

Plant defense mechanisms against heavy metal stress

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ABSTRACT

Heavy metal toxicity adversely affects key physiological processes in plants, including photosynthesis and respiration, resulting in reduced plant growth, development, and productivity. Plants manage the negative effects of heavy metal toxicity through a complex set of mechanisms that can be categorized into two main strategies: avoidance strategy and tolerance strategy. The avoidance strategy serves as the initial defence line for plants facing heavy metal toxicity, showcasing their ability to avert or block the entry of heavy metal ions into the plant. The key mechanisms involved in heavy metal avoidance include the immobilization of heavy metals through root exudates or mycorrhizal associations and the incorporation of heavy metals into the root cell walls. In contrast, the tolerance strategy encompasses all mechanisms that a plant activates when heavy metal ions have already been absorbed, aiming to reduce or neutralize their negative effects. These mechanisms involve the overexpression of genes associated with heavy metal tolerance, along with metal chelation by phytochelatins and metallothioneins, followed by their compartmentalization in the vacuole. Understanding all of these defence mechanisms, as well as the signalling pathways involved in plants' responses to heavy metal stress, is critical for developing strategies to increase crop resilience to heavy metal-contaminated environments.

Keywords: avoidance, chaperons, chelation, compartmentalization, tolerance

INTRODUCTION

Heavy metals (HMs) are all chemical elements with a relative density greater than 5 g/cm³. Some of these elements are classified as nutrients necessary for plant growth, including Cu, Zn, and Fe, while others primarily exhibit toxic effects on plants, such as Cd, Cr, and Pb (Oladimeji et al., 2025). HMs in soils originate from the weathering of parent rocks (natural sources) and from anthropogenic (human-caused) activities. Industrial facilities, excessive use of fertilizers and pesticides containing toxic HMs, and waste management practices are the most significant anthropogenic contributors to HM soil contamination. Unfortunately, due to the irresponsible use of natural resources, approximately 14% to 17% of the world's croplands are contaminated to a greater or lesser extent by at least one toxic HM, which jeopardizes the possibility of producing healthy food on them (Hou

et al., 2025). The seriousness of this issue is particularly evident in the fact that soil contamination with HMs disrupts plant biodiversity, which causes irreparable harm to existing ecosystems.

To effectively reduce the levels of HMs in the soil, it is essential to understand the dynamics of HMs within the plant-soil system. This is a highly complex scientific field, as it involves understanding all the characteristics of HMs, including their availability to plants depending on the soil's physical-chemical properties. Additionally, it demands knowledge of the plant's defense mechanisms against HM stress (Jarin et al., 2025).

The chemical properties of the soil, particularly the pH value and cation exchange capacity, have the greatest impact on the availability of HMs to plants. Generally, a decline in soil pH increases the mobility of most

HMs present in the soil, thereby increasing their uptake by plants. In acidic soils, hydrogen ions (H^+) displace HM ions from their binding sites on soil particles, resulting in higher HM mobility in soil and thus bioavailability. Conversely, in alkaline soils, HM ions can be precipitated as insoluble compounds, such as hydroxides and carbonates, which makes them less available to plants (Golias et al., 2023). Cation exchange capacity (CEC) refers to the soil's ability to retain cations on negatively charged sites within clay minerals and organic matter (Ćirić et al., 2023). Considering that most HMs exist in soil solution as cations, a higher CEC of the soil correlates with a greater capacity of the soil to hold HMs, thereby reducing their bioavailability (Cheng et al., 2025a). The availability of HMs to plants also depends on the plant's genotype; thus, the same concentration of a particular HM in the soil may be highly toxic to one species yet have no adverse effects on another (Angon et al., 2024).

Plants have evolved various strategies to cope with HM stress, allowing them to adjust to environmental challenges. Those that have more effective mechanisms for blocking the entry of HMs into their roots or for excluding them from physiological functions if absorbed demonstrate a higher capacity to adapt to stress conditions caused by HMs (Li et al., 2025a). Plants with effective defense mechanisms against HM stress can be utilized for the remediation of soil contaminated with HMs, provided they absorb these HMs in significant quantities. Nonetheless, for this to be achievable, it is essential to know the defense mechanisms against HM stress in as many plants as possible (Tamma et al., 2025). This review delves into the morphological and metabolic changes that occur in plants exposed to HM stress, alongside the morphological, physiological, and molecular mechanisms that help them adapt. Understanding these mechanisms is vital for creating strategies that enhance crop resilience in HM-contaminated soils.

