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Mechanisms of Heavy Metal Toxicity at the Cellular, Molecular and General Health Levels

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ABSTRACT

Heavy metals such as lead, mercury, arsenic, and cadmium are ubiquitous environmental contaminants that pose significant health hazards. These metals disrupt normal cellular processes by inducing oxidative stress, lipid peroxidation, and DNA damage. On the molecular level, they interfere with enzymatic functions, disrupt calcium homeostasis, and trigger apoptosis or necrosis. Chronic exposure is linked to carcinogenesis, neurotoxicity, nephrotoxicity, and endocrine dysfunctions. This review examines the cellular and molecular mechanisms underlying heavy metal toxicity, highlighting recent findings on oxidative stress pathways, mitochondrial dysfunction, and inflammatory responses. It also discusses current strategies for detoxification and the role of chelation therapy. Better understanding these mechanisms is vital for developing preventive measures and therapeutic interventions to mitigate toxic effects.

Keywords: Heavy metals, oxidative stress, apoptosis, toxicology, DNA damage.

1. Introduction

Heavy metals have various industrial usages but often contaminate the environment due to human activity. Heavy metal exposure is a critical issue because, even with low concentrations, it damages cells, causing disorders such as cancers, developmental issues, and neurodegeneration [1]. Heavy metals can be incorporated into the body via ingestion of drinking water contaminated with metals such as lead, mercury, and cadmium, or via inhalation of mineral dust such as manganese and arsenic. Heavy metals are also accumulated by plants and seafood, which resulted in heavy metal bioaccumulation in the food chain [2]. After entering the body, heavy metals induce excessive reactive oxygen species production or oxidative stress, causing injury via various pathways including depletion of antioxidants, alteration of membrane structures, damage to DNA, and impairment of cell signaling. Because of the excess oxidative

stress, the possibility of handling heavy metal damage can be determined using antioxidants. Antioxidant treatment was shown to significantly ameliorate heavy metal-induced oxidative damage via basic repair mechanisms [3]. However, no review has examined the protective effects of potential antioxidants from the perspective of the cellular pathways of metals' toxicity in detail [4].

Recently, research on oxidative stress and aging has progressed significantly. Aging is driven by cellular damage, such as DNA or protein damage, and endoplasmic reticulum (ER) stress, which triggers apoptosis or senescence [5]. Cellular damage pathways of heavy metals are shared by those of aging, resulting in cell damage, cell cycle arrest, and finally, cellular senescence. However, unlike cellular senescence, heavy metals cause acute damage, leading to excessive cell death [6].

In this review, studies on the molecular basis of the cellular damage caused by heavy metals, and the antioxidants or other agents that ameliorate these effects, are summarized. Heavy metal exposure from environmental pollutants is a crucial risk factor for human health. Heavy metals in the soil and sediment can leach into water and air and diffuse into a wide area. Exposure to these metals can cause a variety of disorders: developmental problems via initial metal exposure during fetal development [7], intellectual disability (ID) caused by lead-induced neural cell death, cancers caused by metal-induced apoptosis or epigenetic changes, metabolic syndrome via metal-induced cellular senescence, and neurodegenerative disorders via metal-induced oxidative stress [8].

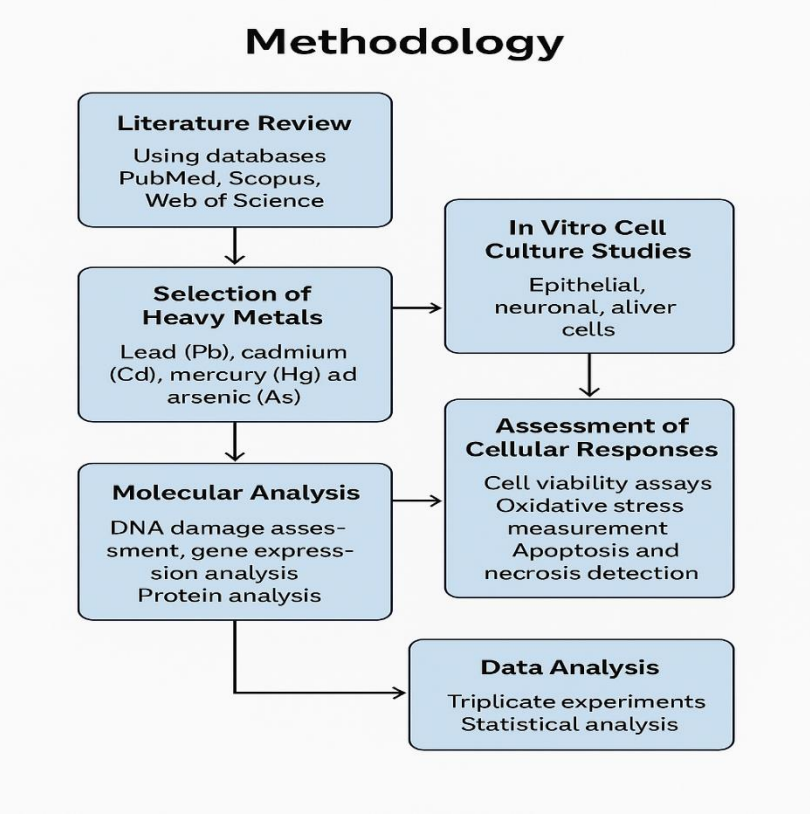

Figure 1. Methodology Mechanisms of Heavy Metal Toxicity at the Cellular and Molecular Levels.

2. Overview of Heavy Metals

Heavy metals can be classified as elements with a specific density (7 g/cm3) and are generally found in the Earth's crust: V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Ag, Cd, Sn, Sb, Hg, W, Bi, and Pb. Exposure to heavy metals occurs through the ingestion of contaminated food and drinking water, inhalation of

polluted air, and dermal absorption from preservatives in cosmetics [9]. Heavy metals are highly harmful because they promote the production of reactive oxygen species (ROS) in various organs throughout the human body, leading to oxidative stress [10]. Antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) are closely related to oxidative stress promoted by heavy metals. Heavy metals interact with the sulfhydryl group of proteins, thereby inhibiting SOD, CAT, peroxidase, and GPx activity and resulting in excessive accumulation of O2− and H2O2, which are responsible for lipid peroxidation (LPO) [11]. Also, production of 8-hydroxydeoxyguanosine (8-OhdG), a well-known marker for oxidative DNA damage, is induced by heavy metals; this can lead to oxidative damage relative to 8-OhdG in DNA. Excessive oxidative stress also enhances the intracellular levels of metal ions [12]. Other mechanisms such as mitochondrial dysfunction, biometal dysregulation, impaired ubiquitin-proteasome system (UPS), proteome instability, inflammation, and apoptosis have also been implicated in heavy metal poisoning [13].

Heavy metal exposure is an emerging public health issue worldwide. Apart from the general toxic effects of heavy metals, it specifically causes toxicity in specific organs or systems, such as the kidneys, liver, brain, endocrine organs, respiratory organs, cardiovascular system, and skeletal muscle [14]. Toxicological effects are critically based on both dosage and exposure time. Once heavy metal poisoning has occurred, toxicological effects may last throughout one's life. Even if exposure is discontinued, heavy metals can still enter many organs through passive transport and dysregulated transporters, leading to toxicity. Prenatal heavy metal exposure also critically affects offspring development and may induce cumulative toxicity and mechanisms of action [15]. Heavy metal exposure is strongly associated with diseases such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) [16].

