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HEAVY METALS IN THE ENVIRONMENT AND THEIR TOXICOLOGICAL CONSEQUENCES ON ANIMAL HEALTH

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ABSTRACT: Heavy metals are prominent pollutants in the environment that are found in all environments due to their toxicity and ability to linger in the atmosphere while they contaminate soil, water, and biota. These contaminants tend to bio-accumulate in human bodies and ultimately endanger human health. Some heavy metals are produced by anthropogenic activities, but majority of them are found in nature. Living organisms may be exposed to heavy metals through the food chain when they interact with other environmental elements including soil, water, and air. This may make heavy metals exceedingly harmful. Humans, however, are more susceptible to a combination of elements than to just one substance. The combination of heavy metals can cause oxidative stress and inflammatory processes, which cause damage to multiple organs. This review enlightens the fate of heavy metals and their toxicological effect on various organs systems. Some metals have an impact on development and biological processes, while other metals build up in one or more organs and can lead to a various illnesses. This article focuses on the disease-causing component as well as the physiological and biochemical implications of heavy metal bio-accumulation in organs. Further, dietary interventions employing alternative treatments may be investigated as a substitute strategy for controlling the long-term negative effects of exposure to heavy metal on public health.

Keywords: Exposure; contamination; heavy metal; health; toxicity.

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1. INTRODUCTION

Metal contamination in the environment has deleterious influence on most of the life forms on earth. The adverse impact of metals and metalloids in the living systems is more apparent with rapid industrialization and urbanization [1-3]. Although, metals like Manganese (Mn), Copper (Cu), Zinc (Zn), Iron (Fe), Nickel (Ni), Cobalt (Co), Molybdenum (Mo), and Selenium (Se) are trace elements needed for biological activities, whereas, elements such as Lead (Pb), Mercury (Hg), Arsenic (As), Chromium (Cr) and Cadmium (Cd), have no known biological role and, are harmful to the animals beyond a certain range [3]. Essential heavy metals are vital to life and are required in very small amounts within the body. An excess or shortage of a necessary heavy metal causes aberrant states or disorders. Priority pollutants known as non-essential metals (NEMs) have the potential to endanger both human health and the ecosystem. However, different categories of creatures, such as plants, animals, and microbes, may have distinct essential heavy metal. This implies that a heavy metal can be necessary for one class of species but not necessary for another. These necessary components are needed in the ideal quantity and act as significant co-factors for a number of catalytic pathways. Beyond a certain concentration these metals can be toxic and adversely affect the physiology and health of most organisms, including humans. Individuals may come into contact with heavy metals at work or in the surrounding environment. Exposure to toxic substances by humans in the workplace is referred to as occupational exposure; exposure to the same chemicals in the general public is referred to as non-occupational or environmental exposure [4]. Non-occupational exposure involves ingestion via contaminated food, water or by skin contact. Additionally, a lot of these metals are released into the air, ground water, and soil by the metallurgical, refractory, and chemical industries, endangering the health of people, animals, and marine life. In mining and industrial settings, workers can inhale in dust or other particulate matter that contains metal particles, exposing them to heavy metal exposure [5]. Workers who extract gold by amalgamation are in contact with mercury fumes. According to reports, welders who were exposed to welding fumes for an extended period of time at work had blood levels of the heavy metals (Cr, Ni, Cd, and Pb) significantly greater than those of the control group. Smoking cigarettes is also a common source of exposure to Cd and other hazardous heavy metals found in tobacco leaves. Food crops grown in environments contaminated with heavy metals causes these elements to bio-accumulate in human food chains via geo-chemical cycles. Chronic poisoning effects on animals have been commonly observed if adequate every day intake amounts are surpassed [6]. Most of the

metallic elements are harmful as they have a tendency to accumulate in soft tissues of animals. Each of these metals has a unique mechanism and biological route of action in the target system [7, 8].

SOURCES OF HEAVY METAL EXPOSURE

Our surroundings naturally contain heavy metals. The lithosphere, hydrosphere, biosphere, and atmosphere all contain them [9]. Their natural sources include weathering of metal-bearing rocks and volcanic eruptions, while anthropogenic sources such as mining, various industrial and agricultural activities also add to the burden of metals in the environment (Fig. 1) [10]. Heavy metals are well-known environmental pollutants due to their toxicity, persistence and bio accumulative nature. These heavy metals can be found in ores found in the earth's crust that are extracted as minerals during mining operations. Certain heavy metals such as Cu, Fe and Co can exist both as sulfide and oxide ores. Heavy metals are released from the ore during these mining operations and dispersed across the open environment contaminating the water. Furthermore, various heavy metals can be found in industrial products including paints, cosmetic products, insecticides, and herbicides. Acid rain, runoff, and degradation are some of the ways that heavy metals can travel over soils and aquatic bodies. In addition, certain fertilizers, herbicides, and involving animal feeding emit larger quantities of As into the environment [11, 12]. It has been discovered that the inorganic forms of arsenic, such as arsenite and arsenate, are more dangerous to human health. They have a high carcinogenic potential and have been linked to skin, liver, bladder, and lung cancer. Humans are exposed to arsenic by means of air, food and water. One of the main causes of As toxicity in over 30 countries worldwide is drinking water as in Africa, Asia, South America and Europe contaminated with As [13]. Long duration of exposure to Pb can result in birth defects, allergies, dyslexia, mental retardation, psychosis, autism, weight loss, hyperactivity, paralysis, muscular weakness, kidney damage, and even death [14]. The heavy metal Hg is considered to be the most toxic to the environment because of their persistent, accumulative and toxic nature, as they sediment in water bodies and enter the food chain. Many industries, including the pharmaceutical, paper and pulp preservation, agricultural, and chlorine and caustic soda producing sectors, release Hg into the environment [15]. Hg may generate both organic (methyl-mercury and ethyl-mercury) and inorganic forms (Mercurous) when it combines with other elements. High concentrations of metallic, organic, and inorganic Hg can harm a developing fetus, brain and kidneys [16]. Cadmium is released into the environment by both natural processes including volcanic eruptions, weathering, and river movement, as well as by some human activities like mining, smelting, smoking tobacco, burning

