Can Vitamin E Intervention Attenuate Heavy Metal Toxicities? A Review

By

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Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “Can Vitamin E intervention attenuate heavy metal toxicities? A review” submitted by SK Sarika Ali (19146044) of Spring, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy.

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Ethics Statement

There are no trials on humans or animals in this study.

Abstract

Heavy metals like lead, mercury and cadmium are elements which can cause severe toxicities like kidney failure, bloody diarrhea, and abdominal cramping. Low-dose exposure is covert and undetectable, leading to neuropsychiatric disorders, fatigue, anxiety, and negative effects on children's IQ and intellectual function. The cellular processes of growth, proliferation, differentiation, damage repair, and apoptosis are all affected by heavy metals. Similar pathways for these metals to cause toxicity are shown by comparing their mechanisms of action, including reactive oxygen species (ROS) production, weakened antioxidant defense, enzyme inactivation, and oxidative stress. This study is done to see if Vitamin E have natural antioxidant properties which decrease the effects of these toxicities. Some studies on animals have been reviewed to show how vitamin E protects from oxidative stress and the cell membrane from damaging.

Keywords: “lead”; “mercury”; “cadmium”; “Vitamin E"; "antioxidant"; “toxicity.”

Dedication

Dedicated to my parents and my brother

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List of Acronyms

HM	Heavy Metals
Pb	Lead
Hg	Mercury
Cd	Cadmium
IARC	International Agency for Research on Cancer
Vit E	Vitamin E
ROS	Reactive Oxygen Species
-SH	Sulfhydryl group
GSH	Glutathione
ALAD	Amino Levulinic Acid Dehydratase
GR	Glutathione Reductase

Chapter 1

Introduction

Heavy metals (HM) are a class of metallic elements having atomic numbers greater than 20 and relative densities greater than 5 g/cm3, as well as characteristics including conductivity of heat, current, and surface lustre (Ungureanu & Mustatea, 2022). Hazardous heavy metal poisoning of water and air is a global environmental concern affecting several hundred millions of people (Balali-Mood et al., 2021). According to Engwa et al. (2019), heavy metals negatively affect the environment and organisms. They pose a serious threat to all forms of life on earth and severely contaminate the food chain as a result. Heavy metals can interact with biological systems on a regular basis by donating one or more electrons and forming metal cations, which are affinities for the nucleophilic sites of important macromolecules. Heavy metals have a variety of short- and long-term detrimental impacts on various human organs (Balali-Mood et al., 2021). Humans, animals, and plants are all hazardous to high tissue concentrations of HMs (Arora & Chauhan, 2021). Abdominal cramps, bloody diarrhoea, and renal failure are just a few of the severe adverse effects that can arise from high levels of exposure to heavy metals, particularly lead and mercury. However, unless low-dose exposure is repeated often, it remains hidden and invisible until its consequences—such as neuropsychiatric diseases like anxiety and fatigue, as well as detrimental effects on children's intelligence and intellectual function—become apparent (Balali-Mood et al., 2021).

Lead (Pb) is one of the most harmful and well-known environmental toxins (Wani et al., 2015; Hezbullah et al., 2016; Mitra et al., 2022). While Pb is mainly absorbed via the stomach and respiratory systems, it can also be absorbed through the skin. Pb exposure has been linked to

oxidative, inflammatory, immunomodulatory, and urinary disorders as well as neurological, pulmonary, and cardiovascular conditions (Balali-Mood et al., 2021). Because of its widespread use in gasoline, paints, cosmetics, children's toys, traditional medicines, pesticides, and lead-acid batteries for automobiles, it has extended into the air, the water, and even the soil. Lead may be present in colouring chemicals, canned foods, drinking water transported through lead pipes or pipes linked with lead solder (World Health Organisation: WHO, 2022; Emsley, 2005; WHO, 2010; CDC, 2015). According to WHO recommendations, the blood lead reference value for lead poisoning is 25 µg/dL of blood in adults and less than 3.5 µg/dL of blood in children (*Blood Lead Reference Value | Lead | CDC*, n.d.). Age and physiological condition of the exposed person have an impact on their absorption (Ungureanu & Mustatea, 2022). There is no known safe blood lead level, even a level of 2 µg/dL of blood lead may cause behavioural problems, learning challenges, and IQ declines in children (Gilbert & Weiss, 2006). With increased exposure to lead, the range and intensity of effects and symptoms also rise (World Health Organisation: WHO, 2022). Due to its high toxicity, Pb impairs neurological, biological, and cognitive processes in humans (Balali-Mood et al., 2021).

Mercury is a heavy metal that can be found in the biosphere and is exceedingly dangerous. It has also expanded far and is getting more prevalent in the atmosphere as a result of human activity (Mitra et al., 2022). It is utilised in a wide variety of industrial processes, such as mining (for the extraction of gold), the electrical industry (switches, thermostats, batteries), lamp manufacturing factories (for fluorescent light bulbs), caustic soda manufacturing, measurement instruments (thermometers, manometers, barometers, mercury switches), nuclear reactors, paint industries, antifungal agents for wood processing, fungicides in agriculture (methylmercury and ethylmercury), soaps, and some skin lightening Mercury can exist in a gaseous state, making it

more dangerous than in a liquid state (Balali-Mood et al., 2021) since it can be breathed (Engwa et al., 2019). Large acute exposures to elemental mercury may have harmful effects on the nervous system, the kidneys, the immune system, and the reproductive system (Bernhoft, 2012; Rice et al., 2014; Tchounwou et al., 2003; Hong et al., 2012). Cellular toxicity poses a risk to both foetuses and children (Rice et al., 2014).

Cadmium (Cd) is another hazardous heavy metal that can be released into the atmosphere by man-made or natural processes, which can affect both humans and animals. (Mitra et al., 2022). According to Ungureanu and Mustatea (2002), cadmium is mostly utilised in the manufacturing of paints, pigments, alloys, coatings, batteries, plastics, glass, electroplating, and welding. Three-fourths of the cadmium needed to make alkaline batteries is used as an electrode component. Industrial processes and cadmium smelters release cadmium into sewage sludge, fertilisers, and groundwater, where it can linger for decades before being absorbed by plants and soil. Consuming contaminated food can expose a person to cadmium (Engwa et al., 2019). In addition to some bone and kidney toxicity, exposure to cadmium can harm the lungs in cadmium-exposed workers (Rahimzadeh et al., 2017). According to Balali-Mood et al. (2002), Cd is categorized by the International Agency for Research on Cancer (IARC) as Group 1 carcinogenic to humans. According to FAO/WHO guidelines, rice can contain up to 0.2 mg/kg of cadmium. In a 70 kg male, 5 gm of Cd is the lowest deadly dose. The limit of detection for blood cadmium content is 0.3 µg/L. Cadmium concentrations in urine equal to or greater than 0.5 µg/g of creatinine are related with kidney impairment, and values larger than 2.0 µg/g of creatinine may translate into significant damage (Rahimzadeh et al., 2017).

Vitamin E (vit E) is a crucial part of the human diet and is regarded as the biological system's most potent liposoluble antioxidant. According to Amanpour et al. (2019), vitamin E is a free

oxygen radical-scavenging antioxidant that is essential for stabilising cell membranes and permeability. By inhibiting lipid peroxidation, it defends the biological systems of the body (Al-Attar, 2011). It is made up of several subfamilies, the most researched of which are tocopherols and tocotrienols. Tocotrienols have three double bonds in their isoprenoid side chains, which makes them structurally different from the other subfamilies and affects how effective and powerful they are as antioxidants (Al-Attar, 2011). In addition, tocotrienols have been shown to lower blood cholesterol levels and inhibit the formation of breast cancer (Al-Attar, 2011).

Superoxide dismutase, malondialdehyde, catalase, and glutathione peroxidase are examples of enzyme-activated antioxidants. Non-enzymatic antioxidants, including selenium, zinc, vitamin C, and vitamin E (Vit E), all play a role in protecting live cells from oxidative damage. In addition, vitamin E prevents bone calcium loss in ovariectomized rats (Norazlina et al., 2000; Al-Attar, 2011), increases bone trabecular development, and prevents bone calcium loss caused by ferric nitrilotriacetate, an oxidizing agent (Al-Attar, 2011).

1.2 Aim

This study is intended to provide a contextual and detailed overview of the heavy metals around the globe that can be silent killers. The aim is to review the recent new findings and mechanisms about heavy metal toxicities, including lead, mercury, and cadmium, and how vitamin E helps to attenuate the toxicity caused by these metals.