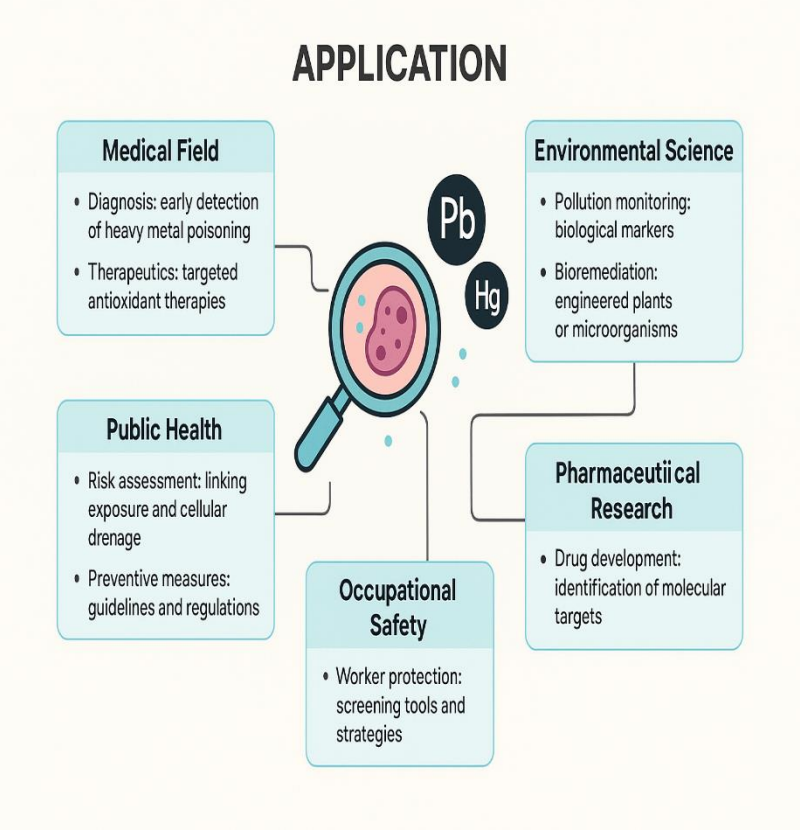

Figure 2. Application Mechanisms of Heavy Metal Toxicity at the Cellular and Molecular Levels.

2.1. Classification of Heavy Metals

Heavy metals (HMs), with a considerable density greater than 5 g/cm3 or atomic number greater than 22, cause toxicity in humans, animals, and even plants. HMs such as lead, cadmium, mercury, copper, and nickel are used widely in industries and essential for biological functions [17].

TMs are classified as essential, non-essential, and toxic metals or as nephrotoxic or non-nephrotoxic metals. Essential metals, such as chromium, manganese, iron, and zinc, are of crucial importance to human health, because they are maintained at low doses in the body and are efficacious in preserving cellular physiology [18].

However, the excess of certain TMs leads to toxicity, intracellular accumulation of these non-nutritional metals, oxidative stress, and ultimately cell failure. Non-essential TMs, including cadmium and lead, are non-nutritional metals, with no documented health benefit. Cadmium and lead exposure leads to bioaccumulation, leading to damage of target intra- or extra-cellular proteins or organelles [19]. Other potentially harmful metals, including aluminium, copper, iron (Fe), mercury, and nickel, are chemical properties are in common with essential ones and are considered by IARC and WHO as possibly causing adverse effects in humans [20].

Furthermore, environmental issues of water pollution are affecting the health of people living in the proximity of industrial plants that use heavy metals, such as tanning, electronics, batteries, pesticides, and dyes. Water contamination is caused by mining activity, dumping tailings without strict measures, and the metalliferous scrap industry [21].

Lead exposure causes neurological impairment, whereas mercury causes severe neurobehavioral disorders. This review addresses the general properties and mechanisms of metal actions and highlights the cellular consequences of exposure to some toxic metals at the molecular and cellular levels relevant to human health [22].

2.2. Sources of Heavy Metal Contamination

Heavy metals (HM) can be defined as metallic elements that have a relatively high density, and that are toxic or poisonous at low concentrations. The twelve metals considered as priority toxic heavy metals include arsenic, cadmium, chromium, copper, lead, manganese, mercury, nickel, selenium, silver, thallium, and zinc [23]. Other metals like cobalt, iron, molybdenum, palladium, platinum, and vanadium are also considered toxic heavy metals. Elevated concentrations of heavy metals in the environment are considered to be a serious threat to human health [24]. As natural elements, they are ubiquitous in the earth's crust, and some of them are considered as essential micronutrients for living organisms at low concentrations. However, excessive concentrations and/or bioaccumulation of these elements in the environment from various anthropogenic activities may lead to toxic effects on plants, animals, and humans [25].

Extrusion of the Earth’s crust, volcanic eruption, natural deposits, meteoric and sea salt spray, tectonic and hydrothermal events, weathering of rocks, microbial colonization, dust storm, and wildfire are some natural sources of heavy metals. Toxic heavy metals enter the environment from various anthropogenic sources [26]. The most common means of entering the environment are from mining, tanning, battery manufacturing, pesticides, paints, pigments, and smelting of metals and other ores. Heavy metal toxicity in experimental animal leads to damage to many organs and widespread and long-lasting toxic effects [27]. In developing fetuses, during the prenatal stage, the effect of heavy metals is critical due to scientific evidence that HS may impair neural development. Susceptibility to heavy metal toxicity in human neonates is uniquely dependent on age [28].

3. Cellular Mechanisms of Toxicity

Heavy metal toxicity is a general term that refers to the biochemical, cellular, and physiological effects of heavy metals. It are essential for normal biological activity in trace amounts, at elevated concentrations they can have adverse effects via a variety of mechanisms. These effects can be classified as general toxic targets that apply to a wide variety of metals [29].

Heavy metals can enter the kidney, pancreas, liver, blood, spleen, heart, and brain, causing toxicity in these organs. They can also damage DNA and RNA and alter gene expression, leading to mutagenic, carcinogenic, teratogenic, and embryotoxic effects [30].

Heavy metals can induce toxicity in vital organs and tissues. Neurotoxicity is most frequently studied for metals that damage the central nervous system (CNS). In humans, exposure during embryonic development, infancy, and childhood can have detrimental and irreversible effects on cognition and behavior [31]. Iron overload during the perinatal stage affects early brain development, with long-lasting life-long detrimental on behavior, learning, and memory. Embryonic exposure to arsenic, cadmium, and lead impairs embryonic brain development. Mercury intoxication affects cognition and social behavior, leaving autistic-like traits in children. Other metals such as cobalt and aluminum have also been linked to neurological disorders [32].