municipal waste, and producing fertilizers. Immediate and long-term intoxication are both possible with Cd [17]. Cadmium builds up in greater amounts in the proximal tubular cells, where it poses a serious risk to the kidneys. Rocks, plants, animals, and soil all contain Cr. It can exist as a gas, a liquid, or a solid. In water sediments, chromium compounds are extremely persistent. Results from various in vitro and in vivo experiments have demonstrated that chromatic compounds can cause damage to DNA in a variety of ways. These include chromosomal aberrations, sister chromatid exchanges, DNA adduct formation, changes in DNA replication, and transcription [18, 19]. In the crust of the earth Fe is the most abundant transition metal. It is a co-factor for numerous essential proteins and enzymes; it is the most significant nutrient for the majority of living things. Since children are exposed to the highest amount of Fe-containing products, they are particularly vulnerable to Fe toxicity [20]. Fe toxicity progresses through four stages, beginning with gastrointestinal symptoms like vomiting and diarrhea, followed by a latent period of apparent recovery. The third stage manifests with severe symptoms such as hypotension, hepatic necrosis, and metabolic acidosis, often leading to fatalities. In the final stage, gastrointestinal ulcerations develop, posing long-term health risks, particularly in countries with high meat consumption due to excess iron uptake potentially increasing cancer risk [21].

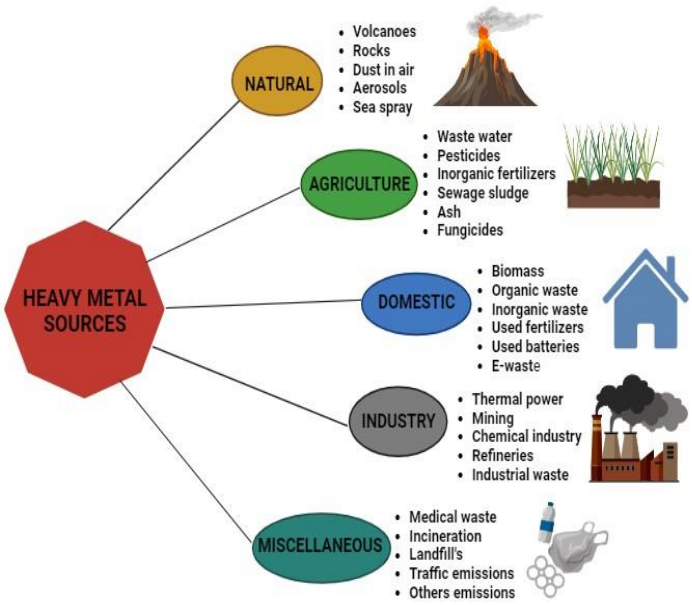

Fig. 1 Overview of the several natural and anthropogenic sources of heavy metal contamination

IMPACT OF HEAVY METALS ON ANIMAL HEALTH

Over exposure to heavy metals (Ni, Cr, Cd, etc.) in the human body has been associated with serious long-term consequences such immunotoxicity, neurotoxicity, and toxicity to development and reproduction [22-24]. Due to prevalence in the environment and As, Cd, Pb and Hg have received the greatest attention in research (Fig. 2) [1]. The net absorption of a pollutant from any source across all possible pathways, including ingestion, direct contact and respiration, is known as bio-accumulation. An organism may have a higher concentration of a pollutant in it than in its prey due to bio-magnification at upper trophic levels caused by bio-accumulation and further transmission of heavy metals into the food chain. Furthermore, it has been discovered that heavy metals affect the mitochondria, endoplasmic reticulum, lysosomes, nucleus, cell membrane, and certain enzymes involved in metabolism, detoxification, and damage repair, among other cellular organelles and components [25]. It has been established that metal ions interact with nuclear proteins and DNA inside cells, causing damage to the DNA and conformational changes that may result in apoptosis, cancer, or altered cell cycle regulation. Numerous physiological functions, such as those of the central nervous system, liver, hematopoietic system, and renal system, can be adversely affected by toxic metals. Because of the distinctive ways in which metals interact with organs, tissues, and cells, they can have a wide range of toxic effects that can be systemic or local, acute or chronic. Acute intoxication are rare; instead, chronic intoxication are more common due to strong propensity of Pb to accumulate in erythrocytes and bone. Lead and Hg poisoning can result in autoimmunity, a disorder where the patient's immune system targets his own cells. This can lead to problems with the kidneys, neurological system, and joints, such as rheumatoid arthritis. The harmful effects of heavy metals on the body when consumed in excess of the bio-acclaimed limitations are known as the bio-toxic consequences of heavy metals. All metals exhibit some degree of toxicity, but the most common symptoms include convulsions and vomiting, gastrointestinal (GI) disorders, diarrhoea, stomatitis, tremor, hemoglobinuria, ataxia, paralysis, depression, and pneumonia when volatile fumes and vapours are inhaled [26]. This could indicate toxicity in terms of neurotoxicity, carcinogenicity, mutagenicity, or teratogenicity, depending on the nature of its effects (Fig. 3). Thorough investigations have demonstrated that pre-chronic toxicity and carcinogenesis in humans can be caused by heavy metals (As, Pb, and Hg). Chromium, As, and Ni are classified as human carcinogens based on epidemiological studies [27, 28], whereas Be, Pb and Cd may also cause cancer in humans. They are used in many commercial applications. Molecular pathway analysis was

carried out to investigate the toxicity and carcinogenic consequences of these metals. According to the research, the metallic materials mentioned above increase the risk of cancer and other illnesses [29].