1.3 Objectives

The objectives of these studies are:

i. to evaluate the toxicities caused by heavy metals.

ii. to evaluate the mechanism how heavy metals causes toxicities.

iii. to evaluate how vitamin E can attenuates the toxicities.

Chapter 2

Methodology

These studies are intended to discuss and compare data on hazardous mechanisms from major scientific databases like PubMed, Web of Science (ISI), Scopus, google scholar, science direct, nature, Elsevier, Mendeley, research gate, NCBI resources which contains peer-reviewed articles.. The literature was searched for research on humans and animals that involved both acute and long-term exposure to the three heavy metals, as well as any detrimental effects on body organs that may have been produced by these exposures and how Vitamin E functions to lessen their toxicity.

The keywords we used to search the terms were “lead (Pb),” “mercury (Hg),” “cadmium (Cd),” “Vitamin E," "antioxidant," “toxicity,” “poisoning,” “intoxication,” “mechanism of toxicity,” “mechanism of action,” and "cancer."

Chapter 3

Discussion

Toxic Effects of Heavy Metals

The heavy metals Pb, Hg, and Cd wear out the main antioxidants in cells, especially those antioxidants and enzymes with the thiol group (—SH). These metals can induce the production of ROS such as hydrogen peroxide (H_2O_2), superoxide radicals (O_2), and hydroxyl radicals (HO). "Oxidative stress" is a condition that results from increased ROS production and can completely destroy a cell's natural antioxidant defenses (Ercal et al., 2001). In particular, in the renal cortex, heavy metals like Pb, Hg, and Cd are nephrotoxic (Wilk et al., 2016). The toxicity of heavy metals depends on their chemical form. Hg has a significant impact on mercury toxicity (Ebrahimpour et al., 2010). According to a study done in Lahore, Pakistan, individuals with cancer and diabetes had relatively greater quantities of harmful heavy metals, such as Cr, Cd, and Pb, than did healthy subjects (Ali et al., 2019). In recent years, it has been thought that opium adulteration with Pb poses a concern to public health (Balali-Mood et al., 2021).

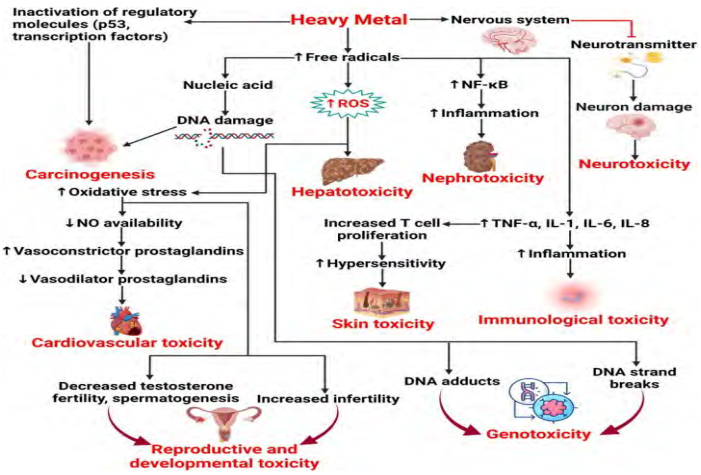

Figure 1: Mechanism of heavy metal toxicity in humans (Mitra et al., 2022).

3.1 Lead

3.1.1 Toxic Effects of Lead

3.1.1.1 Effect of lead on the nervous system

When exposed to lead, the central and peripheral nervous systems are also impacted. According to Flora et al. (2012), the central nervous system is more noticeably damaged in children than the peripheral nervous system is in adults. Lead exposure causes encephalopathy, which is characterised by the progressive deterioration of specific brain regions. According to Mitra et al. (2022), the primary symptoms are headaches, tremors in the muscles, dullness, impatience, short attention span, loss of memory, and hallucinations. More severe symptoms such delirium, ataxia, convulsions, paralysis, and coma may manifest at very high exposure levels. (Flora et al., 2012). Young children and foetuses are more susceptible to lead's neurological effects because their growing neural systems absorb more percentage of lead. Children have a substantially higher proportion of systemically circulating lead that enters their brains than adults do (Flora et al., 2012).

Even with minimal lead exposure, kids can act hyperactive, agitated, and inattentive. Children with elevated lead levels may experience hearing loss, hearing delay, lower intellect, and short-term memory loss. Lead can result in fatalities and lasting brain damage at higher concentrations (Cleveland et al., 2008). Evidence suggests that exposure to low levels of lead has a major impact on a child's behavior, capacity for focus, and attentiveness. Peripheral neuropathy is caused by lead's effects on the peripheral nervous system. It reduces motor activity because the myelin sheath that protects the nerves wears away. This leads to muscle weakness, especially in

the outer muscles, fatigue, and a lack of muscle coordination (Sanders et al., 2009; Flora et al., 2012).

3.1.1.2 Effect of lead on the hematopoietic system

Lead directly impacts the hematopoietic system by inhibiting multiple critical enzymes in the pathway of heme synthesis, hence restricting the synthesis of haemoglobin. Furthermore, it causes the cell membranes of circulating erythrocytes to become more brittle, hence reducing their longevity. These two processes work together to produce anaemia (Flora et al., 2012). Lead poisoning can cause two types of anaemia: hemolytic anaemia, which is associated with acute high-level lead exposure, and frank anaemia, which only happens when the blood lead level is noticeably increased for prolonged periods of time (Flora et al., 2012).

3.1.1.3 Effect of lead on the kidney

Renal impairment is mostly occurs at high lead exposure levels (>60 µg/dL), but damage has also been noted at lower levels (~10 µg/dL) (Flora et al., 2012). Acute and chronic nephropathy are two different forms of renal function abnormalities. Degenerative alterations in the epithelium of tubules and the development of nuclear body inclusions containing lead protein complexes are two visual indicators of acute nephropathy. Functionally, it is shown by a change in the way the tubular transport system works. Although it doesn't result in protein showing up in the urine, it can result in abnormally high levels of amino acids, phosphates, and glucose, a condition known as Fanconi's syndrome. On the other hand, chronic nephropathy is significantly more severe and can result in permanent morphological and functional abnormalities. It is characterized by glomerular and tubulointerstitial alterations that lead to glomerulonephritis,

hypertension, and hyperuricemia (Sk, 2008; Flora et al., 2012); and hyperplasia, interstitial fibrosis, tubule atrophy, renal failure, and hypertension (Mitra et al., 2022).

3.1.1.4 Effect of lead on bone

Bones are the body's main repository for lead (Renner, 2010). To describe the distribution of lead to and from blood, soft tissue, and bone, Hammond (1982) created a three-compartment lead distribution model. Soft tissue, which has a half-life of roughly 40–60 days, and blood, which can be thought of as the longer-term intermediate storage compartment and short-term transit compartment respectively, respectively, of lead. The accompanying diagram (Figure 2) shows the passage of lead from the centre compartment (blood), which is thought of as the long-term storage compartment, to the bone. The smaller arrow shows the movement of lead back from the bone to the blood. Lead builds up in bones for decades at this very slow rate of return to the blood, and in cases of bone remodelling, such as in growing children or during pregnancy, it can return to the blood (National Academies Press (US), 1993).

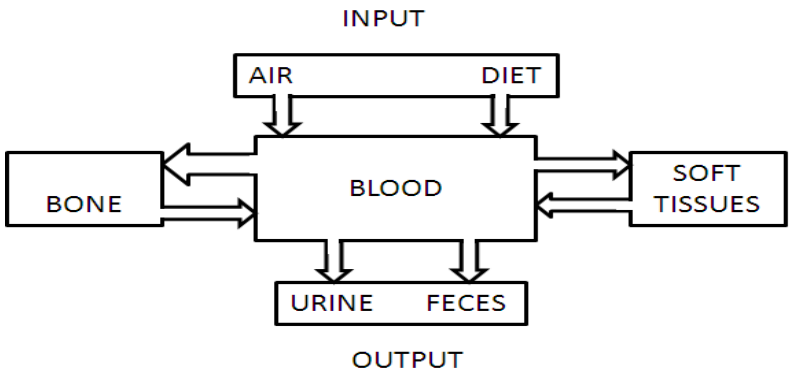

Figure 2: Lead distribution in body compartments (Adapted from Hammond, 1982)

3.1.1.5 Effect of lead as carcinogen

By generating reactive oxygen species (ROS), the carcinogenic chemical lead damages the DNA repair system, genes that control cellular tumor growth, and chromosomal shape and sequence (Figure 1). By removing zinc from specific regulatory proteins, it impairs transcription (Mitra et al., 2022).

