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Innovative detoxification approaches for heavy metal toxicity: A modern perspective

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Abstract

The persistence, bioaccumulation, and toxicity of heavy metals are major risks to human health and the environment. The most common and toxic heavy metals are lead, mercury, arsenic, and cadmium, which are known to cause neurotoxicity, nephrotoxicity, carcinogenicity, and cardiovascular diseases, respectively. The current study therefore reviews recent developments in treatment options, including chelation therapy, nanotechnology, phytoremediation, and bioengineering, to alleviate the toxic effects of heavy metals. Chelation therapy is the current standard of care, and new formulations of chelating agents such as DMSA and EDTA have improved specificity and lower toxicity. Current trends include the application of nanotechnology, in which nanoparticles and nanomaterials are used for the efficient sequestration and removal of metal ions. Moreover, genetically engineered organisms, including plants and microorganisms, are being used to accumulate and transform HM, which is a new concept in bioremediation. The present study also employed multiomics approaches such as genomics, proteomics, and metabolomics to understand the molecular mechanisms of heavy metal-induced toxicity, which may help in identifying potential therapeutic targets. Nonetheless, there are still some issues with new treatments, including the biocompatibility and scalability of the treatments and the potential environmental impacts. This review provides an overview of the progress in the fight against heavy metal toxicity and emphasizes the need for mutual cooperation to create long-lasting solutions.

1. Introduction

Heavy metals are those whose density exceeds that of water. Heavy metals include metalloids that are toxic at highly limited rates of exposure; for example, even at very low exposure rates, arsenic is quite toxic. Widespread concern has arisen due to the increasing recognition of the emergence of ecological and global public health emergencies, which are rooted in the environmental contamination of these metals. This increased accumulation of heavy metals has occurred because of their extensive application in various industrial, agricultural, domestic, and technological resources. Sources of heavy metals in the environment include geogenic, industrial, agricultural, domestic, atmosphere-sourced pharmaceutical, and effluent sources. Pollution is most common in point-source locations such as mine operations, smelters, foundries, and other industries that manage the production of metals (Tchounwou *et al.*, 2014).

Various heavy metals occur in the Earth's geosystem; they can exist in the lithosphere, hydrosphere, atmosphere, and biosphere. Despite the presence of heavy metals in the ecosystem, human exposure may still occur *via* several human actions. In the Earth's crust, heavy metals occur in ores, which are extracted as minerals in mining activities (Rama Jyothi, 2020). In some ores, heavy metals, such as arsenic, iron, lead, zinc, gold, nickel, silver, and cobalt, act as metal

sulfides, whereas others, such as manganese, aluminum, selenium, gold, and antimony, exist as compounds. Some heavy metals, such as copper, iron, and cobalt, also exist as both sulfide and oxide ores. Certain sulfides may carry two or more heavy metals simultaneously, for example, chalcopyrite (CuFeS_2), in which copper and iron may occur together. These mining activities extract heavy metals from the ore and distribute them throughout the environment; they are further deposited into the soil and carried away by air and water to different locations. Furthermore, when heavy metals are mounted by various industries in accordance with distinct industrial applications, the discharge of elements may occur in air, soil, or water bodies during combustion or just as waste disposal. Among industrial goods containing heavy metals, paints, cosmetics, pesticides, and herbicides may act as specific sources. Finally, heavy metals may be transported through the erosional pathways of soil and water bodies exposed to erosion, runoff, or acid rain (Azeh Engwa *et al.*, 2019).

Natural sources, such as volcanic eruptions, some springs, erosion and bacterial action, and human actions, such as the burning of fuel from fossil fuels, industrial processes, agricultural practices and livestock feeding, release heavy metals into the environment (Abd Elnabi *et al.*, 2023). The metals in question can reside in organisms and, by extension, the human body, causing havoc. They are passed from one cell to another, such as the second home store, and are subsequently stored, where they bind to proteins and nucleic acids, deteriorating these macromolecules and interfering with their biological functions. This is why heavy metal toxicity can manifest in the human body in a variety of ways. This can damage the central nervous system, causing mental disorders and harm to the blood, lungs, and liver and weakening the kidneys, which can lead to many diseases.

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Additionally, the gradual increase in heavy metals within the human body allows for the progression of body, muscular and neurological degenerative diseases, analogous to diseases such as Parkinson's disease and Alzheimer's disease. Moreover, chronic exposure to some heavy metals or their compounds can induce genotoxicity and mutations, aromatize as hormones, and disturb the balance of the endocrine-reproductive system, ultimately affecting oncogenic processes (Hama Aziz and Kareem, 2023).

2. Pathophysiology of heavy metal toxicity

Multiple interconnected mechanisms lead to heavy metal toxicity, causing major cell and systemic level effects. These factors include oxidative stress, disturbance of crucial metal ion balance, disruption of enzyme functions, and triggering of inflammatory and apoptotic pathways. The systemic impacts of heavy metal poisoning arise from the accumulation of cellular damage throughout various organ systems (Rani *et al.*, 2013).

Oxidative stress and reactive oxygen species (ROS) heavy metals are toxic mostly *via* the induction of oxidative stress, additionally leading to reactive oxygen species (ROS) production. Lead (Pb), mercury (Hg) and cadmium (Cd) are ROS-inducing metals that include superoxide anions (O_2^-) and hydroxyl radicals ($\bullet OH$) together with hydrogen peroxide H_2O_2 . These reactive species cause damage to cellular components, such as lipid peroxidation, protein oxidation and DNA damage. This damage to lipids leads to compromised cell membrane integrity and a loss of membrane fluidity and permeability,

similar to lipid peroxidation (AMP) (Nazir *et al.*, 2020). For example, cadmium is recognized to increase ROS *via* increased intracellular ROS and reduced antioxidants, such as cellular glutathione (GSH), in wounds, increasing cellular damage and apoptosis. The main contributing factor to the production of ROS by cadmium-containing mitochondrial respiratory chains has been demonstrated through research (Jaishankar *et al.*, 2014). Redox-active metals such as Cr, Cu, and Fe generate ROS directly. In contrast, the redox-inactive metals such as Ni, Pb, Cd, Al, Zn lead to indirect methods of inducing ROS production such as activating NADPH oxidase or damaging antioxidant defenses. The pathway of generating ROS has been considered to involve an alteration of molecular oxygen (O_2) into superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) through Haber-Weiss and Fenton reactions. If too much production of ROS occurs, then oxidative stress and damage to the cell become unavoidable.