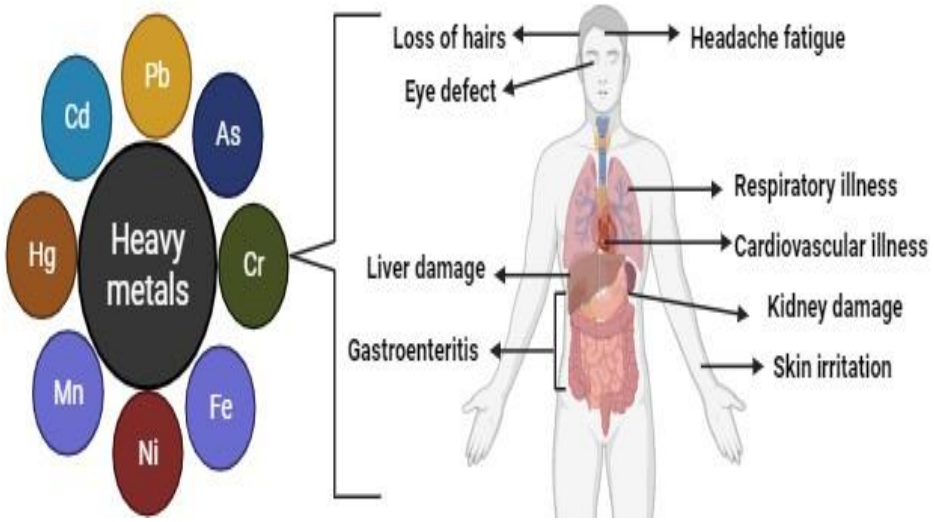

Fig. 2 Impact of heavy metal toxicity on human health

TOXICITY MECHANISM INDUCED BY HEAVY METALS AND METALLOIDS

Hepatotoxicity

The term "hepatotoxicity" describes the harm that different substances and xenobiotics, such as heavy metals can cause to the liver [30]. Because of its important function in the metabolism and elimination of foreign substances, the liver is susceptible to the harmful effects of these substances [29]. Jaundice, which is by an excess of bilirubin in the extracellular fluid, is one of the signs of hepatotoxicity; other symptoms include intense abdominal pain, generalized itching, nausea, fatigue, weakness, skin rashes, edema, weight gain, dark color urine [31]. The liver is susceptible to adverse effects because of its primary function in the removal and metabolism of substances [32]. Bhattacharjee *et al.,* 2016 [33] evaluated the effects of prolonged dose in low quantity exposure to a mixture of Cd, As, and Pb because metals are so common in the environment. Hasanein *et al.,* (2016) [34] four groups of seven male Wistar rats each were randomly selected for the purpose of study. Following the completion of the experiment, the rats were sacrificed, the liver tissue was removed, and blood samples were carefully collected. The results showed a severely damaged liver along with a notable increase in the enzymes ALP, AST, and ALT. On the other hand, the albumin content was low. This indicated that consumption of Lead acetate solution caused hepatotoxicity.

Human liver cells cultured with varying amounts of Cr resulted in intracellular ROS generation within 24h. It was also shown that mitochondrial damage and cell death in the mitochondrial membrane [35]. In a study, the abnormal gene expression in a population of Guizhou, China, was identified using a complementary DNA (cDNA) expression array of human cancer. The patients in the chosen group had at least 6–10 years of exposure to As. Histology revealed vacuolation, localized necrosis, and persistent inflammation in the samples from these individuals. The investigation also identified alteration in the molecular pathway crucial for both carcinogenesis and As-induced hepatotoxicity [36]. The rats undergoing Hg treatment had significant liver damage, where, increases in AST, ALT, and ALP as well as decreases in GSH, GPx, CAT, and SOD in the liver tissue could be associated to liver injury [37]. Free radicals are also produced by Cr (VI) through a variety of processes that lead to peroxidation. Hepatotoxicity results from the per oxidative stress it causes throughout the body. According to recent research, the presence of Cr (VI) causes a considerable drop in antioxidant indicators when peroxidase markers are continuously rising [38]. The liver has been one of the organs that are most impacted by the oxidative stress caused by these heavy metals, which has resulted in several molecular and ultrastructural alterations. This has been linked to the production of ROS, modifications to the antioxidant system, lipid peroxidation, and genomic alterations. It has also been linked to variations in the ER, mitochondrial structure and function, nuclear alterations, and vacuolar degeneration.

Nephrotoxicity

Nephrotoxicity is defined as a rapid decline in kidney function brought on by the harmful effects of drugs and chemicals. The kidney's ability to concentrate and reabsorb divalent ions and metals makes it a target organ in cases of heavy metal toxicity. The type, dose, and timing of exposure all affect how much kidney impairment results. One of the most common diseases in the world today is chronic kidney disease (CKD). It is characterized by a decline in the glomerular filtration rate (GFR) at the end and a permanent loss of nephrons [39]. Due to the widespread presence of heavy metals in the nature, people are frequently exposed to toxins over time that can have a detrimental impact on several organ systems in the body, including the kidney. Eight to sixteen percent of people worldwide are thought to have CKD [40]. Metals that are recognized to be nephrotoxicants and persistent environmental toxins include As, Pb, Hg, and Cd [41]. Decrease in the total glomerular filtration rate (GFR) lead to the accumulation of foreign substances and toxicants in the blood, which can cause metabolic distortion and/or poisoning of organs [27]. Kidney enlargement, histological