3.1.1.6 Effect of lead on liver

Lead has a well-known harmful effect on liver cells. When exposed to it, oxidative stress is increased, which damages the liver. Because organic solvents and lead have many traits, they can harm the liver when combined (Malaguarnera et al., 2012). According to Hegazy and Fouad (2014) and Mitra et al. (2022) persistent lead exposure may be toxic to liver cells, causing glycogen depletion and cellular infiltration that can develop to chronic cirrhosis (Figure 1).

3.1.1.7 Effect of lead on the immune system

Lead exposure, both acute and chronic, has a number of harmful effects on the immune system and triggers a variety of immunological responses, including an increase in allergies, infectious illnesses, autoimmunity, and cancer (Hsiao et al., 2011). Lead exposure has been connected to a greater incidence of bladder, stomach, and lung cancer in a number of demographic groups (Rousseau et al., 2007). According to Kasten-Jolly et al. (2010), lead exposure stimulates the development of B and T cells and even MHC activity. By altering the function of T cells and raising vulnerability to the emergence of autoimmunity and hypersensitivity, it can affect cellular and humoral responses (Figure 1) (Mitra et al., 2022).

3.1.1.8 Effect of lead on the heart

Acute or chronic lead exposure causes a number of problems in the human body. Lead can alter the renin-angiotensin system, alter the blood vessels' response to vasoactive agonists, increase endothelium-dependent vasorelaxation and reduce vasoconstrictor prostaglandins, interfere with Ca^{2+} signalling in vascular smooth muscle, and alter the renin-angiotensin system. Moreover, prolonged exposure increases arterial pressure. (Mitra et al., 2022; Vaziri, 2008).

3.1.2 Mechanisms of Lead toxicity

Table 1: Toxic Mechanisms of lead (Pb) (Balali-Mood et al., 2021)

Heavy Metal	**Toxicity in organs**	**Mechanism of Action**	**References**
Lead	- CNS Injury - Lung Dysfunction - Hematological changes	- Increased inflammatory cytokines IL-1β, TNF-α, and IL-6 in the CNS - Increased serum ET-1, NO, and EPO - Inactivation of δ-ALAD and ferrochelatase (inhibition of heme biosynthesis)	Strużyńska et al., 2006; Dongre et al., 2011; Wang et al., 2013; Boskabady et al., 2014; Balali-Mood et al., 2021

	- GI Colic - Liver Damage - Pulmonary Impairment - Cardiovascular Dysfunction	- Reduced GSH, SOD, CAT, and GPx levels	

3.1.2.1 Generation of reactive oxygen species (ROS):

Through a number of processes, including the suppression of antioxidant enzymes and the disruption of mitochondrial function, lead can produce ROS in the body. Lead's production of ROS can result in oxidative stress, which harms biological elements like lipids, proteins, and DNA. Lead can deplete the body's antioxidant defenses, such as glutathione and vitamin E, making it more vulnerable to oxidative stress (Bhattacharyya et al., 2014).

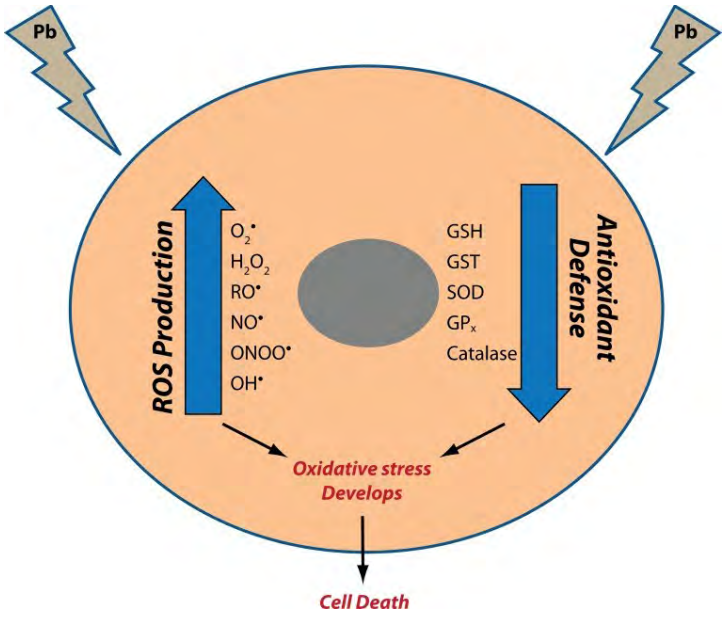

Figure 3: Mechanism causing lead exposure to cause oxidative stress in a cell (Flora et al., 2012)

3.1.2.2 Binding to sulfhydryl groups:

Sulfhydryl groups (-SH), which are crucial for the structure and operation of proteins and enzymes, can bind to lead. Protein conformational alterations brought on by this interaction may impede protein function. One illustration is the way lead binds to the sulfhydryl groups in glutathione to inactivate it. The glutamyl cycle, which is typically ineffective in replenishing the supply of glutathione (GSH), leads to the synthesis of GSH from cysteine (Hultberg et al., 2001). Lead also depresses glutathione levels by inactivating enzymes such as amino levulinic acid dehydratase (ALAD), glutathione reductase (GR), glutathione peroxidase (GPX), and glutathione-S-transferase (Ahamed & Siddiqui, 2007; Flora et al., 2012).

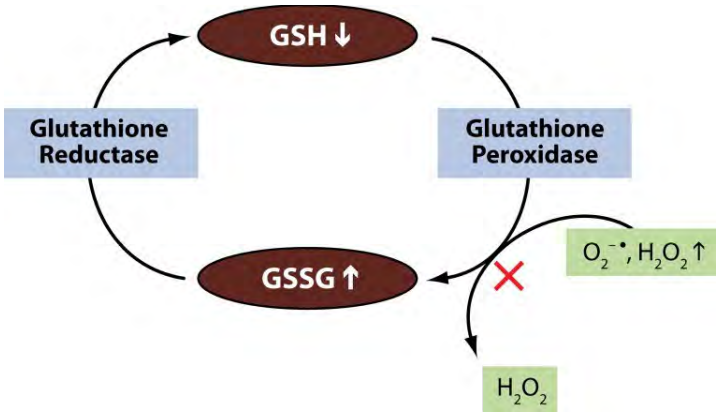

Figure 4: Effect of lead on glutathione (GSH) metabolism (Flora et al., 2012)

3.1.2.3 Disruption of cellular membranes:

Through interactions with the lipids and proteins in the membrane, lead can alter the composition and operation of cellular membranes. Changes in the fluidity and permeability of cellular membranes brought about by lead can have an impact on ion transport, membrane potential, and cell signaling. Lead can also affect membrane transporters and receptors, changing how cells communicate and function (Balali-Mood et al., 2021).

3.1.2.4 Interference with calcium signaling:

Lead can interfere with calcium signaling in cells, which is essential for a number of biological processes. By preventing the release of calcium from intracellular reserves, obstructing calcium channels, and interfering with calcium-dependent signaling pathways, lead can interfere with calcium homeostasis. This may result in altered gene expression and cell proliferation, as well as compromised cellular communication and function. Lead can also imitate calcium and attach to

proteins that are involved in calcium signaling, which further disrupts calcium signaling (Balali-Mood et al., 2021).

Lead can substitute calcium at concentrations as low as picomolar, which affects the main neurotransmitters such as protein kinase C, that regulates long-term brain activation and memory consolidation. Additionally, it has an impact on sodium ions concentration, which are essential for numerous important biological functions, including the generation of action potentials in excitatory tissues for intercellular communication, the uptake of neurotransmitters like GABA, dopamine, and choline, and the regulation of synaptosomes' absorption and retention of calcium. The ability of the aforementioned sodium-dependent activities to perform properly is seriously hampered by this interaction between lead and sodium. (Flora et al., 2012).

3.1.2.5 Interference with gene expression:

Lead's interactions with transcription factors, DNA, and chromatin can affect how genes are expressed. Nuclear Factor-kappa B (NF-κB) and Activator Protein 1 (AP-1) are transcription factors involved in cellular stress responses and immunological function. Lead can block these proteins. Lead can attach to DNA and chromatin, altering cellular function and changing how genes are expressed (Flora et al., 2012).

