can lead to dysfunction and subsequent death of b-cells, ultimately resulting in an insulin-deficient form of type 1 DM. The Third National Health and Nutrition Examination Survey (NHANES III) conducted a comprehensive examination of 8,722 U.S. citizens aged 40 and above. The survey, carried out in 2003, revealed a significant association between elevations in urinary Cd levels and increases in fasting blood glucose levels (110–126 mg/dl), as reported by Schwartz et al., 2003 [57].

6.5 Bone

There is growing evidence suggesting that, in addition to the kidneys, the bone is also significantly affected by the toxic effects of Cadmium (Cd). Since, the 1950s, it has been established that extended exposure to elevated levels of cadmium can lead to the development of bone disease. This condition was initially observed in the Jinzu river basin in Japan and is commonly referred to as *Itai-Itai* ("ouch-ouch") disease, due to the excruciating pain experienced by those affected [58]. The disease is characterized by the occurrence of multiple fractures and deformities in the long bones of the skeletal system, resulting in severe suffering (Järup et al., 1998).

The disease manifests as a combination of primarily osteomalacia and also osteoporosis, accompanied by renal impairment. Several scientific inquiries conducted in the past decade have focused on examining the potential correlation between prolonged exposure to low levels of environmental cadmium and the onset of osteoporosis. Osteoporosis is usually an age-related bone disorder. Osteoporosis, which is identified by reduced bone mass and the deterioration of bone tissue at a microscopic level, leads to heightened bone fragility and an elevated risk of fractures. Osteoporosis, a condition characterized by reduced bone density, is associated with various clinical features. These include heightened morbidity, such as pain, physical limitations, and a decreased overall quality of life.

The link between cadmium and its impact on bone health was further confirmed by Swedish research. In this study, it was observed that individuals with U-Cd levels ranging

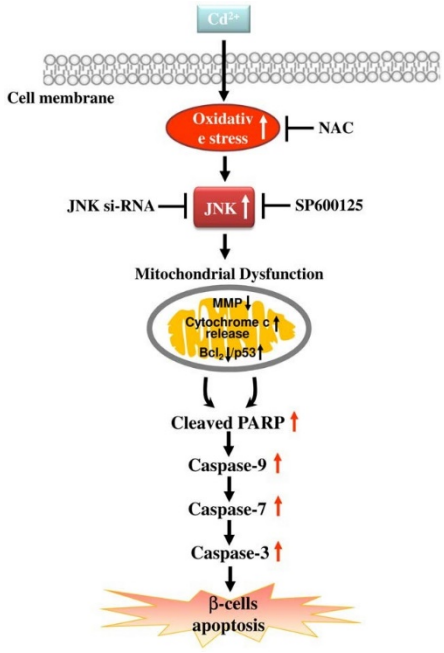

Figure 6: Schematic diagram of the signalling pathways involved in Cd-induced pancreatic beta-cell apoptosis. Chang et al., 2013 [56].

from 0.5 to 3 μg Cd/g creatinine had a doubled risk of osteoporosis, as assessed by a Z-score of b−1 on the non-dominant wrist [59]. These findings provide further evidence of the detrimental effects of cadmium on bone health. With increasing cadmium exposure, there is a corresponding rise in the concentration of bone resorption markers. This effect is particularly noticeable after menopause. Interestingly, even in the absence of cadmium-induced renal tubular dysfunction, individuals exposed to low levels of cadmium in their environment experience an increase in calciuria. This increase in calciuria is accompanied by reactive changes in calciotropic hormones, as demonstrated in the study conducted by Schutte et al., 2008. Notably, both studies found that cadmium exposure was linked to lower levels of parathyroid hormone. This suggests that the calciuria associated with cadmium exposure is primarily a result of increased bone resorption, rather than decreased tubular reabsorption. If the calciuria were solely caused by kidney damage, it would be more likely to observe an increase in parathyroid hormone levels.

The toxicity of Cd in bone is attributed to several mechanisms. One such mechanism involves the activation of fibroblast growth factor 23, which subsequently triggers phosphaturia and reduces phosphate uptake. This process ultimately leads to the development of osteomalacia. The precise mechanisms by which Cd exerts its toxic effects on MC3T3 osteoblasts [60] are not yet fully understood, but it has been observed to stimulate osteoclasts, thereby promoting the onset of osteoporosis. Furthermore, Cd has been shown to decrease serum osteocalcin levels in rats [61]. When these various factors converge, they contribute to the induction of calciuria, heightened bone resorption, and a decline in bone mineral density among children exposed to Cd [62].