alterations, nuclear and mitochondrial damage, decreased antioxidant capacity, elevated metal concentration, and malondialdehyde (MDA) are a few examples of these impacts [12]. There are two distinct kinds of heavy metals in plasma based on their proliferation: those that are complex/ ionized (diffusible) and protein bound (non-diffusible). Metals are stored in various tissues and are rapidly removed from the circulation. Both the bound form and the free form may be present in the luminal fluid of the early proximal tubule. Chronic poisoning result in the conjugation of the protein's bound, inactive form with glutathione and metallothionein, which are then released into the bloodstream by the kidney and liver. These compounds can cause persistent inflammation, fibrosis, and renal failure when they are subsequently reabsorbed in segment S1 of the proximal tubule by an endocytotic mechanism [42, 43]. The apical membrane of the first zone of the proximal tubule is the primary location of heavy metal re-absorption during acute poisoning, but the loop of Henle and the terminal segments may also be involved. The ionized form causes acute kidney injury by disrupting cellular membranes, causing direct cellular toxicity, and uncoupling the mitochondrial respiration pathway. It also releases many apoptotic signals, including reactive oxygen species and cytokines [43]. Yuan *et al*., (2014) [44] demonstrated that rats exposed to a combination of Pb and Cd had kidney injury and also established the cumulative nature of their interactions. Similar results were published by Hambach *et al.,* (2013) [45] who discovered that kidney biomarkers and cadmium are more closely linked when Pb and Cd are exposed together. It has been established that exposure to heavy metals affects the performance of the nephrons that are still functional [46]. These adverse consequences might increase glomerulosclerosis and cell death, which would continuously lower the individual's functional renal mass. As increase the pH and volume of urine, increases the excretion of Ca^{2+}, reduce electrolyte levels, and increase kidney weight. Kidney disease due to Pb exposure is linked to high blood pressure, reproductory, cardiovascular, and neurological disorders [41]. Lead mostly affects the proximal convoluted tubules, where it reduces the absorption of glucose, amino acids, and phosphate and interferes with mitochondrial function [47]. The gastrointestinal tract (GIT) and kidneys are the primary organs affected by Hg salts. Prolonged exposure might result in acute tubular necrosis, immunological glomerulonephritis, or nephrotic syndrome. This is due to the preferential accumulation of Hg ions in the renal tubule epithelial cells. Hence, renal damage is caused by elevated Hg levels [48]. Chronic exposure to elemental Hg vapors, inorganic Hg, and ingesting Hg^{2+} salts have been linked to nephrotic syndrome, which is characterized by acute tubular necrosis, proteinuria, and albuminuria [49].

Neurotoxicity

Metals are easily accumulated by the neurological system, which makes neurotoxicity possible. The nervous system is susceptible to xenobiotics due to a number of factors, including its complex structure, lengthy developmental period, its connection to other organ systems, post-mitotic differentiation composition, their selective transport into the central nervous system (CNS), high rate of metabolism, and myelination. Although every element has a role in metal-induced neurotoxicity, the blood–brain barrier (BBB) and the brain's metabolic activity are considered to be the most significant for metal Hg induced toxicity studies. Aragão *et al*., (2018) [50] showed that oral chronic treatment of $HgCl_2$ to rats resulted in hippocampus injury and cognitive impairment. Additionally, they discovered that whilst with the control group's Hg contents were less than 0.01 μg/g, whereas the hippocampal Hg levels rose to 0.04 μg/g in exposed animals. Another study found that rats given varying amounts of 0.05, 0.5, and 5 mg/kg Hg suffered CNS damage in comparison to the normal saline group. In treated rats, Hg buildup in the brain was also noted [51]. Research on primary cultures of neurons and glia, isolated mitochondria from the mouse brain, and non-neuronal cell lines revealed a close relationship between oxidative stress and a reduction in GSH levels [52, 53]. CNS damage was detected by increased expression of the crucial signal transduction channel, c-fos, in the cortex and hippocampus. There was also evidence of Hg build-up in the brains of the treated rats [51]. Treatment of lead acetate (PbA) (15 mg/kg) to pregnant Wistar female rats resulted in the induction of proinflammatory cytokines in the hippocampus, including TNF-α and IL-1β in the forebrain of immature rat brain. These findings showed that long-term exposure to Pb promotes inflammation in the developing rat brain's central nervous system (CNS), possibly as a result of glial cell activation [54]. In addition, Pb exposure caused necrotic alterations in the kidneys, liver, and brain [55]. Pb exposure poses a particular risk to children under six years old due to its ability to disrupt nerve cell formation, growth, and differentiation, as well as cause harm to bone structure. Even low blood levels of Pb can change neurotransmitters like norepinephrine (NE) and its metabolite, according to research by Bijoor and coauthors [56, 57]. According to other research, Cd reduces the absorption of Zn, Ca, and Co, which lowers dietary intake of these vital nutrients [27]. Yousef *et al*. (2008) [58] suggested that curcumin may be able to prevent carcinogen-induced metabolic alterations in rats' liver and brain [59].

Cardiovascular toxicity

Cardiovascular toxicity comprises arterial atherosclerosis brought on by oxidative stress and inflammation, as well as damage to the heart via toxin-induced electrical abnormalities or/and muscle damage. When combined, these anomalies might hinder circulation and blood flow. It's possible that inflammation and oxidative stress are the main pathogenic factors behind cardiovascular damage [60]. Over the past 20 years, the body of research on the relationship between environmental exposure to heavy metals and the risk of CVD has grown significantly [61]. Provocative evidence has been found in recent research connecting exposure to heavy metals in the environment with higher risks of diabetes and hypertension [62, 63]. High blood pressure and diabetes are significant CVD risk factors. Some of the necessary metals (Co, Cu, Cr, Ni, and Se) and toxic metals (As, Cd, Pb, and Hg) are metallo-estrogens and may raise the risk of CVD by disrupting hormones [64]. Few research, meanwhile, have directly and thoroughly examined the impact of being exposed to several heavy metals, particularly the combined impacts on the risk of CVD. On the contrary, prospective cohort studies have demonstrated a clear correlation between decreased risk of cardiovascular disease (CVD) with high levels of dietary and serum critical trace metals. These findings suggest that supplementing with these metals may offer potential advantages by attenuating the damaging [65]. Acute or chronic Pb exposure causes the body to exhibit a number of problems. Chronic exposure to Pb may result in arteriosclerosis and hypertension, thrombosis, atherosclerosis, and cardiac disease. Long-term exposure also raises arterial pressure [66]. In addition to its carcinogenic qualities, Cd can cause renal, bone, and cardiovascular diseases. Hypertension, diabetes, peripheral arterial disease, chronic kidney disease, myocardial infarction, stroke, and heart failure are all linked to low to moderate Cd exposure [67]. Cadmium has been associated in prospective studies with a higher risk of cardiovascular mortality in the US general population [68]. Human neurotoxicity, nephrotoxicity, and hepatotoxicity have all been linked to Hg exposure. Recent studies have also found cardiovascular harm. Acute cardiac failure, atherosclerosis, and oxidized LDL levels in atherosclerotic lesions have all been related to higher Hg levels [69]. Similarly, Hg inactivates paraoxonase, an extracellular antioxidant enzyme associated with HDL dysfunction, this is directly related to the development of atherosclerosis and the elevated risk of coronary heart disease, cardiovascular disease, acute myocardial infarction, and carotid artery stenosis [70]. Reversible systolic heart depression brought on by cobalt poisoning was identified

from other cardiomyopathy conditions. Co-induced cardiomyopathy can be slowly and fatally lethal [71].