3.1.2.6 Interference with the heme synthesis pathway:

Lead downregulates three essential enzymes involved in heme production, having a major negative impact on the process in a dose-dependent manner. Aminolevulinic acid synthetase (ALAS) is a mitochondrial enzyme that catalyzes the synthesis of δ-aminolevulinic acid (ALA), followed by δ-aminolevulinic acid dehydratase (ALAD), a cytosolic enzyme that catalyzes the formation of porphobilinogen from ALA (Piomelli, 2002). The cytoplasm is where the

intermediate phases of heme production occur, while the mitochondria are where the initial and concluding steps occur (Flora et al., 2012).

3.2 Mercury

3.2.1 Toxic Effects of Mercury

Mercury reacts with aquatic sediments to form the very poisonous methylmercury (Gworek et al., 2020). Methylmercury poisoning occurs in seafood, fish, and other species of animals that have eaten dangerous microorganisms. This poisoning occurs before the methylmercury reaches the human body. It reaches the circulation after being absorbed by the body and results in a variety of neurological problems (Rice et al., 2014; Mitra et al., 2022).

3.2.1.1 Effect of mercury on the kidney

A broad spectrum of clinical symptoms, such as severe dyspnea, changed mental status, stomach discomfort, excessive salivation, tremors, vomiting, chills, and hypotension, are associated with abrupt tubular necrosis, which is caused by unexpected renal exposure to mercury. On the other hand, chronic mercury exposure causes necrosis of the proximal tubule's pars recta and destroys the epithelium. Tubular failure, elevated excretion of albumin and retinol-binding protein in the urine, and a nephritic state with a hallmark of membranous nephropathy are signs of chronic kidney disease caused by mercury exposure. (Lentini et al., 2017; Mitra et al., 2022).

3.2.1.2 Effect of mercury as carcinogen

Mercury's peroxidative action generates huge levels of reactive oxygen species (ROS), which might encourage the development of malignant cells and promote protumorigenic signalling.

ROS can damage cells and increase the development of cancer by destroying cellular proteins, lipids, and DNA. (Reczek & Chandel, 2017; Zefferino et al., 2017; Mitra et al., 2022).

3.2.1.3 Effect of mercury on the immune system

Heavy metal exposure in the laboratory led to several immunological abnormalities in mice and other rodents, including immunosuppression and immunostimulation. When mercury chloride was injected into experimental animals that were not susceptible to mercury, the animals' immune systems became less functional, resulting in immunosuppression in the animals. Mercury increased immune system cellular activity in mercury-sensitive rodent strains, causing the animals to exhibit immunostimulation. Allergies, autoimmune diseases, and infections can be attributed to both immunostimulation and immunosuppression. It doesn't seem that mercury affects the human immune system, despite the claim of Swedish specialists that amalgam, a mercury alloy, has an influence on the immune system (Mitra et al., 2022)..

3.2.1.4 Effect of mercury on the heart

In humans, mercury has been demonstrated to have harmful effects on the liver, kidneys, and nervous system. Recent studies have also found cardiovascular harm. According to Yoshizawa et al. (2002) and Mitra et al. (2002), mercury levels in hair are associated with levels of oxidised LDL in atherosclerotic lesions, acute cardiac failure, and atherosclerosis. Mercury also inhibits the extracellular antioxidant enzyme paraoxonase, which has been linked to HDL dysfunction and is associated with an elevated risk of coronary heart disease, acute myocardial infarction, coronary heart disease, cardiovascular disease and carotid artery stenosis (Kulka, 2016; Mitra et al., 2022).

3.2.1.5 Effect of mercury on the skin

Many skin conditions, including acrodynia (pink disease), a common dermatological ailment in which exposure to heavy metals, particularly mercury, causes the skin to turn pink, have been linked to mercury and mercury-containing compounds (Horowitz, 2002; Mitra et al., 2022). Those who had the red pigments mercury sulphide and cadmium sulphide applied to their bodies may develop localized inflammation 6 months after receiving tattoos (Boyd et al., 2000; Mitra et al., 2022). Acute contact dermatitis caused by compounds containing mercury presents with mild irritation, vesiculation, scaling, and swelling. Many studies have shown that mercury poisoning is the most common reason of dermatological issues (Boyd et al., 2000; Mitra et al., 2022).

3.2.1.6 Effect of mercury on the CNS

The development of the central nervous system is particularly harmed by some mercury compounds, also referred to as teratogenic agents, which are toxic to the growing neural system (Young et al., 2008). Nonetheless, there is ongoing discussion on the connection between mercury exposure and carcinogenesis, one of the most detrimental results of DNA damage (Figure 2) (Crespo-Lopez et al., 2009; Mitra et al., 2022). The reason for the difference in results is that although some studies have shown mercury to have genotoxic activity, others have not shown any evidence of DNA damage (Crespo-Lopez et al., 2009; Mitra et al., 2022).

3.2.2 Mechanisms of Mercury toxicity

Table 2: Toxic Mechanisms of mercury (Hg) (Balali-Mood et al., 2021)

Heavy Metal	Toxicity in organs	Mechanism of Action	References
Mercury	- CNS injuries - Renal dysfunction - GI ulceration - Hepatotoxicity	- Thiol binding (GSH conjugation) - Enzymes inhibition - ROS production - Aquaporins mRNA reduction - Glutathione peroxidase inhibition - Increased c-fos expression	Bottino et al., 2015; Chen et al., 2019; Zhang et al., 2020; Balali-Mood et al., 2021

3.2.2.1 Generation of reactive oxygen species (ROS):

Mercury can produce reactive oxygen species (ROS) in the body in a number of ways, including through direct contact with cellular elements like mitochondria and indirect stimulation of inflammatory cells like neutrophils and macrophages. As a result of oxidative stress, which harms biological components like lipids, proteins, and DNA, mercury can produce ROS. The body's antioxidant defenses, such as glutathione and vitamin E, can be depleted by mercury, rendering it more vulnerable to oxidative stress (Bhattacharyya et al., 2014).

3.2.2.2 Binding to sulfhydryl groups:

Sulfhydryl groups (-SH) found in proteins, enzymes, and other biological components can bind to mercury. Proteins and enzymes may experience structural alterations as a result of this interaction, which may affect how well they work. For instance, the -SH groups in the Na^+/K^+-ATPase enzyme, which is in charge of preserving cellular ion gradients, can bind to mercury. According to Ajsuvakova et al. (2020), this binding has the potential to interfere with Na^+/K^+-ATPase activity and upset cellular ion homeostasis.

3.2.2.3 Disruption of cellular membranes:

Mercury can interfere with the construction and function of biological membranes by interacting with lipids and proteins in the membrane. Changes in the fluidity and permeability of cellular membranes that mercury can bring about can have an impact on ion transport, membrane potential, and cell signaling. Additionally, mercury can affect membrane transporters and receptors, altering how cells function and communicate (Clarkson & Magos, 2006; Unsal, 2018).

3.2.2.4 Inhibition of enzymes:

Enzymes involved in a number of biological functions, such as DNA synthesis, energy metabolism, and antioxidant defence, can be inhibited by mercury. Enzymes necessary for antioxidant defence and detoxification, like catalase, glutathione peroxidase, and superoxide dismutase, can be inhibited by mercury. Succinate dehydrogenase and pyruvate dehydrogenase are two examples of the energy metabolism enzymes that mercury can impede, reducing the amount of energy that is produced. Additionally, mercury can prevent DNA synthesis and repair enzymes, resulting in DNA damage and mutations (Balali-Mood et al., 2021).

3.2.2.5 Interference with DNA and RNA synthesis:

Mercury interacts with nucleic acids and inhibits the enzymes necessary for nucleic acid synthesis and repair, which can affect how DNA and RNA are made and function. Mercury has the ability to bind to DNA and RNA, causing structural alterations and reduced function. Mercury can prevent DNA synthesis and repair enzymes, which can result in DNA damage and mutations (Jaishankar et al., 2014).

3.3 Cadmium

3.3.1 Toxic Effects of Cadmium

3.3.1.1 Effect of cadmium on the nervous system

Amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and multiple sclerosis are just a few of the neurodegenerative abnormalities brought on by cadmium (Branca et al., 2018; Mitra et al., 2022). Cadmium exposure can cause a wide range of clinical symptoms, such as learning difficulties, mental retardation, peripheral neuropathy, olfactory dysfunctions, neurological disturbances, impaired motor function, and behavioural changes in both adults and

children, according to a number of preclinical studies (Miura et al., 2013; Mitra et al., 2022; Marchetti, 2014). Additionally, a variety of biological activities are impacted, including cell differentiation, proliferation, and death. Cadmium is neurotoxic because it kills brain cells through a process called apoptosis (B. Wang & Du, 2013; Mitra et al., 2022). There are a number of causes for this process, including slowed neurogenesis, slowed neuron gene expression, an epigenetic effect, endocrine disruption, etc.