HEAVY METAL TOXICITY EFFECTS ON PLANTS

HMs, when present in excessive amounts in growing media, have adverse effects on plants, including disruptions in numerous physiological processes and metabolic reactions. Plant metabolic disorders in the presence of toxic HMs are intricately connected with their ability to displace essential metal ions from their natural binding sites within enzymes or to interact with thiols (-SH) and other protein functional groups, altering their structure and reducing their functionality (Tamás et al., 2014). Furthermore, redox-active HMs, such as Fe and Cu, produce reactive oxygen species (ROS) directly via redox reactions; in contrast, HMs like Pb, Cd, Ni, Al, Mn, and Zn induce ROS indirectly by activating ROS-producing enzymes like NADPH oxidases. At physiological levels, ROS play a crucial role in various cellular functions; however, the overproduction of ROS leads to oxidative stress (Jalimi et al., 2018).

To better evaluate the detrimental impacts of HMs on plants, it is essential to know the role that the HM being studied plays in the plant, as well as the threshold value at which this HM starts to demonstrate adverse impacts on the plant. Essential HMs, such as Cu and Zn, along with nonessential HMs like Cd, Pb, and Cr, are toxic to plants if their concentrations within the cells exceed permissible limits (Alengebawy et al., 2021). Table 1 illustrates the detrimental effects and the toxicity threshold of HMs in plants.

HEAVY METAL STRESS SIGNALING IN PLANTS

Plants have evolved numerous signaling pathways that regulate their response to HM stress. In general, these pathways in each plant cell consist of signal perception, intracellular signal transduction, and defense response. However, HM stress signaling pathways in plant cells are highly complex, mainly because HMs differ significantly in both their uptake mechanisms and the manner in which they express harmful effects on plants.

MURTIĆ: Plant defense mechanisms against heavy metal stress...**Table 1.** The role, detrimental effects and toxicity threshold of heavy metals in plants

Heavy metal	The role in plants	Adverse effects on plants	References	Normal range in plants (mg/kg)	Toxic value (mg/kg)	References
As	Unknown	Reduction in shoot and root growth; restricted nutrient uptake; reduction in biomass yield	Finnegan and Chen, 2012; Balali-Mood et al., 2021	-	5-100	Kabata-Pendias and Pendias, 1992
Cd	Unknown	Poor root development; decrease in seedling height; reduced leaf area; oxidative damage; leaf rolling and chlorosis	Kazmi et al., 2025	-	3-30	Ismael et al., 2019
Co	It supports the nitrogen-fixing system inside root nodules	Photosynthesis inhibition; oxidative damage; Fe deficiency	Soumare et al., 2020	0.1-10	>10	Shang et al., 2025
Cr	Unknown	Disturbances in the plant's water regime; nutrient deficiencies; changes in the germination process; leaf chlorosis	Sharma et al., 2020a	-	>100	Kacálková et al., 2014
Cu	An essential part of antioxidant enzymes, as well as enzymes that participate in the metabolism of nucleic acids	Lipid peroxidation within biological membranes; enzyme inhibition; oxidative stress; reduction in photosynthesis; inhibition of plant growth; chlorosis	Chen et al., 2022	2-20	20-100	Kabata-Pendias and Pendias, 2001
Fe	An essential element for chlorophyll synthesis, and for the reduction of nitrites and sulfates; an important part of the electron transport chain	Poor plant growth and yield; oxidative stress; damage to root cells and plasma membrane; leaf bronzing; stunted root system	Sági-Kazár et al., 2022; Harish et al., 2023	30-300	<500	Adamski et al., 2011
Hg	Unknown	Enzyme inactivation; oxidative damage; stunted growth; chlorosis	İşkil et al., 2022	-	>0.02	Hussain et al., 2022
Mn	An important role in the photosynthetic electron transport chain; enzyme activator	Enzyme inhibition; decline in plant growth; nutrient deficiencies; brown spots/necrosis on older leaves; interveinal chlorosis on younger leaves; oxidative stress	Alejandro et al., 2020; Khoshru et al., 2023	-	>500	Wang et al., 2023
Ni	Important for Fe absorption and seed germination	Oxidative stress; disturbances in the plant's metabolism and water regime; Fe deficiency; lipid peroxidation in cell membranes	Kastori et al., 2022; Kumar et al., 2022	-	10-1000	Vischetti et al., 2022
Pb	Unknown	Impaired cell division, seed germination, root elongation, photosynthesis, and nutrient uptake	Gupta et al., 2024	-	30-300	Alasmari et al., 2025
Zn	An essential part of antioxidant enzymes, as well as enzymes that participate in the metabolism of nucleic acids and auxin synthesis	Reduction in seed germination; changes in root system structure; reduced photosynthesis; decrease in seedling height; chlorosis of younger leaves	Balafrej et al., 2020; Li et al., 2022	20-60	>300	Li et al., 2020

Additionally, a certain amount of HM in the growth medium can be extremely stressful for some plants, while others may not even experience stress under the same conditions, complicating the understanding of how plant cells perceive and transmit HM stress signals (Mukherjee et al., 2016).