Cytotoxicity

The ability of some substances or mediator cells to kill living cells is known as cytotoxicity. Cytotoxic compounds, such as heavy metals, have the ability to cause either intentional cell death (apoptosis) or accidental cell death (necrosis) in healthy living cells. The predominant form of cell death carried by Pb and Cd co-exposure to isolated RBCs of the common buzzard (*Buteo buteo*) was demonstrated to be apoptosis [72]. The mixture's adverse effects on bone marrow were indicated by the cytogenetic alterations it causes in bone marrow cells. It has been observed that the mixture's constituents cause cytogenetic damage in bone marrow and other cells, resulting in chromosomal abnormalities, micronuclei induction, and sister chromatid exchange (SCE) [55]. Thus, their investigation came to the conclusion that the metal mixture's observed cytogenetic effects may be related to DNA damage caused by oxidative stress, disruption of the process of DNA repair, and replacement of vital metal ions in cells [73]. Pro-inflammatory cytokines soluble mediators released at the site of infection by activated auxiliary immune cells that are known to cause behavioral, autonomic, and endocrine abnormalities are typical [74]. These mediators include tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and interleukin-1alpha and beta (IL-1a and IL-1b). They play significant part in coordinating the inflammatory response to microbial infections, both locally and systemically [74]. It was observed that people exposed to Pb had less lymphocyte proliferation in response to phytohemagglutinin (PHA) than those who were not. Nevertheless, there was no relationship found between blood lead levels (BLL) and the suppression of cell proliferation. Furthermore, in comparison to the control group, Pb exposure had no effect on the cytotoxicity of natural killer (NK) cells. Conversely, people who had been exposed to Pb had considerably higher levels of interferon-γ (IFN-γ). The results demonstrated a strong positive correlation between BLL and IFN-γ level [75]. The study examined the immunological effects of Pb exposure on the proliferation of lymphocytes, the generation of IFN-γ, and the cytotoxicity of NK cells in occupational Pb exposed participants, such as wheeler drivers, battery workers, and silver jewelry producers, as well as in healthy individuals who were not exposed to Pb. The findings shown that, in stimulated peripheral blood mononuclear cells (PBMCs), there is a considerable rise in IFN-γ in comparison to control participants, and that lymphocyte proliferation is suppressed in response to PHA [76].

Genotoxicity

Chemical substances that cause changes in a cell's genetic code, potentially resulting in cancer, are known as genotoxic agents. Although mutagenicity and genotoxicity are sometimes conflated, many genotoxic compounds do not also have mutagenic properties. Exposure to heavy metals is an important source of DNA damage in living beings. Various heavy metals like Pb, As, Mn, Hg, Fe, and other metals are known to produce free radicals and enhance the lipid peroxidation and DNA damage. Genotoxins like heavy metals induces single- or double-strand DNA breaks through various pathways [77]. They induce cellular changes that may influence DNA repair mechanisms. The generation of free radical triggering oxidative stress can also be one of the ways to alter double strand DNA breaks [78]. A number of studies have suggested the loss of DNA integrity due to heavy metal exposure leading to genotoxic disorders in living beings [79]. The question whether heavy metal is genotoxic in vivo is particularly interesting, because exposure to metals in low or high concentration has been known to induce gut related problems, gastrointestinal disorders, diabetes in rats and other models [77]. Therefore, it is very essential to elucidate the effect of genotoxins on organism's health. Hence, in ecological monitoring, double strand break in DNA strand can act as a biomarker [80]. DNA adducts formed by heavy metal exposure in oxidative reactions are generally found to be genotoxic and mutagenic [81]. In populations exposed to multi metal mixtures through drinking water for long duration there have been reports of DNA damage which has been studied via comet assay [79]. This technique is commonly applied to examine the genotoxic impact of metal or any other contaminants on animal models. It helps in assessment of various DNA damage parameters like %DNA in tail, DNA moment, DNA length to measure the genetic risk associated with xenobiotic exposures. This method is the utmost flexible and secure for the identification of DNA strand breakage and alkali-labile sites in various in-vivo models [82]. Early studies carried out on animal models have shown that heavy metals are mutagen and induce genotoxic DNA damage by the production of ROS [81]. Mateos *et al*., (2008) [83] also reported that environmental pollutants were genotoxic to the wild mice living in contaminated area of south western Spain. Breton *et al*., (2016) [2] observed genotoxic effects after co-exposure to Cd and Pb in mice by comet assay. The heavy metals Cd, Cr and Cu in the water column of Orontes River revealed DNA damage in African catfish [84]. This indicated a significant relationship between metals in water and their impact on organisms living in river. The genotoxic and cytotoxic effect of 11 heavy metals were investigated in human cell lines as a representative of target organ colon and liver. The results obtained were in