3.3.1.2 Effect of cadmium on the kidney

Cadmium-induced nephrotoxicity results in severe clinical symptoms such as phosphaturia, aminoaciduria, glucosuria, and Fanconi-like syndrome (Reyes et al., 2013; Mitra et al., 2022). Direct contact with the kidneys has an adverse effect on the proximal tubular epithelium, which leads to elevated levels of cadmium in the urine, aminoaciduria, 32-microglobulinuria, and glucosuria, as well as reduced renal tubular phosphate reabsorption (Mitra et al., 2022). Hypercalciuria, renal failure, and renal tubular acidosis can result from prolonged exposure (Jacquillet et al., 2007; Friberg et al., 2019; Mitra et al., 2022).

3.3.1.3 Effect of cadmium as carcinogen

A hazardous and carcinogenic metal is cadmium. According to the "Toxicological Profile for Cadmium," published in 2002 by Mitra et al., the metal also causes renal, bone, and cardiovascular diseases in addition to cancer. Low to moderate cadmium exposure causes hypertension (Tellez-Plaza et al., 2008; Mitra et al., 2022), diabetes (Schwartz et al., 2003; Mitra et al., 2022), carotid atherosclerosis (Messner et al., 2009; Mitra et al., 2022), and peripheral arterial disease (Navas-Acien et al., 2004). In the general American population, cadmium

exposure has been associated with a higher risk of cardiovascular death in prospective studies (Tellez-Plaza et al., 2013; Mitra et al., 2022).

The International Agency for Research on Cancer has also classified cadmium as a group 1 human carcinogen. Smokers' blood samples had 4-5 times higher cadmium levels than non-smokers (Rahimzadeh et al., 2017) because tobacco is the main case of cadmium absorption in smokers (Engwa et al., 2019). Additionally, according to Engwa et al. (2019), cadmium can lead to testicular degeneration and may be a risk factor for prostate cancer.

3.3.1.4 Effect of cadmium on the liver

The two human target tissues for cadmium are the liver and the renal cortex (Bernard, 2004; Mitra et al., 2022). It builds up in the liver following an initial exposure and is connected to a few hepatic dysfunctions. Oxidative stress and hepatocellular damage are caused by cadmium's modification of the cellular redox equilibrium (Zalups, 2000; Mitra et al., 2022). Cadmium-induced hepatotoxicity, which can be acute or chronic, results in liver failure, which can raise the risk of cancer (Hyder et al., 2013; Mitra et al., 2022).

3.3.1.5 Effect of cadmium on the immune system

Based on the different exposure circumstances, cadmium exposure in the workplace and environment may result in immunosuppressive consequences Humoral immune responses are boosted at low exposure levels, but the consequences of higher exposure levels are still unknown. In contrast, phagocytosis, natural killer cell activity, and host resistance are typically significantly diminished in experimental infections (Mitra et al., 2022). In contrast, phagocytosis, natural killer cell activity, and host resistance are typically significantly diminished in experimental infections (Mitra et al., 2022).

3.3.1.6 Effect of lead, mercury and cadmium on Reproductive and developmental toxicity

The most prevalent pollutants in the environment that can lead to problems in reproduction are heavy metals like lead, mercury, cadmium, and other pollutants. These pollutants put over ten-percent of women at risk of infertility. (Apostoli & Catalani, 2015; Mitra et al., 2022), according to a number of studies by the World Health Organisation (WHO). Research by the WHO found that women are often more likely than men to have infertility. Ovulation issues are frequently the cause of subfertility in women (Upadhyay et al., 2020; Mitra et al., 2022). Reproductive hormones can be used to treat irregular or nonexistent menstrual periods, which are indicators of ovulation issues. Women who were exposed to increasing levels of toxins were more likely to experience infertility due to hormonal imbalances, delay in ovulation, and chromosomal abnormalities in oocytes. Hormonal imbalance is currently the most prevalent cause of infertility in women, and heavy metal poisoning's effects on the endocrine system make this condition worse (Figure 1) (Rattan et al., 2017; Mitra et al., 2022).

3.3.2 Mechanisms of Cadmium toxicity

Cadmium (Cd) is a hazardous heavy metal that endangers both people's and the environment's health. Exposure to polluted food, water, air, and workplace sources can cause cadmium poisoning (Mitra et al., 2022).

Table 3: Toxic Mechanism of cadmium (Cd) (Balali-Mood et al., 2021)

Heavy Metal	**Toxicity in organs**	**Mechanism of Action**	**References**
Cadmium	- Degenerative bone	- miRNA expression	Schutte et al., 2008;

	disease - Kidney dysfunction - Liver damage - GI disorders - Lungs injuries - Disorders in the metabolism of Zn and Cu - Cancer	dysregulation - Apoptosis - Endoplasmic reticulum stress - Cd-MT absorption by the kidneys - Dysregulation of Ca, Zn, and Fe homeostasis - Low serum PTH - ROS generation - Altered phosphorylation	Pan et al., 2013; Pi et al., 2015; Fay et al., 2018; Y. Wang et al., 2018 ; Balali-Mood et al., 2021

		cascades	

3.3.2.1 Disruption of cellular calcium homeostasis:

Although it can enter cells through many pathways, cadmium can also enter cells through protein-dependent permeation. Cadmium, on the other hand, interferes with calcium homeostasis by blocking calcium channels and/or associated proteins. Inducing a disruption of calcium homeostasis, cadmium can also change the amounts of phospholipids in membranes. Cadmium-induced changes in calcium homeostasis cause cell death, autophagy, or cancer (Zhou et al., 2015).

The signaling pathways for the proteins mitogen-activated protein kinase (MAPK) and mTOR can be triggered by calcium overload caused by cadmium and encourage apoptosis. Cadmium also triggers calcium-dependent apoptosis via P53 and GADD45-mediated, c-Jun NH2-terminal kinase (JNK) signalling. GADD45 is most likely not directly involved in genotoxicity stress-induced apoptosis, though. One mechanism that causes cadmium-induced tumours is the rise of intracellular Ca2+. Additionally, phospholipid content in membrane systems can be altered by cadmium, and this can have an impact on calcium distribution, which in turn impacts biological function and signal transmission in cells (Zhou et al., 2015).

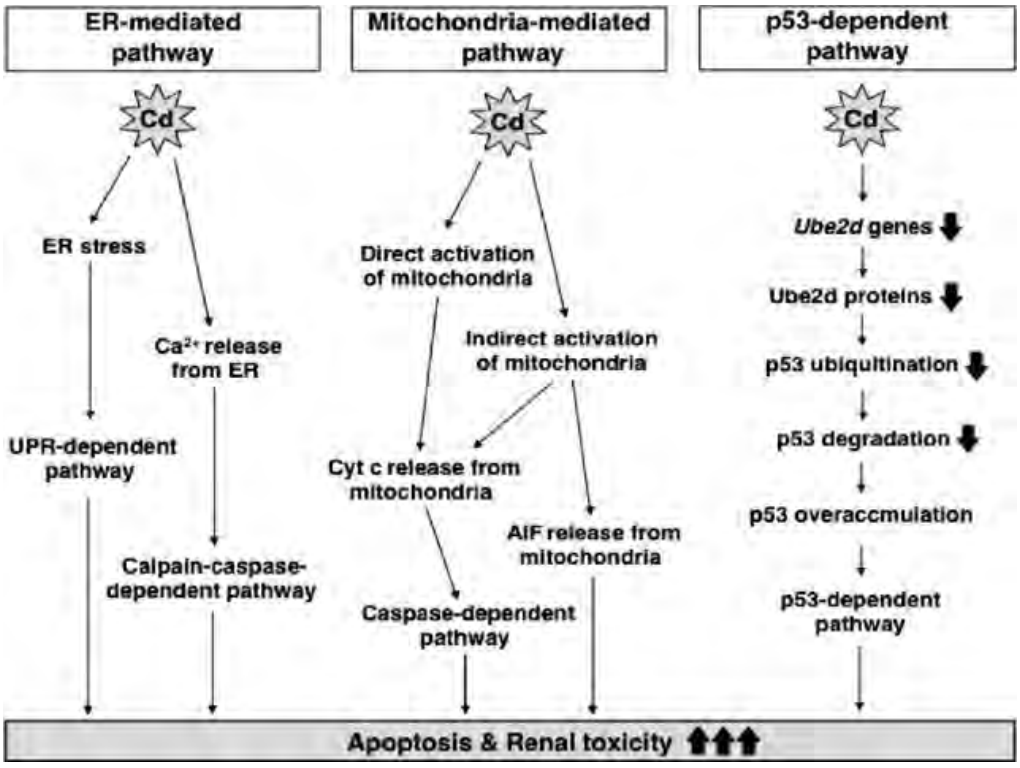

Figure 5: Model for Three Cadmium-Induced Apoptosis Pathways in the Kidney (Fujiwara et al., 2012)

