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Glutathione: A key frontier of heavy-metal detoxification and tolerance in plants

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ABSTRACT

Heavy metal (HMs) toxicity is one of the major critical threats to agricultural plant production and global food security. In this current scenario, eco-friendly and hazardous-free sustainable crop production strategies for detoxifying and tolerating HMs are imperative. This updated study provides the impact of HMs on agricultural plants' growth, physiology, and yield. Further, this study explores the significance of glutathione (GSH) and phytochelatins (PCs) and a series of candidate genes that showed potential role in HMs stress tolerance in diverse plant species. This updated study encourages plant breeders or farmers to develop HMs stress-tolerant plant production through a breeding program. The overall study findings open new avenues of multiomics-assisted plant improvement, and it will help phytoremediation, a clean environment, and smart agriculture for sustainable plant production.

INTRODUCTION

The contamination of agricultural soils with heavy metals (HMs) is one of the serious limitations for plant life, food safety, and human health in the world [1]. The rapid industrialization and urbanization processes are gradually increasing the load of metal and metalloids such as Cd, Pb, Cr, As, Hg, Ni, Cu, Zn, and Co to agricultural soils [2]. In addition, the application of phosphate fertilizers, excess industrial chemical waste, and sewage sludge are actively involved in increasing HMs-toxicity to plants, soils, and environments [3, 4]. HMs toxicity severely inhibit plant growth and alters a series of physiological and molecular changes in different plant species [5-8]. These limitations in plants ultimately lead to a decline in plant biomass yield and productivity. Therefore, updated understating with eco-friendly and cost-effective strategies are highly demandable for sustainable plant production, agricultural soil health, and ensuring toxicant-free global food security.

HMs induce excess reactive oxygen (ROS) species that lead to oxidative stress-induced cellular toxicity, and lipid peroxidation in plant cells [7]. The excess production of ROS and subsequent induction of oxidative stress are sequential consequences in plants. Plants have evolved several mechanisms to combat these toxic pollutants through antioxidant defense systems [9, 10]. In this defense system, plant induces several enzymatic and non-enzymatic antioxidants, which play key roles in detoxifying and/or mitigating tolerance in HMs in plants [6, 10]. Plants produce also low molecular weight thiols, which possess a high affinity to HMs [10]. One of the key frontiers of thiols is glutathione (GSH) [2]. The synthesis of GSH occurs by the consecutive involvement of

enzymes γ-glutamylcysteine synthetase and glutathione synthetase [2]. The GSH (gamma-glu-cys-gly) presents with a high level in living cells and is a major source of non-protein-reduced sulfur (S). The GSH accelerates bio-reductive reactions that lead to enhanced defense against HMs or any other foreign toxic chemicals [11]. The regulation of the S assimilation process is crucial for the adequate supply of S-compounds important for HMs-detoxification and tolerance in plants [10]. S presence in several components including amino acids cysteine, methionine, oligopeptides (GSH, phytochelatins), vitamins, and secondary products [12]. The thiols cysteine and GSH are involved in the redox process through a disulfide conversion system that leads to the homeostasis of oxidative stress in plants [13]. The particular GSH plays a key role in detoxifying HMs through coordination with the −SH group that is mediated by GSH-S-transferase. In addition, the phytochelatins (PCs) are a polymerized version of GSH involved in HMs detoxification by functioning as chelating ligands [6].

This current review explores the toxic impact of HMs in plants and highlights the recent progress of GSH potential in HMs detoxification and tolerance in diverse plant species. This study further suggests the involvement of various candidate genes in HMs tolerance processes and their prospects in developing HMs-tolerant genotypes through breeding programs.

GLUTATHIONE BIOSYNTHESIS IN PLANTS

The chloroplast, mitochondria, plastid, and cytosol are the key locations for GSH synthesis [14]. GSH is synthesized through two consecutive enzymatic reactions whereas ATP is dependent. In the first step, enzyme γ-ECS catalyzes a bond between γ-COOH of Glu and the α-NH_2 group of Cys (Figure 1). In the second step, the GS leads the reaction to bond formation cysteinyl-COOH of γ-GC and α-NH_2 group of Gly, subsequently, the GSH is synthesized from γ-GGC (Figure 1). Hence, the number of ATP is reduced in every reaction, synthesis of γ-GC can act as a rate-limiting factor for GSH synthesis, and the γ-ECS activity depends on Cys-availability. Interestingly, the addition of glutathione S-transferase (GST) to GSH leads to the conjugation process of toxic metals/xenobiotics and transports those metals into the vacuole (Figure 1).