accordance with the several in vitro studies indicating that heavy metals lead to DNA strand break, chromosomal aberrations [85]. All these findings point towards the potential health risks such as neurological, cardiological, hepatological disorders associated to the presence of metals in contaminated food and drinking water. Previous research indicates that the end-points of Pb genotoxic effects have been clearly shown in a variety of in vitro, in vivo, and epidemiological investigations [27]. Furthermore, the genotoxic effect of Pb was also demonstrated by the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) gene and T-cell receptor (TCR) mutation tests, which are most commonly employed to identify the mutations generated by mutagenic agents in somatic cells [86]. In accordance of some studies, Hg is genotoxic. However, other findings do not find a link between genotoxicity and Hg exposure. It has been demonstrated that Hg promotes the creation of ROS, which destroys DNA in cells and may induce carcinogenesis [87]. ROS have the ability to alter the structure of chromosomal segregation proteins, mitotic spindle, and DNA (Sanchez-[87]. Rats' testicles become necrotic when exposed to Cd, as reported by Yang *et al*. In their investigation, rats exposed to Cd had higher levels of MDA and GSH peroxidase (GSH-Px) [88]. They may also interfere with hormone synthesis, metabolism, and function [89]. The relationship between metal exposure and the results of DNA-induced damage is still up for question, however some studies indicate that metals have genotoxic activity [90]. In a dose-response manner, As is thought to be a potentially genotoxic metal to humans. While it is carcinogenic, it can cause chromosomal instability, which has been linked to acentric chromosome formation, higher micro-nucleation indices (MN), sister chromatid exchanges (SCE), and chromosomal abnormalities (CA) in human populations exposed to As [91]. Although the precise mechanism of As-evoked genotoxicity is yet unknown, reactive oxygen species (ROS) generation is primarily responsible for genotoxic potential for As [92]. It has been noted that exposure to As increases the synthesis of 8-oxo-2-deoxyguanosine (8OHdG), a kind of oxidative DNA damage [93]. Numerous previous investigations have suggested that exposure to AS disrupts DNA repair proteins, increasing the risk of genotoxicity [94]. It is known that As prevents base excision repair, nucleotide excision repair, and mismatch repair [95]. According to recent research, As-induced unregulated DNA repair, reactive oxygen species production, and free radical production all contribute to DNA damage that leads to in genotoxicity in humans [96, 97].

Skin toxicity

As discussed above, chronic exposure to high concentrations of heavy metals can cause a variety of

clinical symptoms, including kidney and liver failure. In addition to food consumption and inhalation, skin absorption is a significant pathway for exposure to environmental heavy metals. Therefore, it is well recognized that the human body might sustain serious harm from the absorption of metals. According to Wang *et al*., (2022) [98], human exposure to heavy metals may mostly occur through skin absorption. This is due to the fact that the skin is the biggest organ in the human body and is the first line of defense. Nevertheless, not much is known about the harmful impact that heavy metals have on human skin. As is present in food, water, and the air for humans to breathe. One of the main causes of As poisoning in more than 30 nations worldwide is drinking water tainted with the metal [99]. Human health may be at risk if the amount of arsenic in ground water is 10–100 times higher than that recommended by the World Health Organization (10 μg/L) for drinking water [100]. Arsenical chemicals that are disposed of inappropriately, arsenical insecticides, or natural mineral deposits can all pollute water. Both acute and chronic arsenic poisoning is possible; the latter is known as arsenicosis. Because skin signs are so precise in diagnosis, skin manifestations account for the majority of reports of chronic arsenic poisoning in humans. The particular skin lesions that signify chronic As poisoning include pigmentation and keratosis [101]. Prolonged exposure to As increases the risk of several potential skin conditions, such as hyper-keratosis, hyper-pigmentation, and various forms of skin cancer. Prolonged exposure to As can lead to skin changes most commonly associated with hyper-pigmentation. An early form of skin cancer known as Bowen's disease may be brought on by exposure to As. The soles and palms of the hands are typically affected by As hyper-keratosis [102]. Research has indicated that those who use skin-lightening cosmetics had higher body Hg levels. Thus, prolonged use of makeup containing even trace levels of Hg can result in peripheral neuropathy, skin damage such as discoloration or allergic reactions, and kidney damage [103]. Lara-Torres *et al*., (2021) [104] demonstrated in 2021 that the tested cosmetics entirely broke the European Parliament's Regulation, even if they did not beyond the FDA's recommended limits. Hg toxicity in youngsters and pregnant women has also been reported. There is a case report of a four-year-old Iraqi child who had signs of Hg poisoning three months after using whitening lotion. The symptoms include weakness, hunger loss, convulsions, weight loss, and a body rash with high Hg level in the urine. Furthermore, research on pregnant women using whitening cosmetics in the third trimester showed that their blood Hg concentrations were 15.16 μg L^{-1} [105]. Skin-lightening creams are quite popular in the US, where Nephrotic Syndrome has been recorded, among other places, as well as in India and Africa [57, 106]. After

exposure, skin darkening and arsenical keratosis may develop. A research on the cutaneous toxicity of cultured human keratinocytes revealed the location of β1-integrin. Reduced integrin expression in keratinocytes may cause aberrant apoptosis and skin manifestations [107]. Skin cancer is another risk factor for severe drunkenness. In As-induced carcinogenesis, oxidative damage, chromosomal abnormalities, and altered growth factor expression are potential mechanisms of action [108].

Carcinogenicity

After cardiovascular illnesses, cancer is now the second most common cause of morbidity and death among non-communicable diseases globally, raising serious concerns for public health. According to global estimates for 2018, there were 18.1 million new instances of cancer and around 9.6 million cancer-related deaths across 185 countries with 36 different malignancies. A recent study finds a correlation between early-life Pb exposure and DNA hypomethylation, which is consistent with earlier findings [109]. Renal carcinogenesis, particularly Cd-induced nephron-carcinogenesis, is influenced by the β-catenin signaling system. The transcriptional factor β-catenin protein accumulates in the cytoplasm as a result of this signaling. The overexpression of β-catenin causes the ROS-dependent/β-catenin signaling to be evaded, which in turn aids in the kidney cancer development [110]. Similar to human cancer caused by As, recent research in animal models revealed carcinogenic activity in the skin, liver, bladder, and lung. Common mechanisms of action may thus be at play. Prostate cancer and Kupffer cell cancer are also observed as a result of As exposure. As causes damage to the DNA maintenance system, produces reactive oxygen species (ROS), and modifies epigenetic modifications [111]. The plasma of rural women exposed to low levels of As showed higher levels of proinflammatory cytokines, including TNF-α, IL-6, IL-8, and IL-12. In the exposed population, there was a drop in the level of the anti-inflammatory cytokine IL-10 [112]. Lead is classified as a potential carcinogen by the International Agency for Research on Cancer, whereas inorganic Pb is classified as a likely carcinogen by the same agency [113]. Increased oxidative stress, changes to membranes, compromised cell signaling, and neurotransmission are the causes of Pb-induced carcinogenicity. While there is not much evidence to support direct Pb genotoxicity in humans, increased oxidative stress and decreased DNA repair might lead to indirect genotoxicity [114]. As a known carcinogen, Cd is a metal that is frequently found in the environment, either naturally or as a result of industrial activities. Because of the environment and the body's extreme persistence of Cd, It is a great risk to health. According to a study, pancreatic tumors contain greater amounts of Cd than normal or surrounding tissue, and they

may be partially toxic due to changes in mitochondrial activity [115, 116]. To induce carcinogenesis, metal exposure causes the cellular responses that are typical of the condition: increased oxidative stress, reduced DNA repair, increased production/release of pro-inflammatory cytokines, and altered membrane permeability [115]. There is limited research on animals that suggests Hg exposure may be carcinogenic, and the available evidence does not link Hg exposure to the development of tumors in people [117]. Humans exposed to Hg have shown genotoxic alterations detected by comet formations and micronucleus tests [118]. According to some researchers, Hg acts more as a "promoter" of tumor development via changing downstream methylation [119].