Enzyme inhibition/DNA damage: Heavy metals bind to the enzyme active site, rendering it inactive. For example, mercury and cadmium form persistent complexes with the sulfhydryl (-SH) groups of enzymes, thereby inactivating them. This impairment compromises basic functions, such as cellular respiration, detoxification and antioxidant protection. Cd can interfere with DNA repair enzymes, ultimately causing genomic anomalies and increased mutagenesis. This cancer development is caused by decades of cadmium exposure (Haidar *et al.*, 2023).

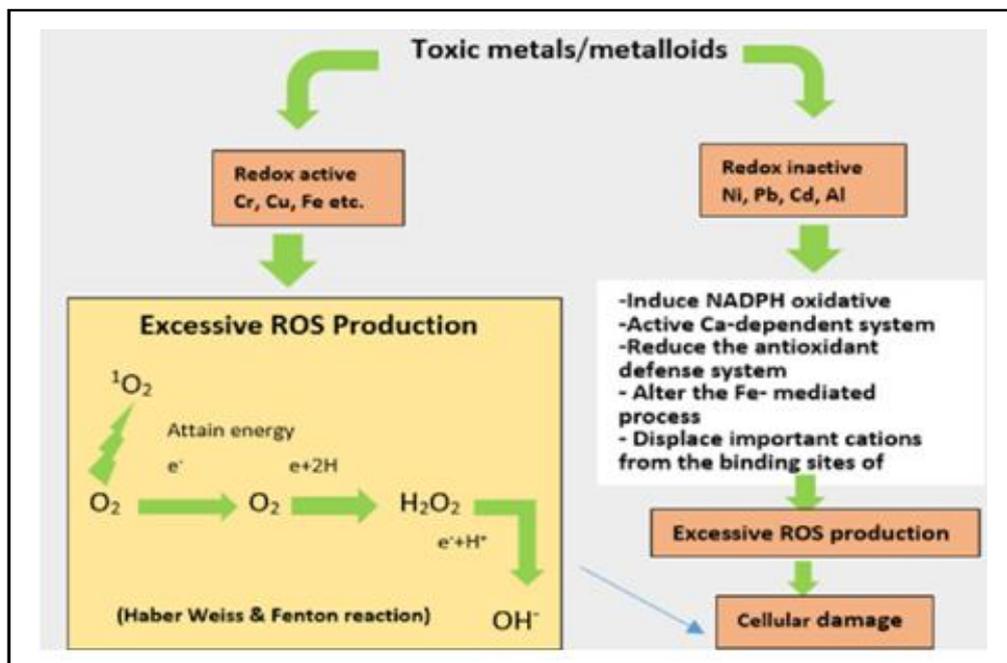


Figure 1: Various mechanism of an excessive reactive oxygen species generation due toxic metals and metalloids elements (Nazir *et al.*, 2020).

Cell suicide/apoptotic activation and inflammation: Exposure to heavy metals activates the cellular stress response through the inhibition of proinflammatory cytokine secretion by apoptosis, and nuclear factor kappa B (NF- κ B) seems to also be activated by heavy metals, which are transcription factors that promote proinflammatory cytokine production. The grave over activation of inflammation causes

additional tissue damage and is the root cause of a plethora of chronic problems (Dukic-Cosic *et al.*, 2020).

When cells encounter cadmium (Cd), it turns on cytochrome P450 enzymes (CYPs), which leads to oxidative stress. This stress sets off a chain of events: it triggers cell death through pathways in mitochondria and death receptors, it ramps up inflammation by

boosting cytokines (IL-5, IL-6, IL-10, IL-1 β , IFN), and it changes neutrophil extracellular traps (NETs) and breathing bursts.

Unbalancing of metal ion balance: Heavy metals disrupt the *in vivo* functions of metal ions such as calcium (Ca²⁺), zinc (Zn²⁺), and iron (II) through mimicking and/or substituting them in living organisms. For example, lead competes with calcium ions for binding sites on proteins and cellular structures, which disrupts processes such as

neurotransmitter release, synaptic function, and skeletal muscle contraction. Similarly, cadmium also competes with zinc ions, which interferes with the activity of all metal-dependent enzymes as well as transcription factors. Replacing iron ions with some heavy metals causes abnormal iron storage and transport, and as a result of the Fenton reaction, which involves irregular iron regulatory proteins, hydroxyl radicals can be created (Koyama *et al.*, 2024).