3.3.2.2 Oxidative stress:

DNA damage prevention, inhibition of DNA repair, and interference with apoptosis are the primary mechanisms of cadmium carcinogenesis (Hanahan & Weinberg, 2000; Patra et al., 2011). Proto-oncogene gene regulation, oxidative stress, cadherin disruption, inhibition of DNA repair, and apoptosis interference are other methods. It is well known that strong cell toxin cadmium can change intracellular glutathione levels and/or raise lipid peroxidation, both of which can lead to oxidative stress. The ubiquitin/ATP-dependent proteolytic pathway is impacted. After cadmium exposure, extremely reactive oxygen species may be produced, which could cause the innate antioxidant defenses of the cell to be systematically activated and depleted. Critical biomolecules like enzymes, proteins, DNA, and membrane lipids are especially

vulnerable to oxidative damage when reactive oxygen intermediates are formed in excess of what these antioxidant defense mechanisms can handle (Patra et al., 2011).

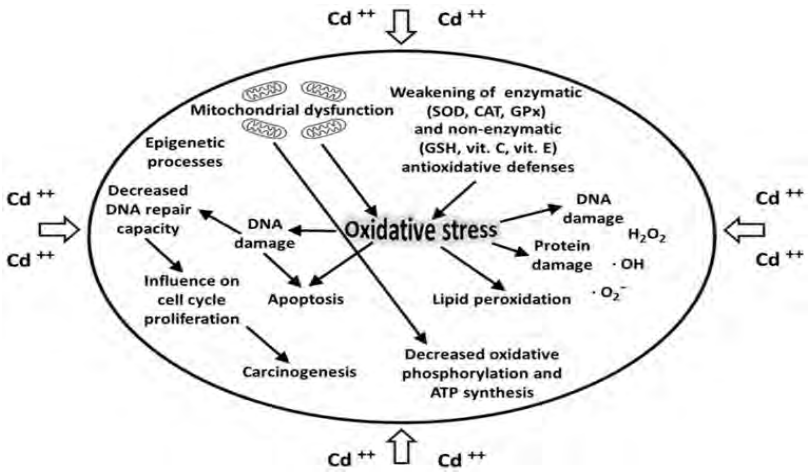

Figure 6: The enzymatic and non-enzymatic antioxidative defences are activated by cadmium's action on mitochondria. Because cadmium causes oxidative stress, proteins, lipids, and DNA are damaged. Cadmium affects cell cycle progression and promotes carcinogenesis by reducing the activity of DNA repair enzymes (Genchi et al., 2020).

3.3.2.3 Metallothionein binding:

The liver is the main target of acute toxicity, whereas the kidneys are the main target of chronic toxicity. The intracellular metallothioneins (MTs) bind Cd ions, which then combine to form CdMT. Chronic poisoning causes Cd to induce the manufacture of new MTs; it is thought that toxicity in cells begins when the load of Cd ions is greater than the ability of intracellular MTs to act as a buffer. When CdMT is released from Cd-damaged organs or administered parenterally for research reasons, it travels through the bloodstream to the kidneys, where it is filtered, endocytosed in proximal tubule cells, and then broken down in lysosomes. Cell structures and

functioning can be directly impacted by liberated Cd. As indicators of tubular injury, the ensuing proteinuria and CdMT in the urine can be employed (Shih et al., 2004).

3.3.2.4 Apoptosis and necrosis:

Cadmium can cause both apoptosis (planned cell death) and necrosis (uncontrolled cell death) by activating different cell death signalling pathways. By triggering signalling pathways that result in the activation of caspases, enzymes that cleave and degrade cellular proteins, cadmium exposure can cause apoptosis. Additionally, cadmium can cause the mitochondria to release pro-apoptotic proteins, which activates caspases and results in apoptotic cell death. By causing oxidative stress, mitochondrial malfunction, and inflammation, cadmium exposure can lead to necrosis. According to Lopez et al. (2003), these mechanisms may lead to tissue damage and the emergence of cadmium-related illnesses.

3.3.2.5 Disruption of cellular signaling pathways:

Cadmium is an endocrine disruptor that may bind to oestrogen receptor alpha and influence signal transduction along the oestrogen and MAPK signalling pathways. It can interact with several hormonal signalling pathways. The cardiovascular system is impacted by low doses of Cd (Fatima et al., 2019). According to epidemiological studies (Reyes-Hinojosa et al., 2019; Genchi et al., 2020), exposure to Cd may encourage the development of musculoskeletal illnesses such osteoporosis, rheumatoid arthritis (RA), and osteoarthritis (OA).

3.3.2.6 Disruption of cell signaling:

Cadmium interferes with crucial signalling pathways involved in metabolism, differentiation, and growth. Protein kinase, hormonal, and calcium signalling pathways are included in this. This increases the overall systemic toxicity of cadmium (Genchi et al., 2020).

Cadmium toxicity is the result of a complex interplay of numerous molecular and cellular mechanisms, including disruption of calcium homeostasis, oxidative stress, interference with metallothionein binding, induction of apoptosis and necrosis, and disruption of cellular signalling pathways (Genchi et al., 2020).

3.4 Vitamin E

3.4.1 Vitamin E as Natural Antioxidant

Vitamin E (α-tocopherol) is a naturally occurring antioxidant that works in the membrane to stop the free radical chain reaction that leads to lipid peroxidation. It is also a fat-soluble vitamin with a wide range of biological actions (Flora, 2002; G. D. Flora et al., 2012). Research has concentrated on its function in suppressing free radicals that the body produces in a variety of pathological circumstances. According to studies, antioxidants can both prevent and treat the damage that free radical production by the body causes. Enzymatic and non-enzymatic natural antioxidants can be distinguished (G. D. Flora et al., 2012).

Enzymatic antioxidants such as glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD) are produced endogenously in the cells, whereas non-enzymatic antioxidants such as carotenoids, flavonoids, vitamins, minerals, etc. are components of many fruits, vegetables, nuts, grains, and some meats. (S. Flora, 2009; G. D. Flora et al., 2012). Just enough antioxidants are present under physiologically normal settings to squelch the free radicals produced at a physiologically normal pace. Oxidative stress can result from an imbalance

between free radicals and antioxidants brought on by any subsequent increase in the concentration of free radicals (due to environmental or natural sources) (Blokhina et al., 2003; G. D. Flora et al., 2012).

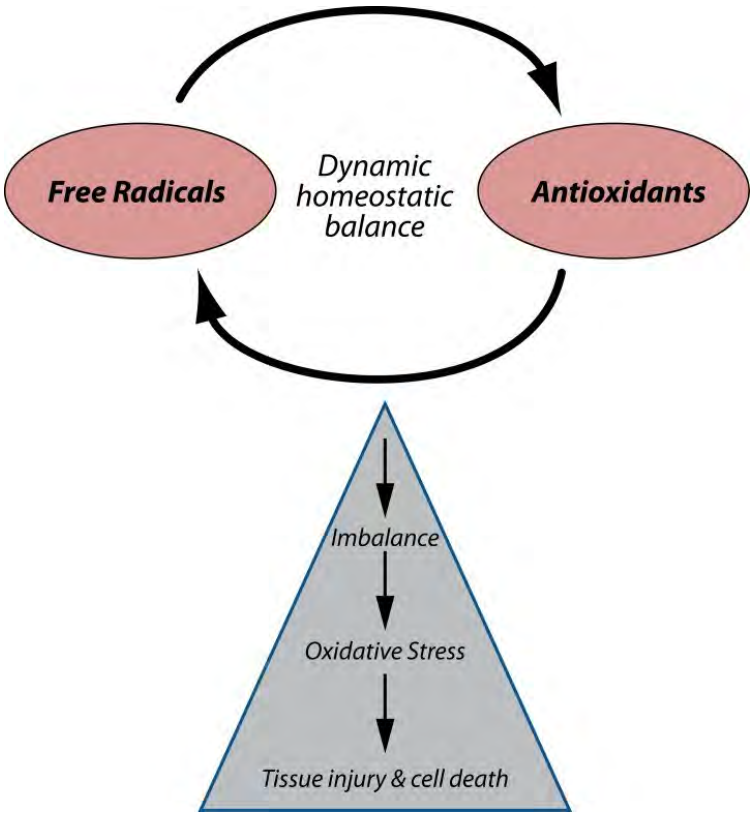

Figure 7: Balance in the body's physiology and the effects of an unbalanced level of free radicals and antioxidants (G. D. Flora et al., 2012).