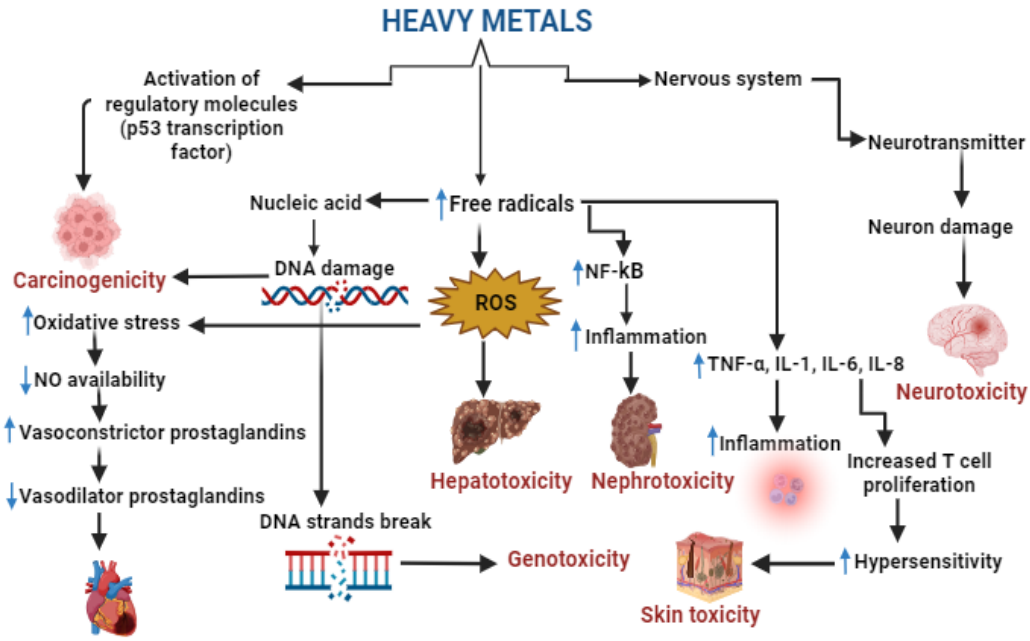

Fig. 3 Mechanism of heavy metal toxicity

2. THERAPEUTIC APPROACH AGAINST HEAVY METAL TOXICITY

Nano technological and Nano Medicinal approaches to treat heavy metal toxicity

The analysis and removal of heavy metals from food and water through the use of nanotechnology is becoming more common. Many nanomaterials have been used to remove heavy metals, including carbon nanotubes (CNTs), magnetic nanoparticles (MNPs), graphene and its derivatives, metal oxide nanoparticles, and more. There are several advantages to using nanotechnology instead of more conventional techniques for heavy metal analysis and removal from food and water resources with high sensitivity, good selectivity, low detection and quantification limits, and a wide linear range are added advantage of this Nanotechnology-based technique could be applied in the

field in a straightforward and secure manner [120]. Nanoparticles are frequently employed to increase selectivity to certain targets and to stop oxidation and aggregation. It may be applied fast to enrich and separate Hg^{2+} ions in different types of matrices. Because of their superior physicochemical properties, carbon nanoparticles are becoming more and more popular as a potential remediation method for heavy metal-contaminated water [121]. Carbon nanomaterials, including carbon nanotubes, graphene, fullerenes, graphene oxide, and activated carbon, offer enormous potential for removing heavy metals from water due to their vast surface area, nanoscale size, and availability of diverse functions. Additionally, it is simpler to recycle and change them chemically [122].

Treatment for neurotoxicity

Numerous treatment strategies and neuroprotective substances have been studied to determine their effectiveness in reducing the neurotoxicity caused by Mn, while accounting for Mn-related toxicity mechanisms and pharmacokinetics [123]. To lessen Mn-induced neurotoxicity, anti-inflammatory substances, synthetic and natural antioxidants, glutamate protectors, and ATP/ADP ratio protectors have been employed. Additionally, the mechanisms and effectiveness of a number of treatment therapies, including levodopa, para-aminosalicylic acid (PAS), and ethylene-diamine-tetra acetic acid (EDTA), have been established. Through control of endoplasmic reticulum (ER) stress and ER stress-mediated apoptosis, an investigation using the polyphenolic extract of *Euphorbia suppina* (PPEES) from a Korean prostrate spurge has demonstrated that PPEES may effectively reduce Mn-induced neurotoxicity via antioxidants. There was also a notable decrease in the levels of malondialdehyde (MDA), a byproduct of lipid peroxidation, and reactive oxygen species (ROS). Simultaneous enhancement of the antioxidant activities of GSH, SOD, and catalase (CAT) was observed. PPEES was also seen in vivo to ameliorate Mn-induced histological changes in the cerebral cortex and striatum [124].