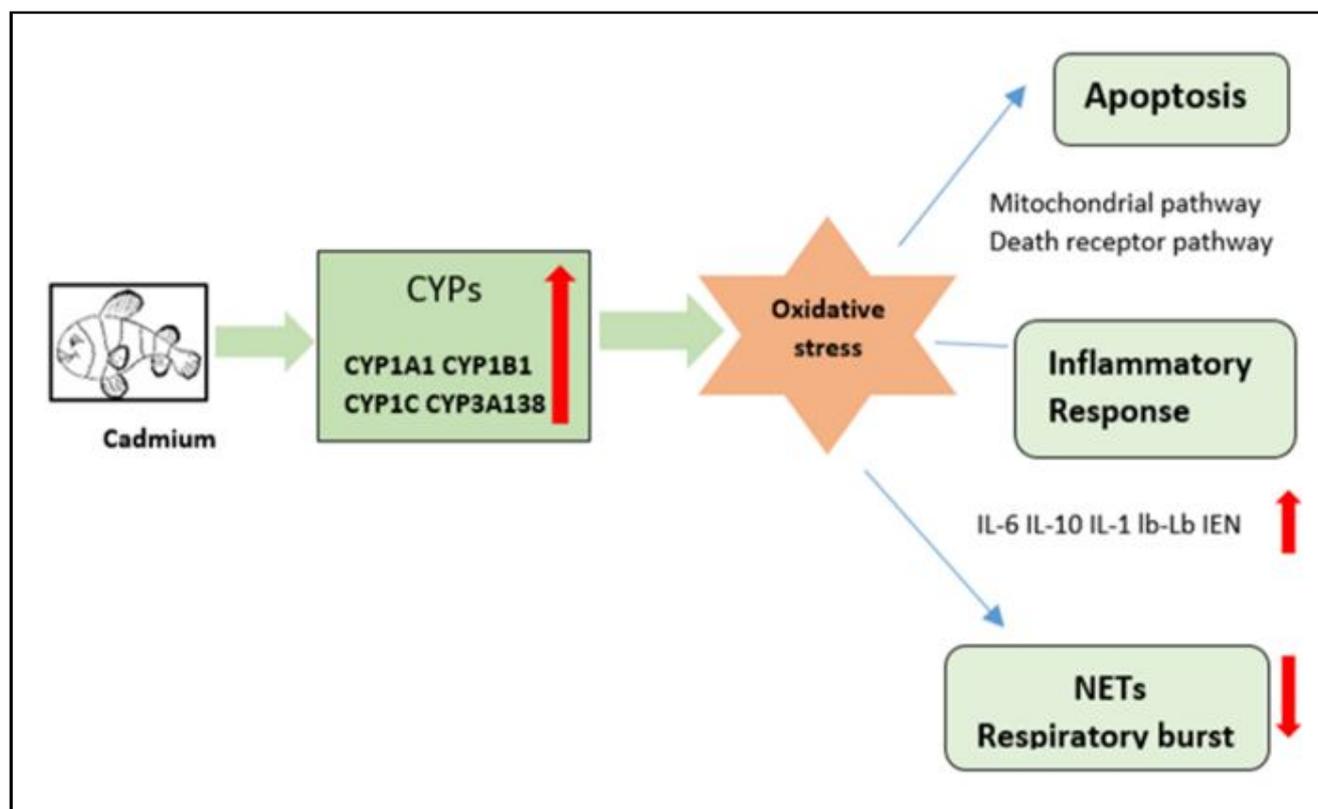


Figure 2: Cadmium-caused oxidative stress and how it affects cell responses (Koyama *et al.*, 2024).

Manifestations of heavy metal poisoning: Harm to cells can be shown in terms of systemic health, which varies by heavy metal and duration of exposure. Neurological diseases are increasing, as metals such as lead and mercury cross the blood-brain barrier, resulting in neurodegeneration, cognitive deficits and developmental problems. Specifically, mercury accumulates in the brain, causing it to interfere with neuronal signaling, leading to tremors and cognitive deficiencies. Lead exposure in children has been associated with a reduced intelligence quotient (IQ) and behavior problems. Cardiovascular consequences include hypertension and atherosclerosis, which are mediated through oxidative stress with endothelial dysfunction. Increased exposure to heavy metals can cause kidney damage since the principal route for metal excretion in the body is through the kidney, and nephrotoxic heavy metals are involved. Increased long-term exposure to arsenic manifests as respiratory diseases, immunodeficiency and cancer (lung and skin cancer, skin exposure) (Fisher and Gupta, 2025). Long-term exposure is linked to respiratory problems, impaired immune function, and cancer development, as evidenced by arsenic exposure, which has been connected to lung, skin, and bladder tumors (Jiaxin *et al.*, 2020). Heavy metal poisoning shows many signs that change on the basis of the specific metal and

how much someone is exposed. Common symptoms include stomach pain, loose stools, throwing up, being tired, and a pin-and-needle feeling in one's hands and feet. In worse cases, people might face life-threatening problems such as odd heartbeats, low red blood cells, and brain fog, causing forgetfulness, trouble breathing, and damage to key organs such as the kidneys and liver. Pregnant individuals risk losing their babies and have a greater chance of developing certain cancers (Cleveland Clinic, 2022).

Specific heavy metals are associated with certain clinical symptoms. Mercury poisoning can have an impact on coordination, weaken muscles, and cause problems with hearing and talking. It can damage nerves in the hands and face, change vision, and make walking difficult. Lead poisoning can present as aggressive constipation behavior, trouble sleeping, and irritability. It can also increase blood pressure, decrease appetite, cause anemia, and cause headaches and tiredness. In children, it can impair memory and cause them to lose their developmental skills. Arsenic exposure often results in red or swollen skin, warts or sores uneven heartbeats, and muscle cramps. When cadmium reaches toxic levels, it can cause fever, breathing problems, and muscle pain (Gotter, 2018).

3. Advances in detection and diagnosis

Recent advances in detection and diagnosis have dramatically increased our ability to monitor and manage health and environmental exposures. Traditional methods, such as urine, hair, blood, and nail analysis, have been widely used since time to assess exposure to toxins, heavy metals, and diseases. These biological samples provide valuable matrices because they enable the assessment of markers of exposure over time. For example, hair and nails provide a much more retrospective time history of exposure than either blood or urine does, where immediate information concerning the presence of toxic substances or compounds associated with diseases can be obtained. In practice, such tests are often insensitive and very extensive in the required sample preparation (Vinothkannan *et al.*, 2023). More sophisticated techniques, including inductively coupled plasma-mass spectrometry (ICP-MS), have emerged as the gold standard for overcoming such constraints. ICP-MS can identify elements at ultratrace levels with excellent precision and sensitivity. This technique is indispensable in toxicology, environmental monitoring, and even nutritional analysis. Its rapid quantification of multiple elements in a single run has made it an important advancement in the field of diagnostics (Chen *et al.*, 2022).

These findings have led to the identification and utilization of exposure biomarkers, which has changed the world of early diagnosis. In search of a suitable analogy, biomarkers are biological markers indicative of the exposure of any given individual to some substance, may indicate the symptomatic effect of exposure, or may indicate susceptibility. Urinary arsenic levels may serve as biomarkers for chronic exposure to arsenic via the consumption of drinking water. Protein or DNA adducts in blood may also indicate exposure to carcinogens, which further helps in diagnosis and preventive work (Kakkar and Jaffery, 2005).

Point-of-care testing (POCT) is a quick, inexpensive, and easy-to-use tool for diagnosing heavy metal toxicity. It solves many problems of traditional lab-based methods. These compact devices detect toxic metals such as lead, mercury, arsenic, and cadmium in blood, urine, or saliva samples immediately where they are needed. POCT systems are simple to operate and yield results in just minutes. This makes them valuable in emergencies, to check workers' health, and in places with few resources. New tools, such as biosensors, microfluidics, and electrochemical detection, have made these tools more accurate and specific. For example, portable machines with advanced sensors can find tiny amounts of lead in blood. This allows doctors to step in before serious harm occurs. Because POCT systems are easy to move and do not cost much, they are key for large-scale screening and monitoring programs. These programs often struggle to provide testing to people who do not have much access to healthcare. These tools play a large role in reducing health problems from heavy metal exposure by helping to spot and treat issues (Cui *et al.*, 2022).