3.1. Induction of Oxidative Stress

Reactive oxygen species (ROS) are generated as endogenous products of cellular metabolism. Mitochondria are the main source of ROS under physiological conditions as a byproduct of oxidative phosphorylation, but ROS are also produced in the cytosol, peroxisomes, and endoplasmic reticulum [33]. Many of these processes are tightly regulated, and a range of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, scavenge ROS.

Imbalance between ROS production and antioxidant defenses gives rise to oxidative stress, which has been implicated in the pathogenesis of various diseases [34]. Excessive production of ROS affects cellular structures, leading to cell death. Lipids, which are abundant molecular species in cellular membranes, are oxidized by ROS, causing lipid peroxidation and dysfunction of lipid bilayer membranes. Proteins are also important targets of ROS [35]. ROS cause various kinds of post-translational protein modifications, such as oxidation of sulfur-containing side chains, and oxidation of methionine inhibits autophagy and exacerbates neurodegeneration. Protein oxidation can also lead to inappropriate protein formation, which causes accumulation and aggregation of misfolded proteins, resulting in cellular damage [36].

Nuclear DNA is also susceptible to the attack of ROS, and oxidized bases such as 8-hydroxy-2'-deoxyguanosine are a consequence of oxidative DNA damage. 8-Hydroxy-2'-deoxyguanosine generation causes cell cycle arrest and apoptosis. Antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase scavenge excessive ROS produced mainly in mitochondria and protect cells from cellular damage [37]. Heavy metals, including lead, mercury, and arsenic, are a major environmental concern. Heavy metals impair mitochondrial functions by significantly increasing ROS production and severely decreasing antioxidant activity, which lead to mitochondrial membrane potential collapse and mitochondrial swelling. Heavy metals alter mitochondrial morphology and transport. In addition, mitochondrial fragmentation has been reported in heavy metal-exposed animals [38].

4. Molecular Mechanisms of Toxicity

Heavy metal exposure can occur through environmental contamination, industrial waste, and the food chain, and lead to health problems. Heavy metals have significant clinical implications, including age-related diseases like Alzheimer's disease. This analysis summarizes pathways of action, clinical

implications, and protective strategies like chelation therapy and natural antioxidants [39]. Heavy metal exposure explores the following topics. Normal cellular metabolism forms reactive oxygen species (ROS) and is controlled by antioxidant enzymes.

An imbalance between ROS production and defense causes oxidative stress. Excessive ROS damages cells through three basic pathways: lipid peroxidation of membranes, oxidative modification of proteins, and DNA damage [40]. Lipid peroxidation by ROS causes membrane dysfunction. Proteins are also a target of ROS. ROS cause various post-translational protein modifications. DNA is susceptible to ROS attack, particularly guanine, which is easily oxidized. Antioxidants, including superoxide dismutase (SOD) and glutathione peroxidase, scavenge excessive ROS and protect against cellular damage. ROS production is associated with heavy metal-induced mitochondrial damage. Lead increases superoxide levels by inhibiting mitochondrial complex NO2–causes cytotoxicity through an ROS-mediated mitochondrial pathway [41].

Cellular cadmium exposure activates ROS production that causes mitochondrial dysfunction and apoptosis. ROS levels increase in the embryonic zebrafish exposed to mercury, which induces mitochondrial damage. ROS has been proposed to be a causal factor in heavy metal-induced cytotoxicity. The expression of SOD1 and p62/Sequestosome 1 (SQSTM1) and an increase of cleaved caspase 3 in the spleen is induced by lead exposure, corresponding to an increase in oxidative stress, apoptosis induction, and dysregulated autophagy. In the liver, lead increases ROS levels and induces mitophagy via the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1)/Parkin pathway [42].

4.1. Protein Misfolding and Aggregation

Protein homeostasis (proteostasis) is essential for cell viability. An imbalance between synthesis, folding and degradation of proteins leads to aberrant protein folding, which is often associated with disease. Heavy metals and metalloids profoundly affect protein homeostasis. Labour force exposure to heavy metals is associated with protein misfolding diseases. Research in the model organism Saccharomyces cerevisiae has revealed surprising insights into the proteotoxicity of metals. This has led to new hypotheses concerning mechanisms underlying neuromuscular degeneration and aging [43].

Protein misfolding and aggregation are molecular hallmarks of several neurodegenerative and age-related disorders, including Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease. There is accumulating evidence that heavy metals and metalloids may influence the aggregation properties of disease-associated proteins and promote certain neurodegenerative diseases through largely unknown mechanisms [44].

Anatomically, neurons and muscle cells of the central and peripheral nervous system are especially sensitive to metal toxicity. Metal ions can bind reversibly or irreversibly to proteins and interfere with their folding, stability and function. In mammals, protein misfolding and aggregation may become especially pronounced with age, when the efficiency of chaperone- and protease-dependent proteostasis mechanisms declines, as might occur in foetal development. Misfolded proteins may cause cell death and spread aggregation in a toxic manner, highlighting the importance of characterizing mechanistic pathways and preventive measures [45].

There is an increasing awareness that heavy metals and metalloids profoundly affect protein homeostasis and cell viability by interfering with protein folding processes in living cells. In particular, chronic occupational exposure to a range of heavy metals, such as copper, manganese, lead, mercury and cadmium, is associated with the development of age-related and neurodegenerative disorders [46]. However, detailed understanding of the molecular mechanisms by which metals interfere with protein folding and promote protein aggregation in vivo is lacking and is thus imperative [47].

4.2. DNA Damage and Genotoxicity

Heavy metals (HM) or metal ions with a density higher than 5 g cm 3 are ubiquitous environmental contaminants which can exert toxic effect. Heavy metal pesticides, minerals (e.g., chromium and lead) and metalliferous ore mining are main sources of HMs in soil, sediments and waters. Discharge of mineral and metallurgical industries, hardening and anti-corrosive treatments, consumer product (e.g. paint, battery, catalytic converters) as well as transportation emissions (e.g. diesel soot) are the anthropogenic sources of HMs in air [48]. There is significant public concern over metal contamination, notably heavy metals (e.g., As, Cd, Cr, Cu), since their accumulation in the environment cannot be attenuated either fundamentally or practically. It is now clear that chronic exposure to certain heavy metals, such as arsenic, cadmium and nickel, may increase the risk of developing cancer [49].

The carcinogenic potential has been documented by epidemiological studies for various metals (e.g., Cr for lung cancer, As for skin and bladder cancers, Ni for lung cancer) [50]. In general, most of these epidemiological studies concern occupational populations exposed to very high metal levels. It is now widely accepted that, at the cellular and molecular level, different mechanisms can be involved in MI (metal-induced) toxicity and carcinogenicity, although less is known [51]. These mechanisms are mainly oxidative stress, alteration of cellular signaling pathways, effects on kinase activities, and changes in gene expression, but also other mechanisms affecting cell growth, mitosis, shape, motility, and cytoskeleton (e.g., apoptosis, cytotoxicity, and genotoxicity).

A major mechanism involved in a variety of stress responses is DNA (deoxyribonucleic acid) damage, which can trigger several cellular responses, including cell cycle arrest, DNA repair, gene expression changes, apoptosis, differentiation, and senescence [52]. DNA damage caused by ionizing radiation (IR), hypersensitivity to IR, and DNA damage repair pathway have been the subject of many studies. It is well known that DNA damaging agents can induce various types of DNA damage, which can be detected by a variety of methods, notably by using specific antibodies or proteins. To date, the cellular response to metals has been far less studied, although the carcinogenic potential of some metals is well established [53].