There is no doubt, however, that the rhizodermal cell walls, composed of pectin, cellulose, hemicellulose, and lignin, serve as the first point for recognizing HMs. Owing to their negatively charged sites ($-\text{COOH}$, $-\text{OH}$, and $-\text{SH}$), the cell wall components have the ability to interact with HMs, which results in changes in cell wall composition. Several studies have demonstrated that these changes trigger the influx of Ca^{2+} or activate ROS, microRNA, or other specific signaling molecules to initiate the appropriate signaling pathways, resulting in the cell's adaptive response to HM-induced stress (Ejaz et al., 2023; Yuan et al., 2024). Peters et al. (2024) have reported that the transport of high amounts of HMs into the cell through cell membranes can also initiate the influx of Ca^{2+} or the activation of ROS, which subsequently activate signaling pathways such as Ca^{2+} signaling pathways, MAPK (Mitogen-Activated Protein Kinase) signaling pathways, microRNA-regulated signaling pathways, and hormone signaling pathways.

Ca^{2+} signaling pathways

The Ca^{2+} signaling pathways consist of three phases: (1) stimulus-specific signaling that promotes the influx of Ca^{2+} into the cytosol, (2) the activation of diverse Ca^{2+} -dependent proteins that activate various signaling pathways to transmit HM stress signals to specific targets, and (3) the restoration of cytosolic Ca^{2+} to its baseline level through Ca^{2+} efflux (Wdowiak et al., 2024).

More specifically, the initial plant cell response to HM stress includes a change in cytosolic Ca^{2+} concentration. This change is recognized, amplified, and transmitted downstream by Ca^{2+} -dependent proteins, including calmodulin/calmodulin-like protein (CaM/CML) and calcium-dependent protein kinases (CDPKs/CPKs). All of them act as secondary messengers, activating various

signaling pathways to transmit HM stress signals to transcription factors that regulate the activity of many genes responsive to HM stress. These genes encode HM stress response proteins, including HM transporters, HM-binding ligands such as phytochelatins and metallothioneins, along with chaperone proteins (Marques et al., 2025).

HM transporters are integral membrane proteins that play a crucial role in preventing or responding to HM toxicity. They achieve these roles by enabling the HM sequestration in vacuoles or by facilitating their efflux (Skuza et al., 2022). The major players among HM transporters include ATP-binding cassette (ABC) transporters, zinc-iron permeases (ZIP) proteins, and organelle transporters (Rekha et al., 2021). Phytochelatins (PCs) and metallothioneins (MTs) are different classes of cysteine-rich, HM-binding protein molecules that act as ligands to facilitate the process of HM sequestration and chelation of HMs. By chelating HMs, they reduce the chances of these ions binding to the functional groups of enzymes or other biomolecules. Chaperone proteins assist in maintaining the structure and, consequently, the functionality of proteins that are essential for the transport and distribution of HMs (Jain et al., 2018).

Mitogen-Activated Protein Kinase Signaling Pathways

The Mitogen-Activated Protein Kinase (MAPK) signaling pathways are highly conserved among plant species and consist of a family of serine/threonine protein kinases that convert extracellular stimuli, including excess HM ions, into a wide range of cellular responses. Each MAPK pathway consists of three protein kinases that are activated in series: a MAP Kinase Kinase Kinase (MAPKKK), a MAP Kinase Kinase (MAPKK), and a Mitogen-Activated Protein Kinase (MAPK). Specifically, the MAPKKKs phosphorylate and activate the MAPKKs, which, in turn, activate the MAPKs. These MAPKs are ultimately transported to the nucleus, where they are involved in the cell's response to HM stress via transcriptional programming (Opdenakker et al., 2012). The transcription factors (TFs) that possess numerous phosphorylation sites, such as basic leucine zipper (bZIP) TFs and heat shock TFs,

are pivotal in this programming (Niekerk et al., 2024). It is important to note that MAP kinases not only activate TFs but also various other cellular components, including different regulatory proteins located in the cytoplasm (kinases, phosphatases, and phospholipases), all aimed at achieving the optimal cellular response to HM stress (Bouzroud et al., 2025).