4. Traditional therapies for treatment

Chelation treatment, a routine medical technique used to address heavy metal toxicity, allows the removal of toxic metals from the body via attachment. Chelators are needed for this process; they form strong complexes with the metal ion, permitting its excretion via the kidneys. The Greek term *chele*, meaning claw, gives rise to the term chelation and suggests how these compounds tightly encase the metals. Chelation therapy is used to treat acute metal poisoning,

particularly lead, mercury, arsenic, and cadmium poisoning. The management of Wilson's disease, which is characterized by the accumulation of too much copper within the body, benefits from this therapy (Flora *et al.*, 2012).

Because of its efficacy in treating lead poisoning, ethylene disaminatoacetate (EDTA) often uses chelating agents that also bind to cadmium, zinc, and iron. Given that it is given intravenously or intramuscularly, EDTA has been a standard treatment for years. Dimercaprol (British antilewisite or BAL), which is primarily used for arsenic and mercury toxicity, is another chelator often combined with EDTA for lead toxicity. For mercury and arsenic poisoning, oral chelating agents, including dimercaptosuccinic acid (DMSA) and 2,3-Dimercapto-1-propanesulfonic acid (DMPS), are effective. Given its successful therapy and safety history, DMSA is especially recommended for children suffering from lead poisoning (Jomova *et al.*, 2024) often used for conditions linked to copper buildup, such as Wilson's disease, penicillin can also bind to other elements, such as lead and mercury. Each chelator's metal specificity, route of administration, and patient health status all affect its application. For example, oral chelating agents are used in less severe cases or under continuous exposure; severe toxicity often calls for intravenous therapy. While effective, chelation treatment can cause renal harm, digestive issues, and electrolyte imbalances, among other side effects. It should hence be administered under close medical supervision. Furthermore, the poor use of chelation therapy for disorders not approved, including autism or heart disease, has met criticism since scientific support is lacking (Flora and Pachauri, 2010).

Standard chelation treatments for heavy metal poisoning may be less safe or effective because few constraints exist. This also refers to their restricted ability to bind poisonous metals without lowering essential trace elements, which might lead to nutrient imbalances and issues. Furthermore, most chelating agents are unable to cross the blood-brain barrier; hence, their ability to clear heavy metals that accumulate in the brain is limited. This is especially worrisome for neurotoxic metals such as mercury and lead, which can cause permanent neurological damage. Especially with long or incorrect use, chelation therapy also presents risks of negative effects, including hepatotoxicity and nephrotoxicity (Kim *et al.*, 2019). Agents such as DMPS and DMSA might cause allergic reactions and stomach issues and might present dangers for individuals with kidney disease given their dependence on kidney elimination. Moreover, conventional chelation treatments are not as good at managing chronic, low-level metal exposure since they are mostly intended for acute poisoning events. Furthermore, their limited availability in low-resource environments owing to their high cost and requirement for medical oversight restrict their universal applicability (Sears, 2013).

5. Recent advances treatment

5.1 Recent advances in chelation therapy

Indeed, the development of specific chelating agents has become a significant area for investigating heavy metals in their management. By definition, chelating agents are substances that attach to heavy metals and convert these harmful species into excretal forms. Traditional chelating agents are often compromised by side effects and a lack of efficacy. The latest approaches in design have entailed more specific chelating agents that aim more precisely at certain heavy metals, thus reducing the eventual risk of side effects and improving treatment outcomes (Kontoghiorghes, 2020).

One strategy to develop selective chelating agents is structure-based design, which mainly involves the creation of molecules that are targeted for binding to specific heavy metals. For example, researchers have developed a chelating agent called 2, 3-dimercapto-1-propanesulfonic acid (DMPS) specifically to bind mercury and arsenic, dramatically reducing their toxicity within living systems. Another is succimer (DMSA), which has been experimentally proven to chelate lead from children, thus reducing lead-induced toxicity (Drisko, 2018).

Selective chelating agents have also been developed *via* combinatorial chemistry and high-throughput screens. This is mainly about generating large libraries from which such molecules would be wise against specific metal ions. For example, combinatorial chemistry has been employed in the development of clioquinol, which specifically chelates zinc and copper for use in treating neurodegenerative diseases (Aaseth and Nurchi, 2022).

In the exploration of compounds as selective chelators, natural products were equally considered. For example, the plant-based compound curcumin, when exposed to iron and copper, was found to specifically chelate these compounds, thus reducing their toxicity

in neurodegenerative diseases. Another example is resveratrol, which selectively chelates zinc and copper to lower their toxicity in cardiovascular diseases (Smirnova *et al.*, 2023).

The development of selective chelating agents with improved safety and efficiency performance would be promising endeavors in this area and await development for the treatment of heavy metal poisoning. Further research is needed to translate these advances into clinical use (Simorangkir *et al.*, 2022).

5.2 Nanotechnology in heavy metal detoxification

Many studies have shown that nanoparticles play an important role in metal sequestration due to their unique property of having more surfaces, having a higher degree of reactivity, and high targeted delivery capability; that is, they act more efficiently in interactions as well as involving metal ions. Additionally, in the binding of such metal ions in the process of metal detoxification in the body, different interactions between different kinds of nanoparticles and metal ions are observed. The mechanisms used in metal sequestration include adsorption, chelation, and ion exchange and can effectively sequester metal ions such as arsenic, lead, copper, and zinc (Baby *et al.*, 2019).