4.3. Disruption of Cellular Signaling Pathways

Most of these metals are critical constituents for living organisms, but they may exert neurotoxic effects in amounts greater than a threshold value. Heavy metals can impair cellular signaling pathways, including receptor-mediated signaling and the nuclear factor kappa B (NF-κB), Janus kinase (JAK) signal transducer and activator of transcription (STAT), and amyloid-β protein precursor (APP)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase (GSK-3β) signaling pathways [54].

The receptor-mediated signaling pathway involving the ionotropic N-methyl-d-aspartate receptor (iNMDAR) and metabotropic muscarinic acetylcholine receptor has been reported as a primary mechanism of heavy metal-induced neurotoxicity. Through the NO–cyclic guanosine monophosphate (cGMP) pathway, heavy metals increase the cytosolic concentration of Ca2+, which leads to the activation of caspases and phospholipases, resulting in increased lipid metabolism and subsequent neuronal cell death [55].

In short, heavy metals, especially Pb, Hg, and Cd, have been implicated in the disruption of cellular signaling pathways, contributing to their toxicity. These metals mainly impair receptor-mediated signaling transduction in signaling pathways critical for neuron normal function and homeostasis. Linking cellular signaling denouement with the observed toxicity of these metals would provide insights into pathogenesis and potential interventional therapies [56].

5. Impact on Cellular Organelles

Organelles are functional unit-substructures of cells, and they are normally loosely organized in mammalian cells with high motility. Organelles also contain toxic materials, such as heavy metals. Therefore, their accumulation and damage would destroy cellular homeostasis and provoke cell injury. Such injury would lead to a second wave of damage at molecular levels as discussed in this section [57].

Mitochondria are dynamic organelles whose normal balance between fission and fusion tightly controls their morphology. Imbalance of this control induces mitochondrial fragmentation and production of free radicals. Lead inhibits mitochondrial dynamics, increasing the expression of fission proteins such as dynamin-related protein (Drp1) and decreasing the expression of fusion proteins such as optic atrophy protein (Opa1) 1 [58]. Moderate and intense induction of autophagy is involved in the clearance of damaged mitochondria. Released cytochrome c and apoptosis-inducing factor (Aif) activate apoptotic and caspase-independent apoptosis pathways, respectively; the latter pathway will be discussed later [59].

Lysosomes are dynamic organelles richer in protons and toxic hydrolyzing enzymes than cytosols and regulate degradation of proteins, organelles, and invading pathogens. One route of lysosomal intracellular transport is via maturation from early to late endosomes [60]. Formation of leaky membranes, release of hydrolyzing enzymes into cytosols, and generation of free radicals by iron and copper are the toxic effects of lysosomal injury. Lead injures lysosomal function due to its accumulation, damaging autophagy and promoting aggregate formation. This injury may initiate a vicious cycle of aggregated proteins and damaged organelles. Some aggregates are accumulated via intercellular spreading of toxic proteins implicated in various diseases [61].

The ER is an intracellular organelle that regulates homeostasis of calcium (Ca^2+), lipids, and redox status. Changes in ER homeostasis induce ER stress, resulting in activation of the UPR. UPR activation initially protects cells, but once this protective mechanism is unravelled, the promotion of apoptosis is an alternative fate of UPR activation [62]. Lead exposure in rats targeting liver in vivo results in inhibition of antioxidant enzymes, SOD and GSH-Px, and elevation of ROS and malondialdehyde products assay. Excessive ROS production in neutrophils and liver tissues is also induced by lead and selenium exposure and is associated with blood lead concentration in children. The UPR is comprised of three branches: IRE1/XBP1, PERK/eIF2a, and ATF6 [63]. Each branch is activated to alleviates stress-induced folding demand. Unfolded protein accumulation in the ER activates the UPR and/or causes pro-apoptotic signaling pathway induction, resulting in CHOP formation [64].

6. Heavy Metal-Induced Apoptosis

Heavy metals induce cytotoxicity by molecular mechanisms, including oxidative stress associated with mitochondrial dysfunction, apoptosis, necrosis, and endoplasmic reticulum stress, which are interconnected. With this background, the current status and future directions of research on the molecular mechanisms underlying heavy metal-induced toxicity are discussed with an emphasis on mitochondrial dysfunction related to oxidative stress and ER stress, including their interaction, as well as protective agents against heavy metal exposure [65].

Mitochondrial dysfunction is one of the main phenomena in heavy metal-induced cytotoxicity. Firstly, heavy metals can induce mitochondrial dysfunction by permeabilizing the mitochondrial membrane, resulting in mitochondrial swelling, the release of pro-apoptotic factors such as cytochrome c, and the opening of the mitochondrial permeability transition pore [66]. Heavy metals can induce the opening of mPTP, which is a critical event in mitochondrial dysfunction. The two large mitochondrial membranes mainly consist of cardiolipin.

The outer mitochondrial membrane is permeable to small molecules, such as pro-apoptotic factors, while the inner one is impermeable. In contrast to the outer membrane, the inner membrane possesses

mPTP, an inner-membrane protein that opens under pathological conditions [67]. Heavy metals can cause mitochondrial dysfunction by damaging the electron transport chain complex. Accumulating evidence suggests that heavy metals, such as lead, cadmium, mercury, thallium, arsenic, and nickel, impair mitochondrial respiration and mitochondrial membrane potential by damaging mitochondrial complex I, complex III, and the Na+/K+-ATPase on the mitochondria [68]. On the other hand, although heavy metals can cause mitochondrial dysfunction by damaging the ETC complexes, some studies have claimed that they can induce mitochondrial hyperpolarization, suggesting the involvement of mitochondrial dysfunction upstream of the ETC complexes. The mechanisms by which heavy metals can cause mitochondrial depolarization and hyperpolarization remain to be fully clarified [69].

6.1. Mechanisms of Apoptosis Induction

Heavy metals exert their toxic effects through various mechanisms, including the dysregulation of intracellular ion homeostasis, inhibition of enzymatic functions, oxidative stress-induced apoptosis, necrosis or autophagy, and endoplasmic reticulum (ER) stress. Accumulating evidence indicates that the induction of apoptosis is a critical event in heavy metal-induced toxicity and is associated with mitochondrial dysfunction and oxidative stress 1 [70]. Induction of the pro-apoptotic Bcl-2 family member, Bax, plays a key role in heavy metal-induced mitochondrial dysfunction and apoptosis. Moreover, cytosolic cytochrome c release and caspase-3 activation are also triggered following the alteration of mitochondrial morphology and function. Knockdown studies have indicated that phospholipid scramblases (PLSCs), a family of four members, are involved in the induction of apoptosis in response to heavy metals [71].

Upon heavy metal exposure, the oxidation of cardiolipin, a unique mitochondrial phospholipid, inhibits Hax-1, leading to the induction of mitochondrial dysfunction and cytochrome c release. In addition to cytochrome c, the kinetics of Smac and apoptosis-inducing factor (AIF) release are altered upon metal exposure. Caspase-3 is activated following heavy metal treatment, and this effect is preceded by the decreased expression of FLIP, an inhibitor of caspase-8 [72].