MicroRNA-regulated signaling pathway

Recent studies in the field of HM stress perception and transduction have demonstrated that HM-regulated microRNA molecules (miRNAs) can also initiate signaling pathways under HM stress conditions (Gielen et al., 2012; Yang et al., 2022). miRNAs are a large group of small noncoding (18-24 nucleotide) RNA molecules that regulate gene expression at the post-transcriptional level. They are generated through the transcription of DNA sequences into primary miRNAs, which are subsequently processed into precursor miRNAs, and ultimately into mature miRNAs (Jia et al., 2025). Mature microRNAs regulate gene expression through two primary mechanisms: translational repression or mRNA degradation. In most instances, miRNAs interact with the 3' UTR (three-prime untranslated region) of target mRNAs to suppress expression. However, recent studies have shown that the interaction of miRNAs with other RNA regions, including gene promoters, can activate gene expression under certain circumstances (O'Brien et al., 2018).

Owing to miRNAs, plants are able to maintain ion homeostasis in their cells, which is of utmost importance for adapting to HM stress conditions (Wu et al., 2021). Several studies have demonstrated that the expression levels of certain miRNAs (miR-164, miR-172, miR-398, and miR-399) significantly increase in response to high concentrations of HMs in the cell's cytosol (Sharma et al., 2015; Ucar et al., 2024). The essential role of miRNAs in maintaining HM homeostasis in cells is based on their ability to regulate the expression of genes required for the synthesis of HM transporters, whose activity facilitates the movement of excess HMs from the cytosol to the vacuole. This approach allows plant cells to minimize the possibility of HMs in the cytosol interfering with

the cell's metabolic processes. In addition to regulating the expression of genes responsible for the production of HM transporters, certain miRNAs also play a role in the regulation of the synthesis of various HM chelators, thereby further enhancing the plant's tolerance to HM stress (Kuang et al., 2025).

Phytohormone signaling in the response to heavy metal stress

Numerous studies indicate that the activity of auxins (AUXs), brassinosteroids (BRs), cytokinins (CKs), gibberellins (GAs), ethylene (ET), and abscisic acid (ABA) undergoes significant changes under HM stress conditions, along with lesser-known phytohormones such as jasmonates (JAs), polyamines (PAs), and salicylic acid (SA) (Bücker-Neto et al., 2017; Nguyen et al., 2021; Biswas and Pal, 2025). In general, when plants are subjected to HM stress, the levels of ABA, ET, PAs, JAs, and SA typically increase in their cells, while the levels of stimulating hormones, such as AUXs and CKs, decrease. The decrease in levels of stimulating hormones due to stress from HMs is expected, as the plant attempts to limit its growth in these scenarios (Piotrowska-Niczyporuk et al., 2020).

ABA is a well-known plant hormone recognized for its crucial function in facilitating the plant's defense mechanisms against HM toxicity. It accomplishes this through the activation of different mechanisms, with the most important being: (1) the closure of stomata, which decreases the transpiration rate, thereby restricting the movement of HMs from the roots to the above-ground parts of the plant, and (2) ABA-responsive gene expression, including those responsible for controlling HM transport within and across plant cells (Hu et al., 2020).

AUXs are plant hormones that stimulate the growth of plant cells, which is undesirable for the plant under HM stress, as a larger root surface area implies a greater potential for the plant to absorb HMs from the soil. Consequently, the plant under HM stress attempts to reduce the flow of AUXs to the root meristem, the area responsible for active growth, and it achieves this through several approaches: (1) by triggering signaling

pathways that inhibit gene expression involved in the synthesis of protein transporters essential for the transport of AUXs from lateral roots to the root apex (AUX1 and PIN2), (2) by activating signaling pathways that result in the expression of genes responsible for the synthesis of enzymes that degrade AUXs, and (3) by activating signaling pathways aimed at producing proteins that inhibit the function of enzymes required for AUX synthesis (Moeen-Ud-Din et al., 2023).