6.6 Blood and Heart

Cadmium affects the cardiovascular system in several ways. Cadmium, which is present in tobacco, air, and food, has been found to have detrimental effects on endothelial functions through in-vitro exposures. Furthermore, in-vivo studies have shown that cadmium accelerates the formation of atherosclerotic plaques, leading to the thickening of artery walls and ultimately contributing to the development of cardiovascular diseases. *In vitro* investigations have demonstrated the association between cadmium and both endothelial dysfunction and carotid intima-media thickness (IMT). After being exposed to cadmium, individuals may experience endothelial dysfunction, which is the initial stage of cardiovascular disease (CVD). This dysfunction leads to the loss of endothelial cell structure, ultimately resulting in cell death. Additionally, cadmium exposure can trigger thrombogenic events. These findings provide evidence to support the hypothesis that cadmium plays a role in the development of cardiovascular disease and myocardial infarction. Hypertension can be caused by the inhibition of endothelial nitric oxide synthase and the suppression of acetylcholine-induced vascular relaxation due to the presence of cadmium. Long-term exposure to it may lead to an increase in the occurrence of peripheral arterial disease as it can stimulate the production of cytokines and induce damage to the endothelial cells. These mechanisms play a significant role in the development of atherogenesis [63]. Excessive exposure to cadmium might elevate the risk of cardiovascular mortality [11].

The extended duration of cadmium's half-life, which spans 30 years, can potentially be attributed to the gradual buildup of cadmium within the body over an extended period. Conversely, the shorter half-life of cadmium in the bloodstream, lasting between three to four months, suggests a more recent exposure to this toxic metal. It is worth noting that the limit of detection for cadmium concentration in blood is 0.3 μg/L [64]. Two different methods were used to measure the levels of cadmium in blood: electrothermal atomic absorption spectrophotometry and inductively coupled plasma mass spectrometry. According to the research conducted in the National Health and Nutrition Examination Surveys (NHANES), the values for cadmium that were at or below the limit of detection in all participants are as follows: 1999-2000: 0.3μg/l, 2003-2004: 0.14μg/l, and 2005-2010: 0.2μg/l [65]. There is some disparity among the literature, yet a significant portion of it provides evidence for the involvement of Cd in the development of hypertension [9] and diabetes [10] with apparent direct toxic impact on gene transcription in the

vascular endothelium [66]. Possible mechanisms that have been suggested include the disturbance of calcium channels, direct constriction of blood vessels, as well as the inhibition of nitric oxide (NO) and potentially other substances that promote vasodilation [67].

6.7 Lungs

The lung is recognized as one of the target organs affected by the toxicity of Cadmium (Cd). Cd can enter the lung through various means such as house dust, smoking, and occupational exposure [1]. Among these, cigarette smoke is the primary source of inhalation-based Cd intoxication. It has been observed that the human lung absorbs 40-60% of the cadmium present in tobacco smoke [54]. Workers who are exposed to fumes containing cadmium have been reported to develop acute respiratory distress syndromes. Inhalation of cadmium leads to respiratory stress and damage to the respiratory tract. High concentrations of cadmium in polluted air have been associated with conditions such as emphysema, anosmia, and chronic rhinitis. The ability of cadmium to induce apoptosis in rat lung epithelial cell lines has been attributed to its ability to induce the production of reactive oxygen species (ROS). This conclusion is supported by the observation that exposure of these cell lines to 20 μM CdCl2 for 24 hours resulted in a significant increase in the oxidized glutathione (GSSG) pool, leading to an imbalance in glutathione homeostasis.