Once activated, caspase-3 cleaves poly-ADP ribose polymerase (PARP), an enzyme that modifies target proteins with ADP ribose chains in response to cellular stress, leading to the inhibition of genome repair systems. Moreover, the activity of caspase-9 is also elevated, although this activation seems to occur later in comparison to caspase-3. Metal-induced apoptosis might be mediated by both intrinsic and extrinsic apoptotic pathways [73]. Nevertheless, heavy metals have the potential to induce necrotic cell death. Methoxy polyethylene glycol–poly nanoparticles containing mercuric chloride selectively induce renal cell necrosis through the downregulation of HSF-1 and HSP70. The necrosis observed is accompanied by cell membrane rupture, and ceramide generation is critical for necrosis induction [74].

7. Heavy Metal Toxicity in Human Health

Heavy metals, such as mercury (Hg), lead (Pb), arsenic (As), cadmium (Cd), and nickel (Ni), are poisonous substances that can cause a wide range of toxic effects and diseases in humans and other living organisms. Heavy metal exposure arises primarily from mining, industrial processes, by-products from fossil fuel combustion, mining and smelting, manufacturing operations, and pesticide application among agricultural workers [75]. Rivers, streams, and lakes contaminated with heavy metals pose serious drinking water hazards. From dietary intake, metal ions can accumulate in the brain and other tissues, resulting in reproductive or developmental effects, central nervous system impairment, or poisonings. About 113 human toxic metals are known 2, with biochemistry and bioavailability remaining a challenge for antihyperglycemic drug development [76].

Metalloestrogens is an emerging class of metals with potential risk factors for estrogen-related

pathologies such as breast and prostate cancers. Some inheritable genomic mutations and environmental factors, including metals, may initiate abnormal cellular events, including metabolic, epigenetic, oxidative, ER stress, inflammatory or immune alterations [77].

Over time and with appropriate co-morbidity, these epigenetic remapping or genomic changes may disturb cellular homeostasis by altering the temporal and/or spatiotemporal expression of a cascade of downstream genes that may individually or synergistically induce estrogens activating those new metabolic circuits enhancing CRF, 5-HT and Glu production. Subsequent changes in the milieu of heavy metals or other endocrine-disrupting compounds (EDCs) ultimately fuel the establishment of estrogen-related pathologies, like cancers [78]. Posttranslational modifications and oxidative modifications of nucleic acid bases, leading to epigenetic alterations, may prime the production of multiple stressor adaptive and repair pathways. Such cellular responses may lead to sequential activation of evolutionary conserved protective pathways, including the Nrf2-Keap1 and HSF1. Several protective pathways converge on transcriptional activation of Notch or Hedgehog pathways, leading to the protective molecular cascades assembling for timely, efficient regulation of global behaviors under stress conditions. Heavy metals fundamentally alter multiple cellular signaling systems and responses to other toxicants, hormones, or growth factors [79].

7.1. Acute Toxicity Effects

On the molecular level, in addition to the formation of free radicals, direct interaction with biomolecules leading to protein unfolding and enzyme inhibition has also been observed. For example, halides (F-, Br-, I-) play this role in activating gluthatione-S-transferase (qGST), whereas cationic heavy metals block the active site of a-KG dependent dioxygenases and inhibit the biosynthesis of collagen [80]. This question also remains open: What is the primary binding partner of non-nutrient metals involved in their toxicity? Is it an element of the transcriptional/oxido-reducing machinery? The nuclei harboring this machinery and consequently the ribosomes are relatively away from the cell membranes, while metal distribution has been claimed to peak within 1 min upon exposure 11 [81]. A possible answer has been provided first by observing that there is a protein of BWZ100 named Ubi4 whose ubiquitination and vending complex formation are accelerated from the first minute after severe copper or cadmium shock. This process is strictly copper- and cadmium-dependent because other non-nutrient metals like manganese, nickel, and cobalt fail to induce it even at much higher external concentrations, as confirmed by western blotting, fluorescence microscopy, and mass spectrometry [82].

Diverse heavy metals disrupt multiple sites on the ribosome at different concentrations, leading to a distinct pattern of impaired performance. Meanwhile, other heavy metals such as cadmium are able to induce stress granules from short-to-long-term, leading to the accumulation of ATP and ark-1-dependent phosphorylation of the a-subunit of yeast translation initiation factor eIF2 [83].

In addition to their distinct cellular response patterns, non-nutrient metals are also categorized into different types based on the total number of their binding atoms. For instance, halides with a total of six electrons and only three binding sites are low-capacity inhibitors causing mostly fast eukaryotic ribosomal pauses (e.g., mercury, silver, tellurium), whereas cadmium and thallium with more than eight electrons and four binding sites lead to ribosomes with folded mRNA, causing errors propagating through slow decoding and induced frameshifts 2. This extensive study has applied the latest high-end technologies, expanding from yeast alone to mammalian systems plus high-throughput sequencing methods and biochemistry, to claim a comparative framework for a better understanding of heavy metal toxicity [84].

7.2. Chronic Exposure and Long-term Effects

Although acute exposure to heavy metals can lead to severe toxicity, many human populations are exposed to lower levels of heavy metals for extended periods. Since long-term exposure to heavy metals depends on bioavailability, human-exposed populations usually experience complex exposures. Also, human exposure is chronic because most of these metals may remain in the body for years to decades [84]. These two issues complicate the study of chronic exposure. Epidemiological studies of long-term effects and animal studies of offspring effects provide important clues for studies of chronic exposure. This section covers two issues: long-term effects and chronic exposure of heavy metals [85].

In review, the available evidence suggests that chronic exposures to lower levels of heavy metals may be more toxic than expected when evaluated based on evidence from high-dose exposures. The mechanisms include structural changes at the molecular level that affect mitochondrial functions, resulting in lasting effects on several systems, including basal ganglia functions, cognitive functions, and serotonergic systems [86]. Targeting endoplasmic reticulum stress and mitochondrial dysfunction may be promising for the development of new treatments for chronic toxicity and may be useful in securing a safe environment. However, these predictions require further confirmation using appropriate methods and careful consideration of solvent, concentration, timing, and the presence of general confounding factors [87].

7.3. Heavy Metals and Cancer

Seven metals (cadmium, chromium, nickel, arsenic, cobalt, mercury, and lead) are known or suspected human carcinogens. Although they do not act as classical mutagens and are not individually classified in that manner, metal-induced carcinogenesis was established by the PHS Tissue Culture Carcinogen Testing Program. Efforts to understand the molecular mechanisms underlying metal-induced transformation revealed that abnormal epigenetic processes are involved [88]. As most epigenetic machinery consists of metalloenzymes, it is not surprising that epigenomic and transcriptomic studies showed global dysregulations in DNA methylation and histone modifications in metal-exposed samples. It is likely that metals directly modify epigenetic proteins and substrates. Orchestrated action of different hierarchically and spatially localized forms of chromatin could underlie cellular perception of the input and the organization of the output [89].