CKs belong to a group of plant hormones that promote cell division. However, this process requires substantial energy resources, which can be detrimental to the plant when experiencing HM stress. Thus, the plant exposed to HM stress predominantly activates signaling pathways that either prevent the synthesis of CKs or promote their degradation (Jorjani and Karakaş, 2024). On the other hand, several studies have shown that some plants can increase the synthesis of CKs in response to HM toxicity (Hajam et al., 2024; Mughal et al., 2024). The explanation lies in the protective function of CKs, which help protect chlorophyll and the photosynthetic apparatus from oxidative stress (Hönig et al., 2018). It is reasonable to assume that the rise in CK levels in plants experiencing HM stress is more significant in hyperaccumulators. These plants adapt to HM stress conditions not by blocking the uptake of HMs but by sequestering them in the vacuoles.

ET contributes to the adaptation of plants to HM stress by participating in the mechanism that prevents the flow of AUXs from the upper part of the plant to the root meristematic cell zones. This role is primarily fulfilled by blocking the protein transporters (AUX1 and PIN2) that are responsible for AUX transport (Thao et al., 2015). Several studies have also demonstrated that ET, when plants are exposed to elevated concentrations of HMs, stimulates the synthesis of glutathione, which is highly important for enhancing the plant's defensive response to stress caused by HMs (Keunen et al., 2016; Fatma et al., 2022). The role of glutathione in bolstering the plant's defense capacities against HM stress is multifaceted: (1) as a key component of glutathione peroxidase, it neutralizes hydrogen peroxide and other ROS, (2)

as a component of dehydroascorbate reductase, it participates in converting dehydroascorbate to ascorbate, facilitating the regeneration of the ascorbate-glutathione cycle and thus continuing the antioxidant function of ascorbate, and (3) it is involved in the synthesis of PCs (Jozefczak et al., 2012).

As reported by Liu et al. (2025), JAs are vital for aiding plants in their adaptation to HM stress by activating signaling pathways that prevent the expression of genes involved in the synthesis of HM transporters, which facilitate the movement of HMs from the roots to the plant's aerial parts. In this context, several studies have confirmed that the exogenous application of JAs reduces the expression of the genes AtIRT1, AtHMA2, and AtHMA4, which are responsible for the functioning of HM transporters (Lei et al., 2020; Wang et al., 2021; Tu et al., 2025). If these transporters do not function properly, it is clear that the transport of HMs within the plant will be greatly reduced. In addition, there are studies that have confirmed the role of JAs in promoting the expression of genes essential for the synthesis of glutathione (Attia and Alamer, 2024; Kılıç et al., 2025), which significantly contributes to the plant's defense mechanisms against HM toxicity and other stress conditions. The majority of scientists focused on this subject support the hypothesis that JAs facilitate the promotion of glutathione synthesis alongside ET, emphasizing that the roles of both hormones are crucial for directing plant cell metabolism towards higher glutathione synthesis (Han et al., 2013; Nazir et al., 2023).

Under HM stress conditions, the concentration of SA in plant cells also experiences a significant rise (Sharma et al., 2020b). Desci et al. (2025) have reported the positive role of SA in alleviating the adverse effects of HMs on plants. This role is typically manifested as SA serves as a signaling molecule, activating signaling pathways that lead to the synthesis of antioxidant components, the production of PCs, and the formation of structural components of the cell wall that bind HM ions, effectively blocking their entry into the cell's cytosol (Bano et al., 2023).

DEFENSE MECHANISMS IN PLANTS AGAINST HEAVY METAL STRESS

In response to HM stress, plants attempt to adapt through very complex mechanisms that can be categorized into two main strategies: avoidance strategy and tolerance strategy. The avoidance strategy is the first line of plants' defense against HM toxicity, referring to their ability to prevent or at least reduce the entry of HM ions into the root system. In contrast, the tolerance strategy encompasses all mechanisms that a plant activates when HMs have already been absorbed, aiming to reduce or neutralize their negative effects (Jutsz and Gnida, 2015).

Heavy metal avoidance mechanisms in plants

Mechanisms of HM avoidance include: (1) immobilization of HMs through root exudates, (2) immobilization of HMs via mycorrhizal associations, and (3) sequestration of HMs into the primary and secondary walls of the root cells (Zhao et al., 2024). It is important to note that all the mentioned mechanisms are interrelated and significantly influence one another, making it quite challenging to observe them separately. For instance, a specific root exudate can directly influence the immobilization of HM ions in the soil, but it can also contribute to the development of a specific rhizosphere microbiome that, in turn, immobilizes the same or other HM ions.