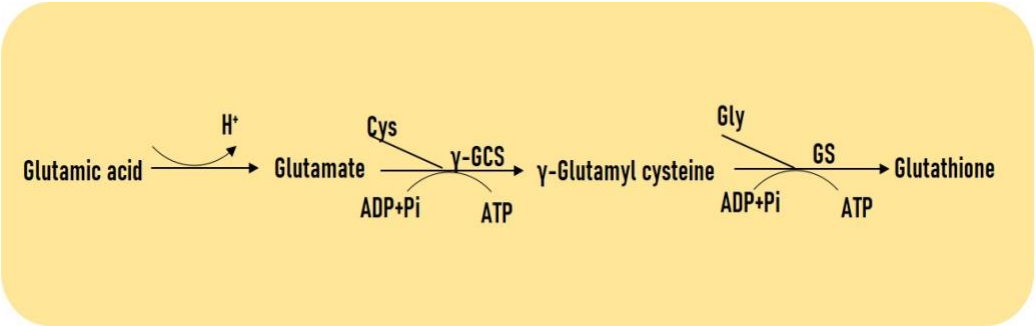

Figure 1. Biosynthesis of glutathione in plants. Abbreviation, H+, proton; Cys, cysteine; γ -GCS, γ-glutamylcysteine synthetase; ADP, adenosine diphosphate, ATP, Adenosine triphosphate; Pi, inorganic phosphate; Gly, glycine; GS, glutathione synthetase.

IMPACT OF HEAVY METAL TOXICITY IN PLANTS

Several metals/metalloids such as Cd, Pb, Cr, As, Hg, Ni, Cu, and Zn cause toxicity in plants [15]. Among them, Cd, Pb, As, Hg, and Cr show highly toxic effects on plant growth, development, and productivity [5, 6, 10, 15]. These toxic elements are involved in regulating a series of morpho-physiological and molecular alterations in several plant

species. In the following sections, we discuss the updated findings on how different HMs negatively impact on different crop plants (Figure 2 and Table 1).

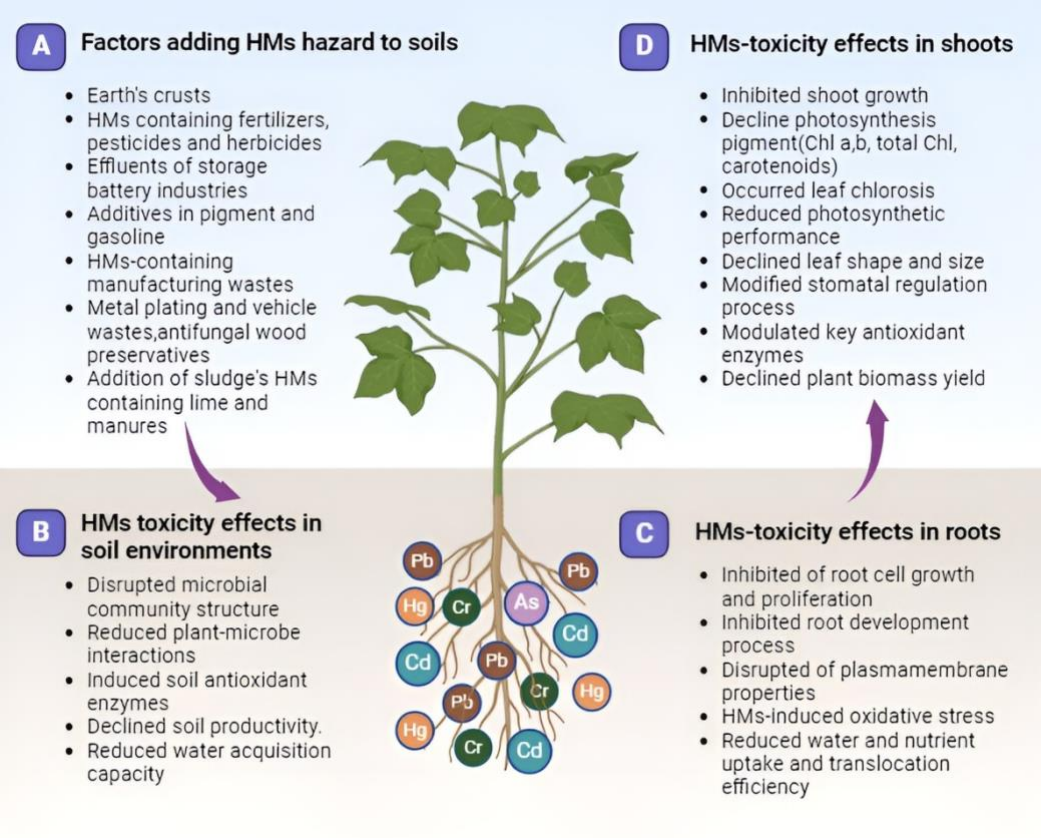

Figure 2. Effects of environmental HMs hazards to soils and plants. Sources of HMs responsible for creating HMs toxicity to soils (A). HMs toxicity effects to soils and microbial environments (B). HMs toxicity effects in root traits (C). HMs toxicity effects in shoot traits (D). Abbreviations, HMs, heavy metals.