Modulation of several components of the cellular machinery governing epigenetic 3D organization altered the response to metal-induced transformation, leading to impaired activation of pro-tumorigenic phenotypes. The affected mechanisms play an important role in normal development and development of malignant tissues [90]. Heavy metals at non-cytotoxic concentrations activate epigenetic writer, eraser, and reader proteins involved in the establishment, maintenance, or reading of DNA methylation and histone modifications. Epigenetic changes lead to transcriptional dysregulation of tumor-suppressing genes. They also enhance expression of Sarcoma oncogenes that are critical for malignancy. Together, they increase the pool of self-renewing stem-like (also termed, aggressive) cells [91].

The role of heavy metal exposure in refining the stemness of non-transformed tissues provides a unifying explanatory framework for the recently reported empirical associations between exposure to certain metals and cancer risk in subsets of exposed populations. Heavy metals can also trigger the acquisition of the malignant phenotype in already transformed cells. Here, epigenetic dysregulation affects the expression and activity of pathways fostering neoplastic cell malignancy, such as angiogenic switch and epithelial-to-mesenchymal transition (EMT) [92]. Endogenous extracellular matrix products become secreted following perturbed chromatin regulation at the fibronectin gene promoter. Secretion activates the EGF-R-ERK/AKT mTORC1 signaling in neighboring non-transformed cells, thereby enhancing malignancy. This concept enables linking a wide array of non-genotoxic exposure outcomes, including epigenetic remodeling, to carcinogenic and other adverse outcomes [93].

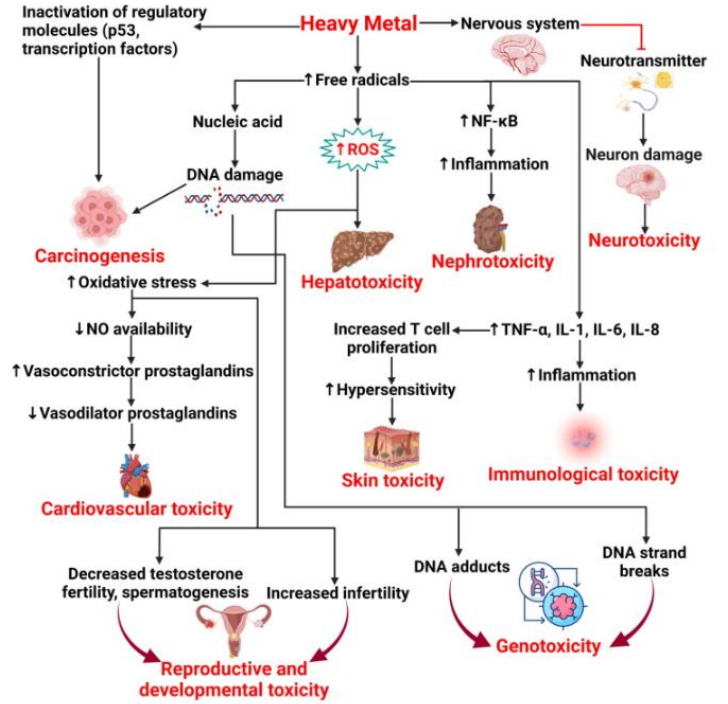

Figure 3. Effects of heavy metal on human health [15]

8. Biomarkers of Heavy Metal Exposure

Modern society demands stricter regulatory policies and preventive measures to control the emission of toxic metal species. Analytical methodologies need to be deployed to monitor the levels of these species. In parallel with measurement, the toxic mechanisms, interactions with the organism, development of bioremediation strategies and the understanding of bioavailable organometallics need to be better understood [94]. In addition to exposure assessment, information regarding which dose and which exposure window is potentially linked to the development of diseases or compromised health is critically sought after. This is especially true for developmental exposure, where known effects on cellular systems, organs, and physiological endpoints must be considered to understand broader health outcomes. Such information is often needed for new pollution scenarios, where basic study is still lacking [95]. Novel approaches are needed to elucidate how a common pollutant exposure dose at the level of the organism can find itself linked to the cellular mechanisms through which it impacts health. In such studies, the causal chain and multi-layered mode of action must be addressed, which means merging various scientific fields and levels of the biological hierarchy – the organism/toxicity, organ/function, cellular/toxicology & systems biology, and molecular/chemical biology level [96].

8.1. Biochemical Markers

Heavy metal toxicity adversely affects various organs, including the heart, liver, brain, lungs, kidneys, and skin. The study has described the detrimental effects of heavy metals, such as cadmium, lead, manganese, mercury, chromium, and arsenic, on cell viability, challenging the notion of normalcy in cellular, biochemical, histological, or metabolic dimensions [97]. However, much of what we understand is based on the loss of normalcy rather than a direct assessment of the biochemical markers. The first section explores the biochemical markers of metal poisoning, looking for a good combination of biomarkers and techniques to highlight the observed changes in cellular, biochemical, and metabolic

activities. The hope is to highlight the multiple mechanisms of biochemical change and to recognize the potential of cross-method translational approaches in aiding the understanding of toxic mechanisms of heavy metals [98]. With the ability to observe the changes in thousands of small molecules (metabolites) that occur within a biological system in a short time, metabolomics is an emerging tool to study the effect of heavy metals on biological systems and the underlying metabolic mechanism. The robustness of the technique is highly attractive when searching for diagnostic metabolic biomarkers. A longitudinal view of recent studies on alterations in the metabolomics of Cu, Hg, Pb, Cd, Cr, and as toxicity on various domains of life (including plants, bacteria, and animals) provides insights into sample preparation, analysis, data evaluation, pathways, and common metabolites. This information forms a basis from which to release potential biomarkers for understanding metal toxicity from a metabolic perspective [99]. Additionally, there is a discussion of the metabolic re-normalizations following detoxication or normalization, which has received relatively little attention. A toxicometabolomics overview and a view of future perspectives complete a review of the discussed topics [100].

8.2. Genetic Markers

Heavy metals such as arsenic, cadmium, chromium, mercury, and lead are highly toxic to various living organisms, including microorganisms, plants, animals, and human beings. The mutagenic effects of heavy metals have been examined extensively, especially in model test organisms, such as prokaryotes. Most heavy metals either exert mutagenic effects directly or lead to the production of cellular mutagens [101]. Trash accumulations in soil and water surrounding mining and metal processing plants marginalize the well-being of fauna and flora. To unravel the effects of heavy metals on microorganisms, an investigation using prototrophic strains of Escherichia coli K-12 as a model organism was conducted to characterize the mutagenic effects of six heavy metals. Mutagenicity of each heavy metal on the proliferation of bacterial cells was assessed to reveal both the commonality and specificity of the mutational changes. It was found that the heavy metals altered the mutation rates and spectrums in a heavy metal-specific manner. It was confirmed that the mutagenic characteristics of individual heavy metals are more extensive than appreciated, even resulting in genetic variation irregularities under environmentally relevant concentrations [102].