Root exudates represent a complex mixture of organic substances that plant roots release into the rhizosphere. While their composition may differ, they are typically defined by a significant presence of organic acids, amino acids, and phenolic and isoprenoid compounds (Zambelli et al., 2025). The influence of root exudates on the mobility of HMs in the soil typically occurs indirectly, as these exudates alter the chemical properties of the soil, including pH value and base saturation. As a result of these changes, available forms of HMs can easily transfer into unavailable forms, and vice versa, depending on whether the changes enhance the mobility of HMs in the soil. Additionally, certain exudates have the ability to form complexes with HMs, thereby reducing the likelihood of their transfer from the soil to the plant roots (Sun et al., 2025).

Root exudates significantly affect the composition and activity of the rhizosphere microbiome. They serve as significant energy resources for microorganisms, which in turn provide numerous benefits to plants, including the conversion of toxic forms of HMs into less toxic ones and the immobilization of HMs through biosorption or biofilm formation. Interactions between plant roots and the soil microbial community not only determine the mobility and subsequent bioavailability of HMs to the plant, but they also greatly affect the plant's ability to thrive in a habitat. Those plants that achieve more favorable interactions with the soil microorganisms are more likely to survive in that particular environment (Barra Caracciolo and Terenzi, 2021). However, the occurrence of such interactions is not solely within the realm of plants and microorganisms but is also significantly influenced by the physical and chemical characteristics of the soil, which greatly determine the nature of interactions between plants and microorganisms. In addition, the interactions between plants and soil microorganisms are significantly influenced by environmental factors (Bao et al., 2025). For instance, any disturbances in the environment, such as high light intensity or extreme cold or heat, can drastically alter the interaction between plant roots and microorganisms, consequently affecting the plant's ability to prevent or at least reduce the entry of HMs into its root system (Gladkov et al., 2023).

Besides immobilizing HMs via root exudates and mycorrhizal associations, some plants try to avoid the adverse effects of HMs by binding them to the cell walls of the root cells, preventing their entry into the interior of the root cells and, consequently, their transport from the underground part to the above-ground part of the plant. Plants with this ability simultaneously hinder the leaching of HM ions from surface soil layers into underground water streams, significantly reducing the negative impact of HMs on the environment (Cheng et al., 2025b).

The chemical composition of the roots' cell walls is the primary factor that determines the ability to incorporate heavy metals into their structure. Key chemical components of the cell walls of root cells are polysaccharides, specifically cellulose, hemicellulose, and pectin.

Pectin, particularly low-esterified pectin with less than 50% esterified carboxyl groups of galacturonic acid, is the most captivating part of the cell wall. This implies that it contains many free carboxyl groups that can bind and retain HM ions (Parrotta et al., 2015). In addition to polysaccharides, cell walls may also contain other carbohydrate components such as uronic acids, which also possess the ability to bind HMs (González-Avilez et al., 2024). Lignins, which can form complexes with HMs, may also be integral to cell walls. Several studies have demonstrated that under HM stress conditions, some plants significantly increase lignin production and integrate it into the root cell walls, to bind HM ions and thereby inhibiting their movement to the aerial parts of the plant (Lao et al., 2023; Khan et al., 2024; Zhao et al., 2025).

Heavy metal tolerance mechanisms in plants

The main mechanisms through which plants exhibit tolerance to HMs are: (1) HM detoxification via chelation within the cell's cytosol, (2) HM sequestration in the vacuoles, (3) involvement of chaperones in HM tolerance, and (4) overproduction of HM efflux pumps (Mohamed et al., 2025).

All the mentioned mechanisms are not independent of one another; in fact, the activation of one mechanism often serves as a precursor to the initiation of another. For example, HM chelation by phytochelatins (PCs) and metallothioneins (MTs) serves as a precursor to the sequestration of these HMs in the cell's vacuole. However, for the synthesis of PCs and MTs to occur, the plant cell must first stimulate the expression of certain genes that are crucial for their synthesis. A similar example of the connection between the HM tolerance mechanisms can also be observed in the formation of chaperone proteins or proteins that block the HM transporters on the cell membrane, as all these proteins require the expression of the corresponding genes.