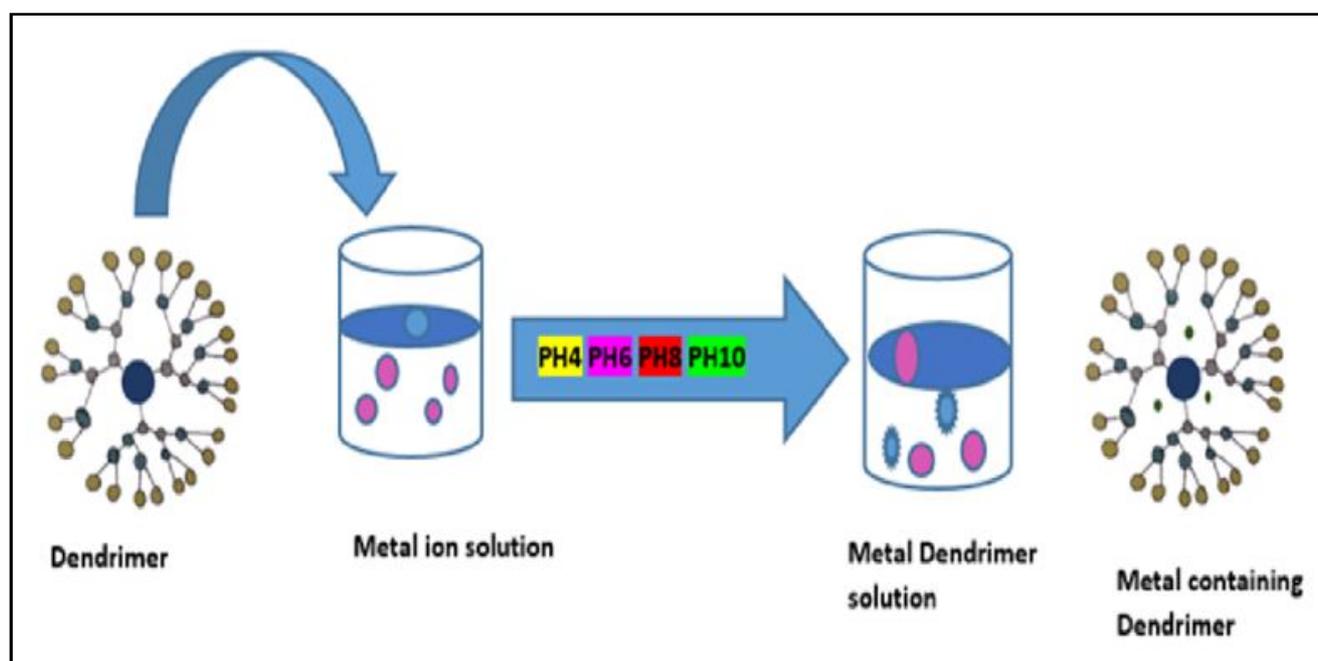


Figure 3: Metal ion adsorption using dendrimers at different pH levels (Baby *et al.*, 2019).

For example, iron oxide nanoparticles effectively sequester arsenic and lead ions, whereas other carbon-based nanoparticles, such as graphene oxides or carbon nanotubes, have shown the ability to effectively remove large amounts of metal ions from aqueous media. Dendrimers, a new type of highly branched nanoparticle, have a chelating agent that has been shown to chelate metals such as copper and zinc effectively. In summary, nanoparticles hold great promise in metal sequestration, providing a more targeted and efficient way of disposing of toxic metal ions from the body (Ma *et al.*, 2024).

The use of nanoparticles in metal sequestration has several advantages over traditional methods, including increased effectiveness, reduced toxicity, and targeted delivery. NPs can be designed to be appropriate for size, shape, and surface chemistry, which can enhance specific

properties of sequestered metals. Nevertheless, further in-depth exploration of metal sequestration from nanoparticles and the issues associated with their use, such as scale-up, economical modes of use, and EHS, is needed (Mehrotra *et al.*, 2021).

Nanomaterial treatment influences medical outcomes in many positive ways. This allows for targeted delivery, which means that nanomaterials can have zero effects on specific cells, tissues, or organs. This reduces side effects and makes treatments work better. Additionally, nanomaterials increase the degree to which the body can use therapeutic agents; thus, doctors can administer smaller doses that are less toxic. These materials can pass through biological walls such as the blood-brain barrier and reach places that were previously difficult to treat. Individuals can change things such as their size,

shape, and surface chemistry to make treatments more effective. In addition, they can decrease the toxicity of agents, leading to safer treatment options. Nanomaterials help therapeutic agents last longer on the shelf, so they do not breakdown. This flexibility helps with personalized medicine because nanomaterials can react to specific biological signals, allowing custom treatments. They also let healthcare providers watch how treatments are working in real time and make changes if needed. In addition, nanomaterials can deliver multiple therapeutic agents at once, which improves combination therapy and treatment results. Moreover, nanomaterials are cost-effective, which increases the availability of advanced treatments and eases the financial strain on healthcare (Patel *et al.*, 2022).

5.3 Bioremediation and biotechnology approaches

By transforming these metals into less toxic forms, microorganisms and their enzymes have increasingly taken advantage of the biologically friendly potential of the world for heavy metal purification. Bioremediation mechanisms employ several metabolic pathways found in bacteria, fungi, and algae to detoxify or immobilize heavy metals (Kapahi and Sachdeva, 2019).

Some bacteria that detoxify toxic metals, including chromium, mercury, lead, and mercury, are *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Shewanella oneidensis* via biosorption, bioaccumulation, and enzymatic reduction. The biosorption of abundant functional groups, including carboxyl, hydroxyl, and amino groups, is a passive process whereby Meerke ions attach to the microbial cell wall (Li *et al.*, 2022). In contrast, bioaccumulation actively transfers metals into microbial cells, followed by intracellular sequestration aided by the synthesis of peptides (such as metallothioneins and phytochelatin) that bind and immobilize metal ions. Some bacteria can also enzymatically change poisonous metals. For example, *Shewanella* species lower soluble Cr (VI) to less mobile insoluble Cr (III), therefore decreasing mobility and toxicity (Kapoor and Viraraghavan, 1997).

Fungi such as *Aspergillus niger*, *Trichoderma harzianum*, and *Penicillium* spp. play key roles in removing heavy metals. These fungi make polysaccharides and enzymes outside their cells stick to

or change metal ions. Additionally, their large networks of thread-like structures increase their surface area to absorb metals. This makes them work well even when there is not much metal present (Mehta and Gaur, 2005). Algae such as *Chlorella vulgaris*, *Spirulina platensis*, and *Scenedesmus* are highly effective at soaking metals such as arsenic, lead, and nickel. These algae use ion exchange on their surface and store metals inside their cells to reduce their toxicity. They can grow in places without many nutrients, which makes them useful for cleaning wastewater (Dinakarkumar *et al.*, 2024).

Enzymes such as oxidoreductases (such as laccase and manganese peroxidase) and hydrolases are key to detoxifying metals. Mercury reductase (MerA), for example, converts toxic Hg (II) into the less harmful volatile Hg (0), which then escapes into the air (Dash and Das, 2012). Similarly, arsenate reductase (ArsC) changes arsenate (As (V)) into arsenite (As (III)), setting the stage for more detox steps. These enzyme reactions are very (Silver and Phung, 2005). precise and often require helpers such as NADH or NADPH to increase their effectiveness. Compared with standard chemical and physical detoxification techniques, microbial and enzymatic methods have several benefits. They are inexpensive, work under mild conditions, and create less secondary pollution. Additionally, microbes can adjust to and grow in polluted areas, making them flexible options for bioremediation. However, problems still exist. The focus of microbes on specific metals, the effects of environmental factors (such as pH and temperature competing ions), and the ability to scale up remain major obstacles. To address these issues, scientists could create modified microbes that can bind more metals and survive under harsh conditions (Zhou *et al.*, 2023).