With the rapid expansion of industrial production and population, exposure to heavy metals such as cadmium, chromium, mercury, and lead is increasing in ecosystems. Heavy metal pollution leads to severe mutagenic, carcinogenic, or teratogenic effects on a variety of organisms[103]. Until now, studies on heavy-metal-induced genetic changes have mainly relied on prokaryotes while little about plant systems .For prokaryotes, heavy-metal-induced genetic changes are usually assessed using mutational changes, such as tryptophan imbalance and biofilms. Mechanisms of heavy metal toxicity are complex and diverse, involving multiple pathways of cellular damage. Heavy metal-induced generation of intracellular reactive oxygen species leads to lipid peroxidation, damage of membrane lipids, proteins, and DNA. Heavy metal pollution can result in increased levels of mutagenic stressors leading to genetic changes, explaining the generous interest in understanding heavy metal-induced mutagenic processes in microorganisms in pollution-remediating environments [104].

9. Mitigation Strategies

Heavy metals are all around us; they are present in soil, water, plants, and animals. Some heavy metals, including Cu, Zn, and Se, are essential for human health, but most heavy metals, including As, Pb, Cd, Hg, and Ni, are toxic to human health. Heavy metal toxicity can cause neurodevelopmental impairment, neurodegenerative diseases, cardiovascular diseases, and cancers. Despite common environmental sources of exposure, the molecular pathways and consequent clinical implications of these heavy metals are distinct [105]. Moreover, while receptor- or organelle-specific delivery and some health effects of these

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heavy metals have recently been unveiled, other aspects, such as these heavy metals' transporters and receptor systems, cellular uptake mechanisms, and cellular events thereafter, are poorly understood. Numerous protective strategies against the deleterious effects of heavy metals have been proposed. This article discusses heavy metals that have been extensively investigated for their health effects as well as molecular pathways of action and cell toxicity mechanisms, providing the relevant therapeutic strategies [106]. Chelating agents are large cyclic molecules that encapsulate and thereby remove a target metal from the cells of the body. Many biological and therapeutic processes may be initiated by the release of the metal from an endogenous chelator. Chelators can be classified by whether their effects are metal-selective or not. The molecular structure of the chelator is crucial because it determines selectivity or binding affinity. The efficacy of the chelator is also influenced by how tightly the chelator binds to the metal and the bioavailability of the chelator [107].

Once through the insulin receptor, the chelators act upon, or bind to, the metals in the cytosol or other intracellular locations. The metal-chelator complex, usually water-soluble, is excreted by the kidneys into urine. Formal chelating agents, which have carboxyl and amino acid functional groups that help complex heavy metals for excretion, are the main treatment for heavy metal poisoning. These agents have different affinities to metals: DMSA is more selective for Pb over As, Cd, and Hg, and DMPS is more selective for Hg over Pb. Other potential chelators, both natural and synthetic agents, either contain functional groups that form coordination complexes with heavy metals or actively increase excretion [108]. Enzyme-based protective strategies against heavy metals have been extensively explored. Glutathione-S-transferases (GSTs), които catalyze the conjugation of glutathione (GSH) to diverse endogeneous and exogenous substrates, including heavy metals, have served as a model enzyme for the exploration of enzyme-based protective strategies [109]. Many strategies, including prodrugs, small molecules, and natural products that activate GSTs and are non-cytotoxic or cytoprotective, have been developed. Statins have been shown to reduce the risk of pd toxicity by enhancing the expression and activity of mitochondrial citrate synthase (CS), which catalyzes the synthesis of citrate and is also a substrate of GSTs. CS also ameliorates the cytotoxicity of long-chain fatty acyl-CoAs in a way independent of GSTs. L-2-oxothiazolidine-4-carboxylic acid (OTC) is a prodrug targeting the cystine/glutamate antiporter, which was highly efficacious in protecting against cells from specific metals. Several metalloid oxoacids, especially those with a higher number of oxygen atoms, including the cationic uranyl oxoacid first, showed different protective efficiencies against as and Ge toxicity [110].

9.1. Detoxification Mechanisms

Cellular detoxification of toxic metals occurs via transporters that localize these metals primarily in the cytoplasm or vacuole as nonreactive complexes. A decreased bioavailability of these metals plays microscopically a dominant role. This mechanism cannot be evaluated with only one identificable toxic metal. Toxicity is not only a function of absolute metal concentrations but depends additionally on the ratio between available and nonavailable equivalents [111].

A differential distribution of reactive metal species within cells was found. Domain-selective sampling and subsequent homeostatic processes in the region of metal influx and efflux were proposed as mechanisms involved in the observations. Heavy metals exposure can exert cellular toxicity through various pathways including altered phosphorylation, elevated ROS levels, or altered metallothionein levels that subsequently induce apoptosis [112]. Erecting protective signaling, students also explored recovery mechanisms after heavy metals challenge. Cellular recovery after cumulated insults demonstrated that all signaling pathways engaged in heavy metal toxicity were, however, not completely turned off in order to allow sustained activity of the protective mechanisms. Following cadmium exposure, cells were, despite a full recovery of initial viability, engaged in pro-survival signaling but later turned off. Thus, not the pro-survival but the failure of the prohibition of apoptotic signaling contributed to increasing vulnerability after exposure to several metals. It is evident that even though the signalling

pathways involved in toxicity and protection were often identical, the balance between effectors activating or prohibiting apoptosis differed considerably between the metals investigated. These observations strongly suggest that the somewhat approximate classification of metals as either neurotoxic or generally cytotoxic needs to be reconsidered and fractions within these categories need to be defined [113].

9.2. Phytoremediation Techniques

Phytoremediation technologies encompass methods to remediate heavy metal-contaminated soils/water using plants equipped with metal stress tolerance mechanisms. The most promising techniques exhibit efficiency that relies not only on the sensitivity of the bioremediation agent but also on metal bioavailability, mechanico-chemical soil properties and bioremediation environmental conditions [114]. Insufficient attention has been paid to phytoremediation efficiency across contaminants and species despite its prominent forward among soil bioremediation technologies. Phytoextraction is one of the dirtiest metal-remediation technologies. It consists in growing plants that hyperaccumulate in their shoots the metal for further harvesting, runoff removal and safe disposal [115]. Phytoextraction is the most studied phytoremediation technique due to the agricultural potential of vegetation before harvests and the option of cropping multiple times in higher-value vegetation products to capture contaminants. This phenomenon results in a diffusion-flux, contrary to a more common solute-optimised bioremediation option in which the soil biota biofiltrates charge-contaminated water. No other bioremediation technologies are so tractor-intense as the phytoextraction of metals [116].

Phytoextraction-rhizodegradation is a case of enhanced turnover of persistently uncertain or gradually sorbed contaminants. A. Biomass disposal or conversion may impede bioassay quantification or improvement over routine endpoints because of difficulty in perturbation, as in more invasive manipulations of traditional bioassays, and/or low bioavailability of target contaminant/chemical combinations. A basic frame to describe rhizodegradation on a volumetric basis was proposed. It shows frequency response patterns found in contaminated sediments and wetlands, including convergent and mixed period behaviour on time scales longer than the effect of treatments [117].