Heavy metal detoxification via chelation and compartmentalization

Toxic heavy metals such as Cd, Hg, Cr, and Pb interfere with cellular homeostasis, prompting the plant cell to quickly neutralize the excess HM ions present. Chelation, or the binding of HMs to chelating agents, known as chelators, is the most prevalent mechanism for neutralizing HMs within cells. PCs represent the key group of chelating agents found in plant cells. They are produced from glutathione via the enzyme PC synthase, highlighting the importance of glutathione for the synthesis of PCs and the efficient detoxification of HMs in plant cells (Agarwal et al., 2025). Another important group of chelators in plant cells is MTs, which are defined by their low molecular weight and richness in cysteine. In the model plant *Arabidopsis thaliana* (L.) Heynh., six different MTs (MT1a, MT2a, MT2b, MT3, MT4a, and MT4b) have been identified, with the differences among them largely pertaining to the type of cysteine residue in their structures (Guo et al., 2008). The majority of these MTs have been found to be very effective in neutralizing Cd and Cu (MT1a, MT2a, MT2b, MT3) (Zimeri et al., 2005; Hu et al., 2025), and some have also shown effectiveness in neutralizing Zn (MT4) (Hegelund et al., 2012; Imam and Blindauer, 2018).

In addition to PCs and MTs, various organic acids and amino acids can also serve as chelators in plant cells. Among organic acids, oxalic, citric, and malic acids are particularly effective as chelating agents, while proline and histidine are notable among amino acids (Vega et al., 2022). Nicotinamide, also known as niacinamide, is another organic compound that has been shown to possess chelating properties. The activity of this compound is particularly pronounced under stress conditions caused by elevated concentrations of Fe, Cu, and Zn ions (Smolik and Sędzik-Wójcikowska, 2024). A simple diagram illustrating the mechanism by which a plant cell promotes HM chelation and vacuolar compartmentalization is shown in Figure 1.

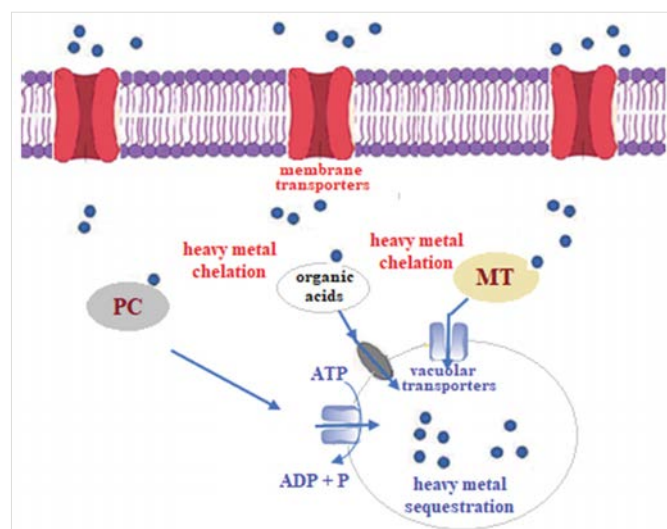


Figure 1. Vacuolar sequestration of heavy metals in plant cells

Involvement of chaperones in plant tolerance against heavy metal toxicity

Elevated levels of HMs within the cell's cytosol are likely to interact with different proteins, leading to damage in both their structure and function. As a direct result, these proteins become inactive, and indirectly, there is a disturbance in all physiological processes that involve these proteins. To prevent or at least reduce this series of events, a plant cell subjected to HM stress triggers a mechanism for producing chaperones (Hasan et al., 2017). Chaperones are a group of proteins that play a crucial role in helping plants adapt to stressful conditions. The role of chaperones in plant cells under HM stress conditions is multifaceted: (1) they prevent the aggregation of newly synthesized proteins or those denatured due to stress, (2) they prevent incorrect folding of newly synthesized proteins, (3) they promote and ensure the accurate assembly of protein complexes, and (4) they assist in the repair of stress-damaged proteins or in the degradation of denatured proteins (Figaj, 2025). In accordance with the mechanism that enables them to fulfil their roles, chaperones are classified into three categories: foldases, holdases, and unfoldases. Foldases are ATP-dependent chaperones that assist in the proper folding of proteins, whereas holdases prevent misfolding and aggregation via intermolecular interactions, functioning without external energy input. Unfoldases use

energy from ATP hydrolysis to facilitate conformational changes that mechanically denature protein substrates, subsequently translocating the polypeptide via the entrance pore into a degradation chamber (Macošek et al., 2021).

Overproduction of heavy metal efflux pumps

HM efflux pumps regulate HM homeostasis at both cellular and whole-plant levels. They are protein transporters located in the plasma membrane and tonoplast that transfer toxic HM ions out of cells or from the cytosol to vacuoles (El-Sappah et al., 2024).