Nephrotoxicity treatment

When oral Cd administration occurs, it results in chronic Cd toxicity, which gravely damages the kidneys. With curcumin pretreatment, the histologic modifications brought on by Cd have improved. Urinary excretion significantly dropped from the Kidney Damage Molecules, Osteopontin, lipocaline-associated neutrophil gelatinase, metalloproteinase 1 tissue inhibitor, and netrin-1. Utilizing curcumin has a substantial preventive effect against Cd-induced nephrotoxicity [125]. In the renal tissues of mice treated with royal jelly, there was a significant increase in the levels of lipid

peroxidation, renal injury molecules-1, metallothionein, interleukin-1b, tumor necrosis factor-i, nitric oxide, and apoptosis regulators Bax and caspases-3. Additionally, antioxidant enzyme activity, glutathione levels, and the apoptosis inhibitor Bcl-2 were significant. Histopathological examinations reveal vacuolation and congested glomeruli in the renal tissue of the mouse treated with royal jelly [126] (Almeer et al., 2019). Additionally, protocatechuic acid treatment enhanced the total protein level in the cd-induced toxicity [127]. According to a study, silymarin and dimercaptosuccinic acid lower blood lead levels and protect against genotoxic effects [128].

Treatment for hepatotoxicity

Through lowering oxidative stress and increasing antioxidant stress activity, salidroside (SDS) can improve liver tissue structure and cure lead acetate-induced liver damage. It is feasible to eradicate Pb-induced hepatotoxicity using this method [129]. Berberine was also found to increase serum albumin, which lessens the hepatotoxicity caused by Pb [34, 130]. Additionally, thymoquinone, curcumin, and carnosine dramatically decreased Pb-related hepatological and histological consequences. Selenium was discovered to be an effective chemoprotectant against Cd in a study. Selenium treatment has been demonstrated to dramatically lower hepatocyte death and morphological alterations brought on by Cd [131]. Selenoenzyme (glutathione peroxidase, GPX) activity was elevated, reduced glutathione (GSH) levels were raised, and ROS production was simultaneously suppressed by Se. These actions contributed to the attenuation of oxidative stress caused by Cd. Ultimately, it was shown that Se may prevent hepatotoxicity caused by Cd by blocking the ER stress response [132). The effect of diets based on *M. oleifera* on Ni-induced hepatotoxicity in rats was examined in a different investigation

Carcinogenicity treatment

According to a recent study, DMA and sodium arsenite exacerbate long-term bladder exposure. Carcinogenesis is associated with the expression of metallopeptidase 9 matrix (MMP-9) and survival. These biomarkers might be utilized to identify bladder mediated carcinogenesis. The amount of oxidative damage that reduces the risk of cancer is reduced. MiADMSA could be helpful in the case of systemic arsenic-induced blood carcinogenesis.

The information showed that the amount of TBARS, ROS, tissue As concentration, catalases, and SOD activities were dramatically enhanced by sodium arsenite and DMA exposure [133]. Reduced carcinogenicity, decreased overall DNMT activity and Nrf_2 DNA methylation in nickel-exposed rat livers, elevated histology modifications in Ni-exposed livers, decreased expression of inflammatory

markers in Ni-exposed mouse livers, and protection against Ni-induced hepatic dysfunction are all achieved by quercetin [134].

Cardiovascular toxicity treatment

Cd and Hg are very dangerous substances that may seriously harm an animal's or human's heart. The protective effects of vitamin C against these metals in rabbits were examined in a study, and positive results regarding heart toxicity were found [135]. In another research, rats administered 300 mg/kg of *C. aurantium* peel extract significantly decreased the histopathological and biochemical changes found in the rat heart following exposure to $K_2Cr_2O_7$. Their results showed that *C. aurantium* peel extract might stop $K_2Cr_2O_7$-induced cardiac damage because of its antioxidant properties [136]. A new study shows that Sulforaphane (SFN) decreased oxidative stress, hematological alterations, structural disorder, cardiomyocyte apoptosis, and cardiac malfunction produced by $K_2Cr_2O_7$. Sulforaphane increased the levels of Sesn2, NAD(P)H quinone oxidoreductase-1, heme oxygenase-1, nuclear factor erythroid 2-related factor 2 (Nrf_2), phosphorylated adenosine 50-mon, and decreased the levels of p53, cleaved Bcl2-associated X protein, caspase-3, interleukin-1, and nuclear factor kappa-B [65].

Skin toxicity treatment

To find out if extract from the peel of *Solanum melongena* may treat Bowen's disease caused by As, research was done. Eight people with As-induced Bowen's sickness were selected from the two As-endemic locations. Each patient received an ointment comprising peel extract and instructions to apply it to the lesion site twice a day for a few weeks. There was a noticeable improvement in the lesion of Bowen's disease [137]. In a different study, two male patients with chronic contact sensitivity to Cr were treated with PUVA treatment. One patient who was simultaneously photosensitized responded really well; his light tolerance increased and his skin lesions cleared entirely. This was followed by the extinction of patch-test reactivity and a decrease in photo patch test reactivity on PUVA-exposed (pigmented) skin. In both situations, PUVA treatment increased lymphocyte stimulation while decreasing the number of T cells that form rosettes. According to Jansén *et al.* (1981) [138] PUVA treatment appears to primarily mitigate contact sensitivity and photosensitivity through local processes in the skin, but it may also have some systemic immunological effects. Also used to treat acne vulgaris is epigallocatechin-3 gallate [139].

2. CONCLUSION

The majority of heavy metals are found naturally in the environment. Human activity releases certain hazardous heavy metals into the environment. The human body is either exposed to heavy metals from external sources or the environment, where the metal is already present in nature. There might be variations in the ingestion pathways. It is essential to comprehend the rate of mortality, the degree of toxicity, and the mechanism by which heavy metals enter the body. Excessive levels might manifest as neurological problems, hepatic and renal illnesses, respiratory disorders, carcinogenicity, GI blockage, etc. and cause severe harm to all organs in the body. Long-term low-dose exposure to many elements poses a serious risk to public health in many metal-polluted areas, especially in areas where metal pollution is pervasive. Furthermore, our investigation suggests that the heart, brain and kidneys appear to have a higher compensatory role than the liver. Thud, comprehending the molecular underpinnings of interactions between heavy metals is crucial for assessing and mitigating health hazards linked to chemical combinations. Therefore, further research is needed to fully understand the molecular process and implications for public health that arise from exposure to combinations of hazardous metals. In order to maintain and manage the public health, the findings of this study highlight the urgent need for further research on the interactions between low-dose hazardous metals and necessary metals.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

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The authors declare no competing interests.

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