Rhizodegradation extraction or conversion rates are more effective in lower permanently nutrient-rich or organic/metal-poor soil. There are significantly bigger contaminant mass losses at higher rates among the comparable sites with high heavy concentrations in regularly nutrient-rich and clayey or patterned soils at quicker depositional rates. Expected faster etched release of organic- and contaminant-philic metal complexes from bioexcessively exceeded phytoextraction sites explains a shorter wait for any effect improvement. Phytomining is similar to phytoextraction but is applied to less-loaded substrates. Exotic metal-hyperaccumulating plants are grown in waste heaps where metals become concentrated in the shoot. Be deferred to biodiversity and to ensure taxonomic distinctions or correct plant designation in trade and planting [118].

10. Regulatory Framework and Guidelines

Heavy metals are chemical elements with high densities that are known to be toxic in lower concentrations. The heavy metals of global concern include lead, cadmium, mercury, arsenic, and chromium. Heavy metals have been mined and utilized for various purposes; however, they tend to accumulate in the ecosystem. Eventually, they contaminate drinking water from soil and might be uptaken by animals and vegetables, which are eventually consumed by humans [119]. Hence, there is an urgent need to investigate the molecular pathways of heavy metal toxicity, clinical implications, and relevant protection strategies. In this review, the cellular and molecular mechanisms of heavy metal toxicity are summarized, and the potential clinical implications and protective strategies from heavy

metal toxicity are discussed

10.1. International Standards

In the context of heavy metals and metalloids toxicity, one major theme is that their toxicity and, with it, their carcinogenicity depend mainly on what is often called the biopalooza: the biological processing of these metal species. This biopalooza is not too dissimilar from the winezation of grapes, for instance: this process can produce various sorts of wines from the same species of black grape, depending on the nature and value of the grape, the method of crushing and fermentation, and so on (to give only a few parameters): similarly, one same elemental heavy metal or metalloid can produce a whole range of toxicity through various chemistries, reactions with biological macromolecules and catalytic mechanisms of action [120]. To account for the variety of wines for any grape variety, a scale of quality for each grape is currently used; bands of prices according to this quality (with prices from a couple of euros to hundreds) provide illustration that need not explain anything further. It is pitiful that such a quantitative and objective scale of quality, high enough in order to account for toxic and cancer risks for heavy metals and metalloids, does not presently exist. Hence it seems of utmost importance to examine a potentially large panel of metal species in order to get bands of toxicity of different orders of magnitude for these metals [121]. Another theme is that exposure to metals (from the weakening of the frontal lobe for large doses of MeHg to neurofibrillary tangles for long-term exposure to Pb, Mn or Cd) likely does not lead to a homogeneous distribution of stress in the cells: it is well known that the cell surface can bind and concentrate some metals and that metal-permeable transporters may produce much higher intracellular concentrations for some metals than for others [122]. A second set of considerations deals with the problems faced in making sense of the wide range of dose-effect curves of heavy metals (and supposedly low metals) produced by the laboratory. On the one hand, it is usually deemed fairly unsafe to expose biomaterials or cell lines to metal concentrations above a given order of magnitude, even when it is suspected that some induced bioprocesses may saturate with higher doses (the various assays need to be devised); on the other hand, bands of different kinds of action, usually far from simple saturation, are commonly found for positive controls [123].

11. Future Directions in Research

There is insufficient understanding of the cellular and molecular mechanisms of heavy metal toxicity. Future studies should aim to identify the mechanisms of heavy metals-induced toxicity from a comprehensive perspective by clarifying protein expression changes during metal exposure, including upstream signaling pathways, and by utilizing state-of-the-art proteomics technology, gene expression analysis, and network analysis .

11.1. Emerging Technologies

While there are many studies examining the mechanisms of heavy metal toxicity, a considerable proportion of those studies using in vitro methods rely on transient exposure methods. In recent years, however, large-scale in vivo studies using newly developed technologies have started to emerge, enabling screening studies at the molecular level [124].

With the application of various elemental mass spectrometry techniques, elemental distributions can be analyzed at a wide range of spatial scales, from ensuring an observation of a single cell to accessing an organism containing many non-visible cells. In particular, a newly developed imaging mass spectrometry technology based on secondary ion mass spectrometry (SIMS) is capable of high-resolution imaging (i.e., single-cell level) and producing data on isotopic and molecular ions without preprocessing [125]. Recent study using this technology have elucidated the distribution and mechanisms of toxicity of ionized metals on a cellular scale. The detailed and multi-faceted insights into heavy metals obtained by this technique

could greatly enhance tomorrow's focus on potential therapeutic care. Uncovering the toxicological action mechanism of heavy metals at about 50 nm resolution provides a unique opportunity to complement in vivo results and strategies in which the input dose/control is typically rough [126]. Targeting heavy metals is a possible and worthwhile endeavor in preventing disease, and the results from both large-scale in vivo and targeted studies will need to be carefully considered. A joint effort to tackle the problem from different angles with a variety of techniques is needed for effective care to be established .

11.2. Potential Therapeutic Approaches

Heavy metals are divisive among human pathogens. The etymology of their toxicity arises from long and persistent qualities. Water-soluble heavy metals are often pursued into tissues over time, ultimately inflicting difficult-to-cure vanished damage through highly adaptive mechanisms [127]. More surprisingly, one action also causes false-positive proteasome inhibition. On this challenge, impairment of cellular pigmenting-mitochondria retrograde trafficking could explain impaired proteasome degradation and precipitate neurodegeneration. Chelation therapy offers promise because, unlike the treated head-injured patient, there is time to shunt the damage pathways from chronic neurodegeneration and diminish injury during exposure [128].

An early success was a harmless chelator natural to beet greens, seized on in sushi bars, which promptly lowered liver copper in Wilson's disease, affording blessing for patients. Prior to that, a similar product primarily for treating cystinuria was reeled in for continuing cystine spiking episodes [129].

12. Conclusion

Heavy metals are the most toxic and hazardous substances in the environment, and exposure to heavy metals can lead to a range of health problems, including cancer, high blood pressure, headache, nausea, fatigue, irritability, and mood and memory problems. Heavy metals are often found in soil due to mining, the improper disposal of industrial waste and sewage sludge, and the application of fertilizers and pesticides. They can contaminate drinking water via fissures and cracks in the soil. Because of their toxicity, heavy metals pose a serious threat to human health. Consequently, extensive research has been conducted on the molecular pathways that lead to cellular damage due to heavy metals. On the other hand, there also have been many efforts to formulate curation therapy for heavy metals. Chelation therapy is a traditional treatment for heavy metal toxicity. However, it has recently been reported that various antioxidants, including herbal medicines and natural compounds, are effective in treating heavy metals-induced damage. This has led researchers to investigate how antioxidants, which are traditionally adopted to counteract cellular damage due to various ROS-inducing agents, affect the toxicity and cellular damaging effects of heavy metals. Considering that heavy metals are a serious environmental risk, elucidating the concerns and risks associated with heavy metals, the cellular and molecular basis of exposure to heavy metals, and possible safe agents that are effective in treating heavy metal toxicity remains a critical topic. In this review, the molecular basis of heavy metals-induced cellular damage and its relationship with aging is introduced. The clinical implications of heavy metal toxicity are summarized, and prospects for new agents with protective effects against heavy metal damage are discussed.

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