Studies on microbial groups that mix different species to work together in the cleaning of metals look promising. Additionally, combining cleanup methods with tiny tech, such as the use of enzymes attached to supersmall particles or increasing microbial activity with nanomaterials, could improve these processes on a larger scale. More research to understand how genes turn on and off how to tweak microbe metabolism and how microbe communities interact will help us use them even better to eliminate heavy metals (Liu *et al.*, 2024).

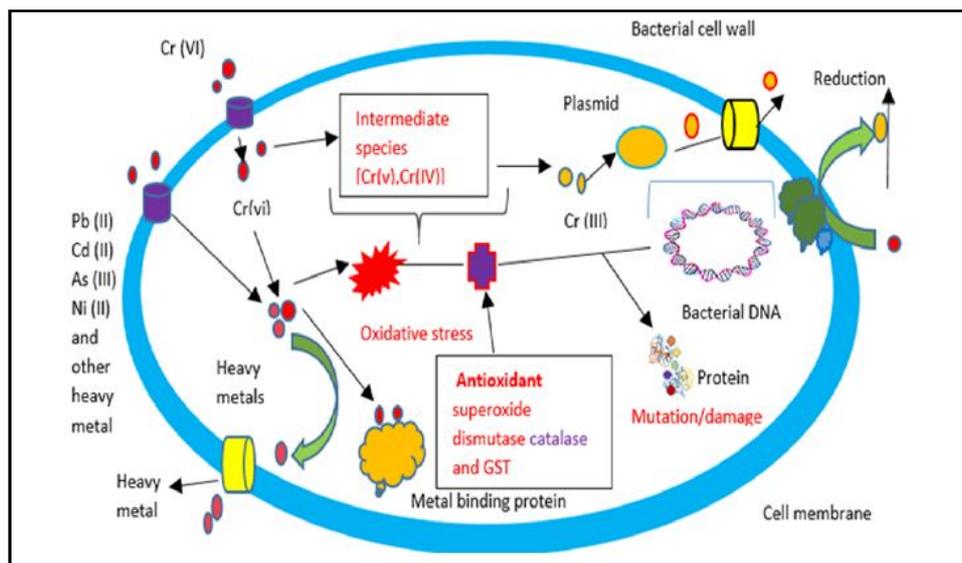


Figure 4: The occurrence of oxidative stress as a result of Cr (VI) exposure engages in complex interactions with cellular defense mechanisms (Liu *et al.*, 2024).

Genetic engineering has become an effective means to harness the ability of microbial bioremediation to reduce the effects of metal toxicity on organisms. Thus, the use of genetic manipulation will afford genetic engineering an unprecedented opportunity to develop more efficient microbes for the remediation of heavy metal contamination, the main approach possibly being the overexpression of metal-binding proteins such as metallothioneins and phytochelatins, such as those that enhance the ability of bacteria and fungi to sequester toxic metals such as cadmium, lead, and mercury. (Valls and de Lorenzo, 2002). Other genes encoding reductases, such as mercuric ion reductase (MerA) and arsenate reductase (ArsC), have been cloned and inserted into potent microbial hosts, such as *E. coli* and *Pseudomonas*, to improve the ability of microbial taxa to reduce metals to less toxic forms (Wang *et al.*, 2014).

Modern genetic engineering tools such as CRISPR-Cas systems and synthetic biology allow for increasingly precise editing of microbial genomes. The CRISPR-Cas9 system, for example, has been used to knock down genes that could decrease function for pathways targeting metal detoxification or could introduce novel genes that increase tolerance to metals and detoxification ability. Synthetic biology positioning allows creative designs to be constructed for biosensing that can detect certain heavy metals and then respond by activating detoxification pathways only in the presence of contaminants, which will help save energy (Singh *et al.*, 2006). With the genetic introduction of biofilm-forming genes, more heavy metals are immobilized on microbial surfaces, further increasing biosorption efficiency (Misra *et al.*, 2024).

While genetically modified microorganisms offer significant application advantages for heavy metal bioremediation, their use is constrained by regulatory hindrances, potential ecological risks, and public concern about the use of GMOs in such settings. Addressing this issue may take the form of developing bio containment systems and confining transfer genes. With more advanced approaches in genetic engineering and synthetic biology, the development of safe, effective, and versatile microbial systems for the removal of heavy metal contamination will surely proliferate (Ali *et al.*, 2013).

5.4 Phytoremediation and plant-based solutions

Phytoremediation is a method that has great benefit because it is eco-friendly, economical and sustainable for removing heavy metal toxicity from polluted soil and water. It is a bioremediation technique that uses plants to absorb, sequester or degrade toxic heavy metals from the environment. Different plant species, especially hyperaccumulators such as *Brassica juncea* (Indian mustard), *Helianthus annuus* (sunflower) and species of *Populus* (poplars), are reported to hold great potential in obtaining metals (cadmium, lead and arsenic) from contaminated sites (Clemens, 2006).

Plants employ intrinsic detoxification mechanisms, including the synthesis of metal-chelating compounds such as phytochelatins and metallothioneins, which bind heavy metals and thereby reduce their toxicity within plant tissues (Zhao *et al.*, 2008). Among the various phytoremediation approaches, phytoextraction involves the uptake and accumulation of metals in harvestable plant parts, whereas phytostabilization limits metal mobility by immobilizing contaminants in the soil, reducing leaching and bioavailability. A notable example of phytostabilization is vetiver grass (*Chrysopogon*

zizanioides), which is extensively used due to its deep root system, high biomass production, and remarkable tolerance to heavy metal stress (Rajkumar *et al.*, 2009). In addition, plant-microbe interactions, particularly those involving rhizosphere-associated bacteria, significantly enhance phytoremediation efficiency by increasing metal solubility, availability, and subsequent uptake by plants (Kumar *et al.*, 2022).

Phytoremediation is a promising method; however, it is limited by slow remediation rates (<10 years) and demands site-specific selection of plants for maximum efficiency. The findings of this study provide practical implications for the future; the challenges above can be addressed by combining plant-based strategies with other remediation methods, which include the application of chemical amendments or genetic engineering of plants exhibiting increased metal tolerance and accumulation potential. Land contamination with the metallic waste of lead, copper, cadmium, and mercury 257 disrupts sapling development, with concern for the increase in metal toxicity throughout the food chain; thus, phytoremediation represents an ecofriendly action to remediate heavy metal contamination when contrasted with conventional cleanup while preserving earth health and biodiversity (Van der Ent *et al.*, 2012).