In Figure 7, it illustrates the balance between free radicals and antioxidants under normal physiological conditions. Any disruption of this balance can result in oxidative stress, which eventually kills cells (G. D. Flora et al., 2012).

This is where exogenous antioxidants play a crucial role. To keep the ratio of antioxidants to free radicals in check and avert a host of detrimental consequences, including heavy metal poisoning, inflammation, cancer, ageing, cardiovascular disease, and brain problems, they are consumed through food or as supplements (Willcox et al., 2004; G. D. Flora et al., 2012).

According to reports, people who consume an antioxidant-rich diet are more likely to experience a variety of health advantages. Food is always preferred over supplements to increase antioxidant levels since it includes thousands of antioxidants, whereas supplements are typically rich in just one or a few (G. D. Flora et al., 2012). According to Sajitha et al. (2010), giving rats vitamin E prevented oxidative stress and counteracted the harmful effects of heavy metals. This was accomplished by scavenging free radicals. It was discovered that the therapy with vitamin E restored the inhibition of δ-aminolevulinic acid dehydratase (ALAD) in the erythrocytes caused by heavy metals (Rendón-Ramrez et al., 2007; G. D. Flora et al., 2012).

It has also been demonstrated that vitamin E helps restore thyroid dysfunction by protecting the architecture of the hepatic cell membrane, which has been subtly changed by lead-induced lipid peroxidation. It has been demonstrated that taking vitamin E alone does not have the same visible effect as taking it in combination with other antioxidants. Rats that receive vitamin E and the thiol chelator monoisoamyl derivative (MiADMSA) concurrently recover from lead load more quickly, according to S. J. Flora et al. (2003). Interestingly, by changing ferric iron into ferrous iron, α-tocopherol can function as a pro-oxidant. G. D. Flora et al. (2012) state that whether or not all of the α-tocopherol is used up in converting the ferric to ferrous iron, or whether any is left over to scavenge the ensuing ROS, determines whether or not it can act as a pro-oxidant (reducing agent) or antioxidant.

3.4.2 Effect of Vitamin E on Animal Studies to reduce heavy metals

There is currently no information on how vitamin E affects the renal and testicular toxicities caused by exposure to a combination of heavy metals (Pb, Hg, and Cd) in mice or other mammals. Additionally, the particular mechanism of action of vitamin E is not entirely understood, and additional research is still needed to understand how vitamin E affects renal and testicular cells. Al-Attar (2011) created the study in order to explore whether or not the administration of vitamin E could mitigate the kidney and testicular damage brought on by heavy metals (Al-Attar, 2011).

3.4.2.1 Effect of vitamin E on Lead:

Long-term exposure to lead (Pb^{2+})has been associated with memory and learning deficits; vitamin E alleviates cognitive impairments. Using a passive avoidance learning model, Khodamoradi et al. (2015) investigated the effect of vitamin E on Pb^{2+} exposure-induced learning and memory impairments in rats. Here, fifty-six Wistar male rats (weighing 230–250 g) were divided into 8 groups (n = 7) for the current investigation. And, for the Pb^{2+} exposure, three different lead acetate solution dosages (0.05%, 0.1%, and 0.2%) were gavaged to the rats for 30 days, while three different vitamin E doses (10, 25, and 50 μg/rat) were used. After 30 days, the rats underwent an acquisition test that involved a passive avoidance task. 48 hours following the training, a retrieval test was undertaken, and step-through latency (STL) and time in the dark compartment (TDC) data were collected. Khodamoradi et al. (2015) used ANOVA for the statistical analysis of the data and followed Tukey's post hoc analysis. Differences were deemed significant in every instance if $p<0.05$ or higher. According to the Khodamoradi et al. (2015) finding, long-term exposure to high levels of Pb^{2+} markedly increased the number of trials necessary for learning as well as the TDC, while adversely affecting the STL in the passive

avoidance test. The effects of Pb^{2+} on animal behavior in the passive avoidance learning and memory task were lessened by vitamin E administration. According to Khodamoradi et al. (2015), learning and memory deficits in rats exposed to Pb^{2+} are dose-dependent and can be prevented by antioxidants such as vitamin E.

Again, vitamin E treatments are particularly successful in preventing oxidative damage. According to Trivedi et al. (1998), Pb at both low and high doses generated lipid peroxidation in the liver, but rats given a high dose of Pb showed signs of heart lipid peroxidation, while the amount of lipid peroxidation in the kidney did not vary considerably. Rats pretreated with vitamin E had reduced liver and heart lipid peroxidation compared to those given high doses of lead without vitamin E (Al-Attar, 2011).

3.4.2.2 Effect of vitamin E on Mercury:

Researchers Agarwal et al. (2010) investigated the effects of vitamin E pre- and post-treatment on acute toxicity caused by mercury in rats. Mercury (12 mol/kg b.w., single intraperitoneal injection) resulted in tissue histological alterations, metallothionein mRNA synthesis, oxidative damage, and organ accumulation. In rats given mercury, vitamin E's ameliorative potential was seen (24 mol/kg b.w., single intraperitoneal injection). their results show that vitamin E offers total defense against liver mercury damage with both pre-and post-treatment. Agarwal et al. (2010), even observe that vitamin E post-treatment provided greater kidney protection than pre-treatment because mercury is nephrotoxic and neurotoxic. On oxidative stress measurements, there was some partial protection in brain tissue. Agarwal et al. (2010) findings thus imply that vitamin E post-treatment may be more advantageous than vitamin E pre-treatment in mercury intoxication.

3.4.2.3 Effect of vitamin E on Cadmium:

In addition to being harmful to human health, heavy metals like cadmium also present a number of environmental issues. In animal models, cadmium has been shown to be embryotoxic and to produce abnormalities of the brain, limbs, and craniofacial region. Oxidative stress and lipid peroxidation are two of the many pathways for cadmium toxicity that have been proposed. In cultured cells, vitamin E has been shown to have antioxidant and cytoprotective effects, but its impact on the toxicity of cadmium to developing organisms is yet unknown. As a representative embryonic tissue, day-8 whole-mouse embryos were employed to produce epithelial-like cells. It was discovered that cadmium toxicity in these grown cells was time- and concentration-dependent. Five microM $CdCl_2$ was significantly less hazardous following exposure to fifty microM alpha-tocopherol or twenty-five or fifty microM alpha-tocopherol acetate. However, the administration of vitamin E in the absence of cadmium was found to increase growth generally, indicating that the apparent cytoprotective advantages might not be entirely specific. (Warren et al., 1999).

Hassan and Awad (2007) showed that vitamin E is efficient at reducing oxidative stress in mice given Cd and that vitamin E activity may be significantly influenced by decreases in enhanced lipid peroxidation brought on by Cd toxicity. According to Hassan and Awad's (2007) research, exposure to Cd led to a noticeably increased degree of lipid peroxidation and a decrease in SOD. Additionally, they showed that vitamin E therapy considerably lessened alterations brought on by Cd exposure in all parameters tested (Al-Attar, 2011).

3.4.3 The Mechanism of Reducing Heavy Metal toxicities by Vitamin E

There is evidence that vitamin E attenuates toxicity induced by decreases heavy metal distribution. Studies in animals show that vitamin E in the diet can counter the effects of lead concentration (fish: El-Shebly, 2009; rabbits: De Rosa, 1954). Their work suggested that vitamin E has a stimulatory effect on haem synthesis, apparently through its action on δ-Aminolevulinic acid synthetase. Moreover, added vitamin E in diet resulted in a marked and significant reduction of basophilic 'stippling' (a marker of toxic injury to the bone marrow, indicative of megaloblastic anaemia). Levander et al. (1978) found that vitamin E can decrease the fragility of red blood cells in the presence of lead.

3.4.3.1 Prevention of oxidative stress by vitamin E:

Strong antioxidants like vitamin E break down chains of oxidation by preventing reactive oxygen species molecules from being created during fat oxidation and from spreading free radical reactions (Burton et al., 1983; Rizvi, 2014). Its concentration ratio may be as low as one molecule for every two thousand phospholipid molecules, although it is mostly present in cell and organelle membranes where it can have the greatest protective effect. In order to prevent lipid peroxidation, it serves as the first line of defense, shielding the cell membranes from oxidative damage (Figure 8). According to studies, a combination of tocopherols inhibits lipid peroxidation in human erythrocytes more potently than alpha-tocopherol alone (Howard et al., 2011; Rizvi, 2014). It also safeguards the polyunsaturated fatty acids found in plasma lipoproteins and membrane phospholipids due to its peroxyl radical-scavenging activity (Tran et al., 1996; Rizvi, 2014).