Furthermore, it has been reported that cadmium exposure (10-50 μM CdSO4 for 1-3 days) can downregulate the expression of cystic fibrosis transmembrane conductance regulator protein in human airway epithelial (Calu3) cells, subsequently impairing chloride transport within the cells. Furthermore, cadmium has been demonstrated to induce pulmonary oxidative stress, emphysema, and persistent airway inflammation in rat models that replicate the conditions observed in individuals with chronic obstructive pulmonary disease (COPD). In a study conducted on Sprague-Dawley rats, nebulized Cd was administered via inhalation (0.1% CdCl2 in 0.9% NaCl) during a single exposure lasting 1 hour. This resulted in an acute increase of GSSG in the bronchoalveolar lavage fluid (BALF) of the rats, which was counterbalanced by a simultaneous increase in GSH. Animal groups that underwent repeated exposure to Cd for 35 weeks, with each exposure lasting 1 hour, exhibited a progressive increase in BALF-GSH levels. Additionally, a population-based study investigating environmental exposures to cadmium revealed a significant correlation between higher levels of 24-hour urinary cadmium excretion (doubling of excretion) and increased risks of both lung cancer and overall cancer [68]. Additionally, the transcription factor Nrf2, which acts as a universal antioxidant, has recently been implicated in a wide range of responses associated with both the initiation and progression of lung injuries caused by smoking. The involvement of cadmium in the development of lung cancer in humans has been confirmed through various studies.

6.8 Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified cadmium compounds as carcinogenic to humans [69]. Cd is associated with the development of malignancies in various organs, including the lungs, kidneys, and prostate [70]. Additionally, there is a potential link between Cd exposure and the occurrence of breast cancer in females, as well as endometrial cancer. Hartwig (2010) examines the fundamental molecular mechanisms involved. Although Cd does not possess direct mutagenic properties, it acts as a potent co-mutagen. Additionally, these organs may develop resistance to Cd by increasing their tolerance to reactive oxygen species (ROS) or activating cellular pathways that oppose apoptosis. The combination of these processes ultimately results in hypermutability, impaired growth and cell cycle control, and resistance to apoptosis, all of which contribute to the initiation and progression of cancer. The persistence of DNA damage is attributed to indirect mechanisms, including the heightened formation of reactive oxygen species (ROS) caused by Cd's inhibition of cellular antioxidant defense. Additionally, Cd disrupts the DNA damage response system and induces epigenetic alterations in DNA methylation patterns, ultimately resulting in genomic instability. Furthermore, ROS signalling may stimulate cell proliferation and activate redox-sensitive transcription factors that contribute to the development of cancer. However, the sensitivity of these mechanisms to Cd ions can be attributed to their dependence on metal-binding proteins, specifically Zn-finger proteins and calcium-binding proteins. These proteins play crucial roles in DNA binding and protein-protein interactions. Cd ions have been found to affect these proteins, leading to inhibition or damage of DNA repair enzymes, cell cycle control proteins, pro-apoptotic and tumour-suppressing proteins (such as PARP-1 and p53), Zn-containing transcription factors, enzymes involved in DNA methylation, and even E-cadherin.

Several studies have indicated a potential association between cadmium exposure and various types of malignancies. Specifically, it has been suggested that cadmium may play a role in the development of liver, hematopoietic systems, bladder, and stomach cancers. Furthermore, a separate study has proposed a link between cadmium exposure and pancreas cancer, as it may induce an increased risk for neoplasia in this particular organ [68]. The involvement of cadmium in carcinogenicity is attributed to various cellular and molecular mechanisms. These mechanisms encompass the activation of proto-oncogenes, the inactivation of tumor suppressor genes, the disruption of cell adhesion, and the inhibition of DNA repair processes [71]. Indeed, the impairment of DNA strands or the formation of DNA-protein crosslinks can effectively impede the growth of cells. These activities have the potential to directly or indirectly

influence the development of cancer.

6.9 Reproductive organs

Cadmium adversely affects the reproductive functions**.** Cadmium exposure predominantly hinders testicular function by causing damage to various components such as the vascular endothelium, Leydig, and Sertoli cells, intercellular connections, and inducing oxidative stress. This leads to a compromised antioxidant defense mechanism and an intensified inflammatory response, resulting in morphological and functional alterations like the inhibition of testosterone synthesis and impairment of spermatogenesis. Additionally, cadmium disrupts prostate function, affecting its hormonal activity, secretion, and ultimately diminishing fertility in males.