Heavy metal pollution is a risky issue, and hyperaccumulator plants are essential in bioremediation because of their unique characteristics. They are difficult to kill, and they can take in and store many metals in their tissues without harming the overall health of the plant. The plants, *Thlaspi caerulescens*, *Pteris vittata*, and *Alyssum murale* are well-known examples, as they can live off zinc, cadmium, arsenic, and nickel, respectively. Hyperaccumulators take in heavy metals from the soil at a higher rate than other plants do, and they can also store the metals in parts of the plant, such as vacuoles. The resistance of these plants to high concentrations of heavy metals is due to active root absorption, high efficiency of xylem loading, and metabolism of the metal into less harmful chemicals (phytochelatins and metallothioneins) (Chaney *et al.*, 1997).

Phytoextraction is the process of hyperaccumulators recovering metals from soil, which plants then store in their aboveground parts. Plants such as *Brassica juncea* are able to remove cadmium, lead, and chromium from contaminated places, making them extremely useful for phytoextraction. These plants lower the concentration of metals in the earth, which prevents harmful substances from seeping into the groundwater. As a result, they protect the environment as well as human beings. Hyperaccumulators also generate biomass that can be useful in the recovery of some metals, a technique known as phytomining (Ahmad *et al.*, 2014).

Advances in farming techniques have altered how heavy metals are taken in from contaminated soils and increased the efficacy of phytoremediation. Organic matter and soil amendments, including chelators such as ethylenediaminetetra acetic acid (EDTA), help increase the availability of heavy metals in soils to plants; simultaneously, an elemental response is the use of biofertilizers. EDTA, for example, is employed to improve the effectiveness of phytoextraction in *Brassica juncea* and *Helianthus annuus*. Other materials used in amendments, such as biochar and compost, not only improve soil fertility but also help immobilize metals and hence reduce their leaching and toxicity (Qin *et al.*, 2024).

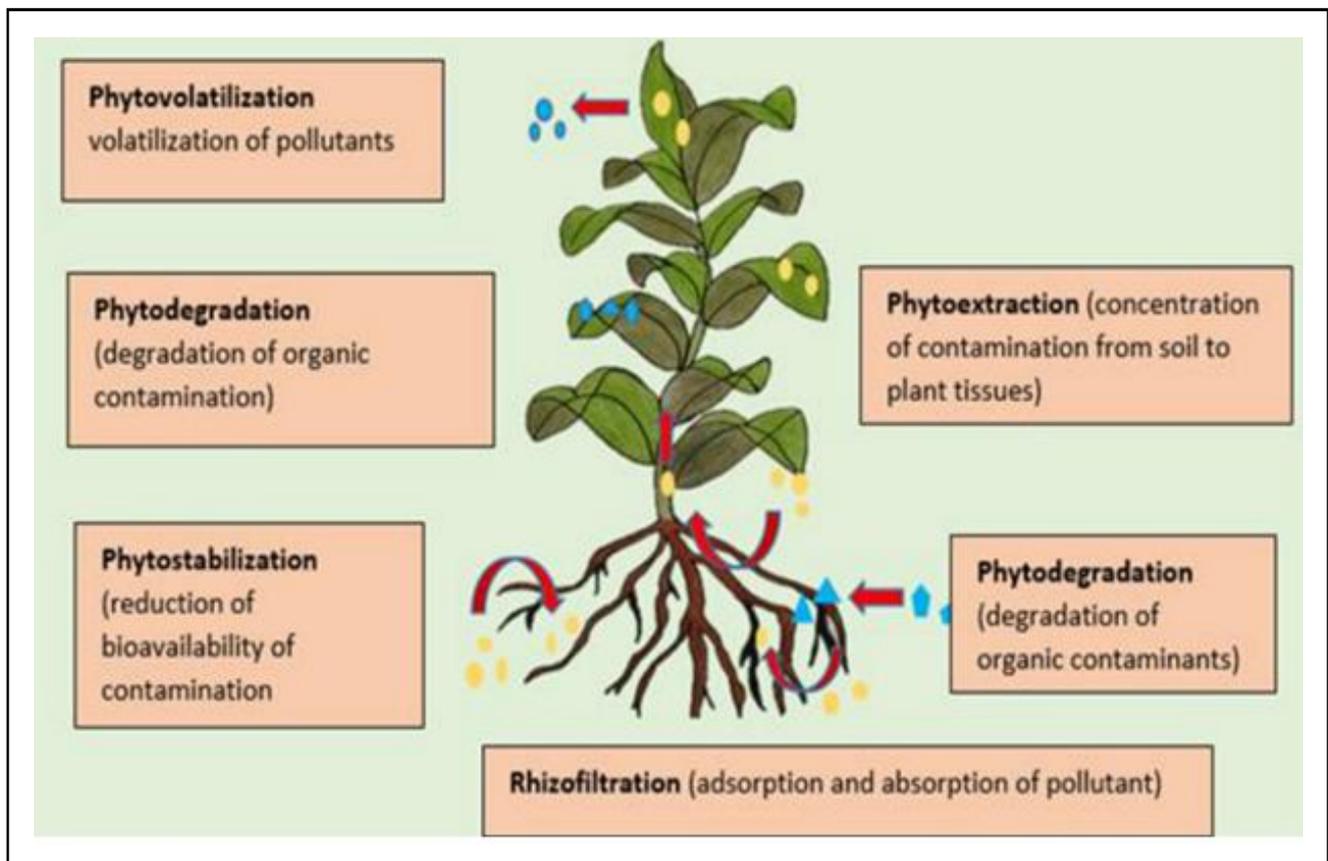


Figure 5: The process of pollutant removal through phytoremediation involves five distinct mechanisms (Flora *et al.*, 2008).

Another improvement is the use of plant growth-promoting rhizobacteria (PGPR). These microorganisms help to increase plant tolerance to metal toxicity by acting as iron transporters, dissolving metals, and regulating stress hormones, including ethylene. Research into *Pseudomonas* and *Bacillus* species, for example, revealed that these bacteria improved metal intake in plants without harming crops. In part because genetic engineering produces transgenic plants with better metal uptake, transport, and detoxification abilities, it has also helped to improve farming methods. Genes encoding metal transporters, metallothioneins, and phytochelatins have been introduced into tobacco and rice, therefore significantly improving their soil-remediation potential (Flora *et al.*, 2008).