The tocopheroxyl radicals produced can either:

(1) oxidize other lipids,

(2) go through additional oxidation to produce tocopheryl quinones,

(3) react with another tocopheroxyl radical to make non-reactive tocopherol dimers, or

(4) be reduced by other antioxidants to tocopherol.

It has been discovered that although gamma-tocopherol captures and neutralises the free radicals that are already present, vitamin E (alpha-tocopherol) primarily inhibits the generation of new free radicals (Rizvi, 2014).

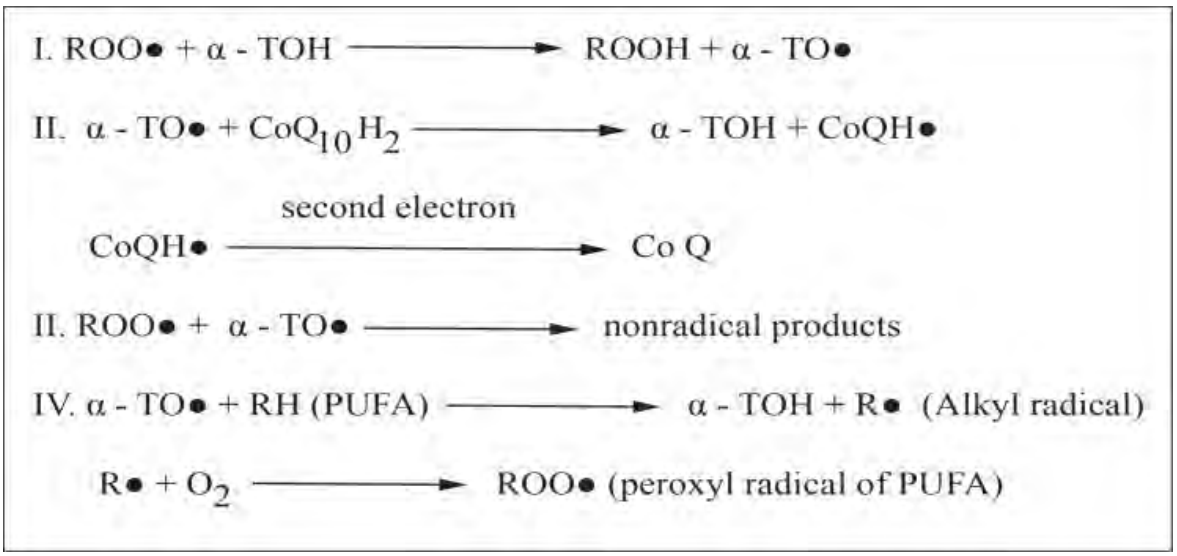

Figure 8: The way that vitamin E (alpha-tocopherol) affects lipid peroxidation in low-density lipoproteins (Rizvi, 2014).

3.4.3.2 Protection of the cell membrane by vitamin E:

Vitamin E improves the orderliness of the lipid packing in the membrane, enabling a tighter packing of the membrane and, as a result, higher cell stability. By supplementing cultured myocytes with alpha-tocopherol, Howard et al. (2011) shown that vitamin E is essential for

maintaining correct skeletal muscle homeostasis (Szczeklik et al., 1985; Rizvi, 2014). This happens because oxidants frequently target the membrane phospholipids, and vitamin E effectively inhibits lipid peroxidation. Contrarily, when cultivated cells are exposed to an oxidant assault without alpha-tocopherol supplementation, the repair is notably inhibited. Comparative measurements show that an antioxidant must link with the membranes, like alpha-tocopherol does, or be able to regenerate alpha-tocopherol, in order to promote the repair. Since oxidised phospholipids could hypothetically interfere with membrane fusion events, vitamin E promotes membrane repair by inhibiting their synthesis (Rizvi, 2014).

3.4.3.3 Regulation of Platelet Aggregation and Protein Kinase C Activation:

It has been discovered that elevating the level of vitamin E in endothelial cells inhibits platelet aggregation and causes the endothelium to release prostacyclin. This impact was assumed to be brought on by a decrease in the vascular cell adhesion molecule (VCAM-1) and intracellular cell adhesion molecule (ICAM-1), which make it more difficult for blood cell fragments to adhere to the endothelium. Additionally, as a result of vitamin E's upregulation of cytosolic phospholipase A2 and cyclooxygenase-1 in the arachidonic acid cascade, more prostacyclin is released, which has been shown to be a potent vasodilator and inhibitor of platelet aggregation in humans (Brigelius-Flohé et al., 1999; Rizvi, 2014). Other research indicates that tocopherols may prevent platelet aggregation by preventing protein kinase C (PKC) and enhancing the activity of nitric oxide synthase (Steinberg et al., 1989; Rizvi, 2014)

3.4.3.4 Vitamin E has a chelation effect:

Vitamin E can also act as a chelating agent and bind to heavy metals, reducing their bioavailability and toxicity. Chelation involves the formation of a complex between a metal ion

and a ligand, which can reduce the metal ion's reactivity and toxicity. Vitamin E can bind to heavy metals such as lead, mercury and cadmium and reduce their toxicity by preventing the further formation of ROS (G. D. Flora et al., 2012).

3.4.3.5 Regulatory role on gene and protein expression:

Depending on the tissue, distinct genes were modified by vitamin E supplementation, which suggested that changes in gene expression are indicative of tissue function and the tissue-specific regulation of vitamin E. The vitamin E forms employed for intervention also had a varied impact on the level of gene expression and the kinds of genes whose expression was changed. Metabolite analyses have improved understanding of the vitamin E metabolic route and generated proof that vitamin E regulates the metabolism of glucose, lipids, and energy (Kim & Han, 2019).

3.4.3.6 Vitamin E enhances immune responses:

In animal and human models, vitamin E has been demonstrated to improve immune responses and to offer protection against a number of infectious diseases. These changes may be mediated by one of three possible mechanisms: (1) the inhibition of COX2 activity, which lowers NO production and reduces PGE2 production; (2) the enhancement of effective immune synapse formation in naive T cells and the beginning of T cell activation signals; or (3) the modification of the Th1/Th2 balance. Vitamin E was found to increase NK activity and alter dendritic function by reducing IL-12 synthesis and migration, although the underlying processes still need to be clarified (Lee & Han, 2018).

Chapter 4

Conclusion

Humans can be exposed to heavy metals through a variety of channels, such as food, water, contaminated air, skin contact, and work-related exposure. Even though certain heavy metals are necessary for specific body processes, high concentrations of these metals can have detrimental effects on health. Many heavy metals are hazardous in small quantities. The production of free radicals, cellular molecule destruction, DNA damage, and neurotoxicity are the primary mechanisms of heavy metal toxicity. Certain types of toxicity can be acute or chronic, resulting in harm to various organs such as the kidney, liver, brain, and lungs, and ultimately leading to different diseases (Engwa et al., 2019; Mitra et al., 2022; Ungureanu & Mustatea, 2022)

A study shows, in rats infused with heavy metals, vitamin E treatment dramatically protected the kidney and testis structures. Treatment with vitamin E may lower cardiovascular disease and uremia, which are associated with chronic renal failure. Lipid peroxidation is inhibited and fewer reactive antioxidants are produced when vitamin E stops the chain of events that produces free radicals. Moreover, it lessened the alterations in parameters brought on by exposure to heavy metals, indicating that antioxidants offer a reliable safeguard against overconsumption. Vitamin E might be a useful prophylactic. In conclusion, vitamin E may be a valuable preventative agent due to its protective effects on the oxidative stress and damage caused by heavy metals (Al-Attar, 2011).

4.2 Limitation of the study:

During the review, just a few limitations were found. The following are some of the study's limitations:

i. Some articles were unreachable as they were paid.
ii. There were not much recent articles available.
iii. Only few researches have been done using vitamin E.
iv. There were no research done with vitamin E on human trail.
v. There were no information available in context of Bangladesh.

4.3 Future study plan:

Future research can be done on human studies on how vitamin E can decrease and heals the toxicities caused by the heavy metals. Moreover, to widen up the research the studies can be done on pregnant animal models or pregnant woman to study on the outcome of the fetus.

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