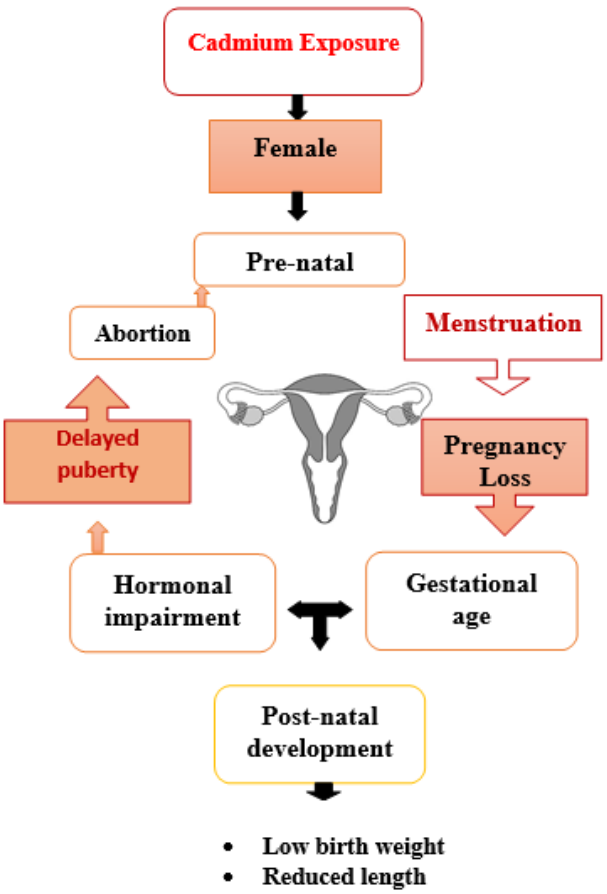

Figure 7: Female reproductive health effects of Cadmium during pregnancy. Ali et al., 2023 [72]

The impact of cadmium on reproductive health is predominantly observed in females, where it is recognized as a reproductive toxin. Extensive research has established a robust body of evidence linking cadmium exposure to impairments in reproductive health. Cadmium exposure in rats has been associated with premature vaginal opening, elevated uterine weight, and enhanced development of the mammary glands. The primary concern in the initial stages of pregnancy lies in the occurrence of spontaneous abortion, which represents a major challenge to reproductive health. Breast milk samples obtained from individuals in Austria exhibited an average cadmium concentration of 0.086 μg/L. The presence of an excessive amount of cadmium in the placenta triggers an upregulation of the Metallothionein gene family. Metallothionein, a protein rich in cysteine, functions as a protective barrier, preventing the translocation of toxic metals across the placenta. Cadmium has the ability to displace zinc within the fetus. Zinc, a trace element essential for the normal growth and development of the fetus, is adversely affected by cadmium. In order to safeguard the developing fetus metallothionein sequesters cadmium, but unfortunately, this leads to a reduction in the bioavailability of zinc for the fetus affecting cellular division and differentiation [73].In addition to its effects on the placenta, cadmium can also hinder the production of progesterone, increase the concentration of corticosterone, and diminish the synthesis of the leptin hormone [74].

Gennart et al., 1992 [75] found no discernible variance in fertility levels between males who were exposed to Cd in their occupations compared to a control group with matching characteristics (n = 118). However, it was noted that a hospital-based sample from the general population experiencing infertility issues exhibited notably higher levels of blood and seminal Cd in comparison to the control group. The median seminal plasma Cd was 0.282 μg/l among infertility patients, as opposed to 0.092 μg/l in the controls. Furthermore, there was an inverse correlation between the percentage of motile sperm, sperm concentration, and seminal plasma Cd among infertility patients ($r = -0.20$, $P < 0.04$) [76]. Studies suggest that cadmium has been reported to reduce the density, volume, and quantity of sperm in comparison to animal research, while also leading to an increase in immature forms of sperm [77].

7 REMEDIATION:

The mitigation of Cd toxicity demands the implementation of secure and efficient measures. Previous research has demonstrated that incorporating dietary supplements can significantly contribute to the reduction or prevention of Cd toxicity. The utilization of dietary strategies offers several advantages, primarily the ease and cost-effectiveness of incorporating essential nutrients into the diet to counteract the adverse effects of chelation therapy. In this review, we explore various potential dietary strategies, including essential micronutrients that counteract Cd, probiotics, as well as edible plant and dietary phytochemical supplements. The increased absorption of cadmium (Cd) may be attributed to the inadequate intake of calcium (Ca), zinc (Zn), iron (Fe), selenium (Se), vitamin C (VC), vitamin D (VD), vitamin E (VE), and/or other trace elements. Consequently, the accumulation of Cd not only disrupts the normal physiological processes of cells and organelles but

also impedes the absorption and metabolism of calcium [78].