Plants have different types of membrane transporter proteins that help in maintaining HM homeostasis, including ATP-binding cassette (ABC) transporters, cation diffusion facilitator (CDF) transporters, Zrt/Irt-like protein (ZIP) metal transporters, and natural resistance-associated macrophage proteins (NRAMPs) metal transporters (Dahuja et al., 2021; Bui and Inaba, 2024).

ABC transporters play a vital role in enabling plants to tolerate HMs by actively transporting toxic HM ions and their complexes into vacuoles, which in turn decreases their cytosolic concentrations and toxicity. In the model plant *Arabidopsis thaliana* (L.) Heynh., two distinct vacuolar ABC transporters (AtABCC1 and AtABCC2) crucial for sequestering Cd- and Hg-phytochelatin complexes into vacuoles have been identified (Park et al., 2012). Another study indicated that *Glycyrrhiza glabra* L., a plant capable of enduring extreme stress conditions, contains 181 different ABC transporters (Devi et al., 2024).

CDF transporters also play an important role in the detoxification of HMs, efficiently transporting HMs from the cytosol to either the extracellular space or intracellular compartments by utilizing the proton-motive force or other cation gradients. They transfer various HMs but primarily show a preference for Zn, Fe, and Mn (Gustin et al., 2011). One of the most important CDF transporters in the model plant *Arabidopsis thaliana* (L.) Heynh. is AtMTP1, which contributes to tolerance to Zn through vacuolar Zn sequestration (Kobae et al., 2004).

ZIP transporters, commonly referred to as 'ZRT, IRT-like proteins,' play an essential role in maintaining homeostasis of Zn and Fe in plant cells (Shuting et al., 2022). The iron regulated transporter gene, known as the IRT1 gene, is the first identified member of the ZIP family in plants and is expressed in response to Fe deficiency (Soviguidi et al., 2025). Alongside Fe and Zn, ZIP transporters possess the capability to transport a range of divalent cations, including Mn, Ni, Co, and Cd (Ajeesh Krishna et al., 2020). Several studies have indicated that ZIP transporters are significantly more abundant in HM-hyperaccumulating plants than in non-hyperaccumulators (Milner and Kochian, 2008; Bhat et al., 2025). This overexpression actively contributes to the increased uptake and translocation of HMs, primarily Zn and Fe, into vacuoles, enabling these plants to adapt to HM-rich soils.

The NRAMP family of HM transporters is well-known for its capability to transfer a diverse array of HMs, including both toxic and essential ones. Tian et al. (2021) reported that NRAMP transporters promote the uptake and translocation of several HMs, including Cd, Zn, and Fe in potato plants, and that overexpression of NRAMPs leads to an increase in plant tolerance to toxic HMs. Among NRAMP transporters, AtNRAMP1 has been characterized as a transporter that enables the uptake of Fe, Mn, and Cd, while AtNRAMP2 directs the subcellular partitioning of Mn via vesicular trafficking pathways. AtNRAMP3 and AtNRAMP4 are responsible for Mn remobilization from vacuoles through tonoplast efflux transport. AtNRAMP5 is involved in the transfer of Cd and Fe from the rhizosphere to rhizodermal cells, while AtNRAMP6 regulates the symplastic transport of Cd through endomembrane-mediated subcellular compartmentalization (Li et al., 2025b).

CONCLUSIONS

This review summarizes the main findings on signaling pathways and the response of plants exposed to HM stress. Plants have evolved a complex network of defense mechanisms to avoid or tolerate the toxic effects of HMs. Among avoidance mechanisms, immobilizing

HMs via root exudates or mycorrhizal associations is particularly effective in alleviating heavy metal toxicity. The key HM tolerance mechanisms in plants include HM efflux from the cell, as well as their compartmentalization within the vacuole. Notable advancements in molecular biology have shed light on the specific strategies that plants utilize at the cellular and molecular levels to combat HM stress. In this context, the PCs and MTs are becoming particularly interesting in relation to HM detoxification. Their role appears to extend beyond simply being HM-chelating peptides. Therefore, the application of transgenic plants that overproduce PCs or MTs represents a hopeful advancement for phytoremediation purposes or for improving plants that do not produce adequate levels of PCs or MTs. Furthermore, the exogenous application of plant hormones and chelating agents that can enhance plant tolerance to HM stress, such as SA, proline, and histidine, shows great potential ahead. Generally, a thorough understanding of all defense mechanisms and the signaling pathways that are involved in how plants respond to HM stress is vital for creating strategies to improve crop resilience in HM-polluted environments.

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