5.5 Role of antioxidants in mitigating oxidative stress

By countering reactive oxygen species and lowering the oxidative damage to cellular lipids, proteins, and DNA, antioxidants are vital for preventing and reducing the oxidative stress caused by heavy metals. Metalloids, such as lead, mercury, cadmium, and arsenic, cause the production of reactive oxygen species (ROS), which destroy cellular lipids, proteins, and DNA *via* oxidative stress. Endogenous antioxidants include glutathione, catalase, and superoxide dismutase, dietary antioxidants such as vitamins C and E, polyphenols, flavonoids, and fruits, with an antioxidant required for detoxifying ROS. Antioxidants can donate electrons to scavenge ROS to block further cellular damage. Antioxidants also increase the activity of detoxifying enzymes by turning on genes that advance the cellular defense response via specific signaling pathways, including nuclear

factor erythroid 2-related factor 2 (Nrf2). Some studies have indicated that the consumption of antioxidant supplements helps alleviate heavy metal-induced toxicity, and therefore, restoring the redox balance improves the physiological outcomes. Therefore, antioxidants could be promising treatments for reducing harm caused by heavy metal poisoning (Maurya *et al.*, 2024).

5.6 Role of AI and computational biology

Our capacity to predict, relieve, and grasp the consequences of heavy metal toxicity has been greatly transformed by artificial intelligence and computational biology. In the area of toxicology and the environment, machine learning and deep learning algorithms that process large quantities of data that uncover some possible hidden patterns or correlations previously unattainable by normal analytical techniques are used. AI forecasts where heavy metals bind to proteins, reveals how metabolic pathways and signaling pathways are affected, and gauges the level of toxicity across species. Computational biology promotes AI by generating molecular models and simulations that depict heavy metal interactions with biological molecules such as DNA, proteins, and lipids at the molecular level. These models help to highlight possible therapeutic aims and key biomolecules for exposure and/or toxicity detection. Furthermore, artificial intelligence drug discovery platforms often use tens of thousands of compounds to screen for chelation potential in eliminating heavy metals or reducing toxic effects, therefore accelerating the development of effective therapies (Miller *et al.*, 2023).

Therefore, AI and computational biology together supply, consequently, an important stretch for exposure risk assessment, which merges some environmental exposure data and care with health outcomes to make more exact regional predictions. Advanced tools, such as neural networks and systems biology approaches, are being used to simulate whole-biological systems, enabling complicated questions concerning chronic heavy metal exposure, such as cadmium or arsenic exposure. Collectively, these technologies provide a systems-level understanding of heavy metal toxicity and promote treatment and prevention through precision medicine (Kumar *et al.*, 2017).

6. Challenges and future perspectives

Therefore, a multidisciplinary approach that guarantees practical solutions is needed, and heavy metal toxicity presents many issues governing its control and sequestration. One major problem is long-term exposure to and risk from the persistence of nonbiodegradable heavy metals, including lead, cadmium, mercury, and arsenic, in the environment. Even with advanced biological and environmental samples, finding low heavy metal levels is often difficult, even when conventional techniques are time-consuming and costly. The complex processes of heavy metal toxicity, oxidative stress, genotoxicity, and disturbances to cell signaling pathways are further complicated by this variability in genetic makeup, coexposure to several toxins, and individual susceptibility levels. Incomplete metal removal, side effects, and difficulties in recovering normal physiological functions all limit the use of therapeutic techniques such as chelation therapy.

Future views include the integration of cutting-edge technologies such as nanotechnology, artificial intelligence, and omics-based tactics to more effectively address these obstacles. While artificial intelligence and machine learning are employed to improve predictive models for evaluating toxicity and to make drugs, nanotechnology offers fresh options for targeted drug delivery and heavy metal removal. Systems biology and multiomics techniques, which include genomics, proteomics, and metabolomics, provide a more thorough understanding of the molecular basis of toxicity as well as possible early detection and therapy biomarkers. Reducing heavy metal exposure depends in great part on policy-based strategies such as more strict environmental rules and public health initiatives. A combined approach emphasizing ingenuity, interdisciplinary studies, and prevention techniques would help address the long-term health and environmental effects of insecticide exposure (Angon *et al.*, 2024).

7. Discussion

Heavy metal poisoning is a major global environmental and medical issue because constant advancements in both detection and treatment are needed. Traditional chelation therapy is strong, but it has drawbacks, including side effects and nonspecific metal binding. Modern advances have improved medical and diagnostic accuracy. The advanced sensitivity and specificity of heavy metal detection enabled by nanotechnology and AI-driven computational models make early action feasible. Chelation therapy, which increases metal removal efficiency and reduces toxicity, has been changed by the development of new chelators and drug delivery systems based on nanocarriers. In popularity as a secondary therapy to help protect against damage from heavy metal exposure due to oxidative stress, antioxidant treatment also helps to provide some protection. Together, these advances serve to enhance the results of therapy and patient experience.

By means of phytoremediation and bioremediation, biological methods that use plants and microorganisms to absorb and counteract pollutants provide low-cost, ecologically friendly solutions for heavy metal detoxification. Artificial intelligence and computer modeling are improving revolutionized drug design, perfected chelating structures, and predicted toxicity patterns, thereby helping to accelerate the development of strong underwriting products. Although still challenging, concerns about the safety of nanotechnology, legal problems, and the scalability of biological treatments translating these advances into clinical applications are still quite difficult. Future research should focus on including many treatments, developing personalized medical technologies, and addressing the source of environmental pollution. A multidisciplinary collaboration among chemists, data scientists, biotechnologists, and toxicologists is also needed to ensure practical solutions for treating heavy metal toxicity. Refining these changes will rely on this collaboration as well.

8. Conclusion

New detoxification methods are bright promising prospects towards the treatment of heavy metal toxicity by the integration of nanotechnology and bioremediation, with chelation therapy. New approaches not only amplify detoxification but are geared toward even higher safety and environmental sustainability in these modern strategies. As with any field in rapid development, continued research and cross-disciplinary collaboration are needed to fully realize their promise in applications both clinical and environmental.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Aamir Y. Khan: Contributed to supervision, critical review, and overall guidance of the manuscript; **Saffura Saher:** Contributed to literature survey, data curation, and critical analysis of published studies; **Ibtisam Ummehani:** Contributed to literature survey and data curation; **Raheela Sultana:** Contributed to software handling, reference management, and visualization of review content; **Masuma Begum Laskar:** Contributed to writing the original draft, reviewing, and editing of the manuscript; **Maher Unissa:** Contributed to validation of scientific content, critical revision, and final approval of the manuscript.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

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