Furthermore, numerous animal and human studies have demonstrated that a deficiency in essential metals such as calcium, zinc, or iron can lead to greater absorption and toxicity of Cd [79]. Therefore, it is reasonable to hypothesize that supplementing essential metal elements could potentially play a role in preventing Cd poisoning. VC supplements have been found to effectively reduce the accumulation of Cd in various organs such as the liver, kidneys, testicles, and muscles, as demonstrated by Grosicki in 2004 [80]. On the other hand, VD has shown some resistance against Cd poisoning. Animal experiments have revealed that rats exposed to Cd and deficient in VD experience significantly stronger toxic effects on their kidneys, bones, and hematopoietic system compared to rats with a normal diet [81]. *In vivo* studies conducted on mice have demonstrated that supplementation with VE leads to increased urine excretion of Cd and improved oxidative stress. Furthermore, *in vitro* studies have indicated that Cd enhances the Bax/Bcl-2 ratio through the mitochondrial pathway, activates caspases in rat testicles, and induces apoptosis. However, VE has shown a protective effect against Cd-induced apoptosis. Furthermore, the combined effect of trace elements exhibits a synergistic response that can counteract the toxic effects of Cd. On the other hand, Cd disrupts the activation of VD-activated parathyroid hormone in kidney cells, leading to an increase in urinary Ca excretion, a decrease in Ca absorption from the intestine, and interference with Ca entry into bone cells [81]. Consequently, the supplementation of VD and Ca holds immense importance in the context of Cd poisoning.

Various vegetables such as curry leaf, garlic, ginger, onion, green tea, and soybean are rich in vitamins and essential metals. These components have the potential to alleviate oxidative stress and even reverse the harmful effects of Cd. For instance, the consumption of curry leaf has been shown to enhance the activity of cardiac antioxidant enzymes while reducing cardiac LP and Cd levels. Recent research has also demonstrated that a soybean-based diet can mitigate the oxidative stress induced by Cd in the aorta of rats. This suggests that soybean protein possesses notable antioxidant properties and provides a certain level of protection against Cd poisoning. Moreover, research has indicated that the utilization of artichoke leaf extract (ALE) can significantly enhance the immune suppression, activate the antioxidant system, and mitigate liver and kidney function impairment caused by Cd poisoning. As a result, ALE exhibits a certain level of protective effect against Cd toxicity. It is worth noting that while certain green leafy vegetables, such as cabbage, lettuce, and kale, are prone to accumulating Cd and can serve as significant sources of Cd intake, they also contain nutrients and active ingredients that mitigate the toxicity of Cd. Consequently, the consumption of Cd-free vegetables plays a crucial role in the prevention and management of Cd poisoning.

Additionally, fruits possess inherent resistance to Cd toxicity. For example, studies have demonstrated that tomatoes can diminish the absorption of Cd in rats and facilitate its elimination, thereby reducing its accumulation in the liver. Similarly, grapes have also been found to effectively counteract the detrimental effects of Cd poisoning. Additionally, the administration of Spirulina, a type of algae, has a preventive effect on pregnant mice exposed to high doses of Cd. It significantly reduced the occurrence of fetal anencephaly, micromaxillary deformity, and bone abnormalities caused by Cd [82].

Probiotics are microorganisms that have a positive impact on the human body by improving the balance of gut microbes and preventing the growth of harmful pathogens. This, in turn, benefits the overall health of the host [42]. Furthermore, probiotics have demonstrated a strong potential to mitigate the toxicity of Cd (cadmium) in humans. One notable advantage of probiotics is their lack of side effects and high stability. Both *in vivo* and *in vitro* experiments have provided evidence that probiotics can protect organisms or cells from acute and chronic Cd poisoning. This protection is primarily attributed to the ability of oral probiotics to effectively reduce Cd absorption in the gut, minimize Cd accumulation in the body, and exert antioxidant effects. As a result, probiotics can alleviate oxidative stress and reverse damage to the liver, kidneys, and DNA [83]. Additionally, probiotics have been found to possess strong binding capabilities with Cd. *In vitro* digestion models have shown that *lactobacillus* can reduce the bioaccessibility of Cd by 24.7%–41.6% (Kumar et al. 2017). A recent review conducted by Bhattacharya, 2020 [84] concluded that seven probiotics, including *lactobacillus*, *Bifidobacterium longum*, *Escherichia coli* (genetic engineering), *clotting bacillus*, *Streptococcus valerate*, *Streptococcus thermophilus*, and *Saccharomyces cerevisiae*, exhibited significant protective effects against Cd toxicity in preclinical studies. Further research is required to investigate the specific mechanism and impact of probiotics on the removal of Cd in the human body, as the current evidence-based clinical trials are insufficient.

8 APPLICATION OF NANOMATERIAL IN THE DIAGNOSIS OF CADMIUM POISONING

Nanomaterials possess diverse applications, including tissue and organ engineering, medical instruments, drug delivery, diagnosis evaluation, prevention, and management [85]. The utilization of nanotechnology in the diagnosis and elimination of toxic metals, such as cadmium, can effectively address cadmium intoxication and enhance environmental safety [86]. Numerous nanoparticles have been employed in the field of diagnostics. Among these nanoparticles, quantum dots (QDs) have gained significant attention. QDs are composed of fluorescent markers made from cadmium selenide or zinc sulfide. In cases of cadmium poisoning,

these QDs are released and enter cells that contain zinc ions. By capping the QDs with ZnO, the formation of cadmium is effectively prevented, resulting in improved coverage of the material. The efficacy of this coating was determined through a gene expression test [87]. Aluminium oxide (Al_2O_3) nanoparticles have the ability to adsorb cadmium (Cd). In general, these nanoparticles are suitable for the removal of both zinc (Zn) and cadmium from solution or sorbent systems. Specifically, Al_2O_3 nanoparticles with low citrate concentrations are employed for the elimination of Cd and Zn from solutions that are contaminated with these metals [88]. Metal ions in aqueous solutions can be effectively eliminated through the use of carbon nanotubes (CNTs) [23]. In the case of wastewater contaminated with cadmium, nanosized TiO_2 particles have proven to be successful in removing this particular metal ion [89].

9 CONCLUSION AND FUTURE PERSPECTIVES

Cd is a trace metal that is present in various forms in the environment, and it has been associated with a range of harmful reactions. When plants and aquatic organisms are exposed to Cd in the environment, they can transfer it through the food chain. Regardless of the route of exposure, Cd tends to accumulate in different organisms, leading to toxic effects. To better understand the impact of Cd within the food chain, further research is required to examine its bioavailability. Additionally, studying the molecular mechanisms underlying Cd-induced toxicity is crucial. Through these future studies, we can gain a deeper understanding of the potential risks associated with Cd exposure and develop strategies to mitigate its harmful effects. The contamination of Cd has resulted in significant damage to both the environment and human health. This serves as a reminder for us to prioritize and implement measures to reduce Cd pollution. To begin with, it is crucial to conduct population-based research in order to identify the sources of Cd contamination. This is particularly important in countries and regions with high levels of Cd pollution. Furthermore, comprehensive health risk assessments should be carried out to further identify and control the various sources of pollution, including the atmosphere, water, soil (dust), and food. It is worth noting that the human living environment may contain other toxic heavy metals alongside Cd, which can potentially impact human health. Therefore, it is essential to also identify and monitor other heavy metal pollutants such as plumbum (Pb). In order to effectively mitigate the adverse health effects caused by Cd exposure, it is imperative to focus on reducing Cd pollution through the implementation of appropriate legislation and enforcement. Furthermore, in terms of individual prevention and control, it is crucial to decrease the bioavailability of Cadmium (Cd). One approach to achieve this is by supplementing essential elements that are beneficial for the human body, such as Calcium (Ca), Zinc (Zn), Iron (Fe), Selenium (Se), and vitamins. These elements have the ability to counteract the toxic effects of Cd and reduce its bioavailability within the body. It is important to pay special attention to individuals who follow a vegetarian diet and women in the reproductive stage, as they may have lower intake of these essential nutrients. Additionally, it is imperative to develop more cost-effective dietary strategies to effectively prevent Cd poisoning. Therefore, further research is necessary to gain a deeper understanding of the toxicity mechanism of Cd on the human body, which will enable the implementation of personalized prevention and control measures.

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