Table 1. Effects of HMs-toxicity on plant traits.

Plant species	HMs-treatment with duration	HMs effects on plant traits	Ref.
Sassafras tzumu Hemsl.	5 mg/kg-100 mg/kg Cd; 5 times in a year; 15d interval	Inhibited sassafras growth, declined biomass yield, SOD activity, increase POD	[39]
Capsicum annuum L.	5 mg Cd/kg; 7d	Decreased growth characteristics, soluble sugars, proteins, and amino acids; increased POD, SOD, and CAT activity	[16]
Beta vulgaris subsp. vulgaris	10 μM $CdSO_4$; 14 d	Impaired morphological traits; Occurred cellular damages	[9]
Oryza sativa cv. Meixiangzhan-2; Xiangyaxiangzhan	400, 800, and 1,200 ppm $Pb(NO_3)_2$; growth period (145-150 d)	Reduced chlorophyll, carotenoid; reduced yield and yield component	[21]
Triticum aestivum L. cv. Punjab-81, AARI-11; Kohistan-97, As-2002, Barani-70, and Pari-73	Plant sample collected: 5-45 μg/kg As present in grains	Influenced chlorophyll, grain yield, biological yield, and straw yield differentially in sensitive and tolerant cultivars	[40]
Medicago sativa L.	40 μM Hg; 14 d	Declined morphological and photosynthetic, and yield traits	[10]
Brassica napus L.	5-20 mg/L Hg; 10d	Inhibited the growth, biomass yield, and nutrient accumulation	[41]
Triticum aestivum L.	2.5-25 μM Hg;	Inhibited root and shoot growth, content of chlorophyll and total soluble protein	[42]
Oryza sativa L. cv. normal and hybrid	100 μM $K_2Cr_2O_7$; 14 d	Influence germination energy (%),percentage (%),index (%), time (%), and vigor index	[35]
Miscanthus sinensis Andersson. cv. Kosung	50-1000 μM $K_2Cr_2O_7$; 3d	Inhibited root growth and plant biomass yield, altered oxidative stress indicator and protein content	[43]

Abbreviation; SOD, superoxide dismutase; CAT, catalase; POD, peroxidase

Cadmium toxicity

Cadmium (Cd) is one of the most toxic hazards exposed in industrial workplaces, and agricultural plants and soils due to frequent use of Cd-containing fertilizers, pesticides, and herbicides (Figure 2) [16]. The threshold level of Cd toxicity for plants ranges from 3–30 mg kg−1 Cd concentration in plant tissue exceeds [17]. The Cd toxicity causes chlorosis, growth and photosynthetic inhibition, and biomass yield reduction in alfalfa [6]. Haque et al found Cd-toxicity triggers plant growth retardation, chlorosis, low photosynthesis performance, and low Fe, S, and Zn concentrations in sugar beets, which were related to decline FCR activity and *BvIRT1* gene expression, suggesting the negative effect of Cd-toxicity on Fe acquisition process in sugar beet [7]. In this same study, the candidate genes *BvHMA3* and *BvNRAMP3* showed upregulation patterns in response to Cd-toxicity, suggesting that these candidate genes are involved in Cd uptake processes. Mittra et al explored Cd-induced alterations physiological and proteomic alterations in Brassica, where Cd-severely declined plant growth, occurred leaf chlorosis and induced a series of candidate proteins involved in antioxidant defense system and sulfur assimilation-involving Cd-detoxification processes in *Brassica* [5]. Cd-toxicity not only changes the morpho-physiological and molecular attributes but also these impairments lead to a decline in biomass yield and productivity in plants (Table 1). For instance, Kabir et al stated that Cd (10 μM $CdSO_4$) significantly declines elemental concentration, photosynthetic performance, and biomass yield in sugar beet [9]. Cd-toxicity (1 mg L^{-1}) severely impairs mineral acquisition and yield traits in wheat at the seedling stage, exploring the toxic consequence of Cd at different developmental stages in plants [18]. Recently, Sana et al found genotypic differences in Chili plants in response to several doses of treatment Cd (3-5 mg Cd kg^{-1}) in soils, where Cd-caused growth retardation, reduced sugars, proteins, and amino acids concentrations, along with biomass yield reduction [16]. The above investigations suggest that Cd-toxicity can vary based on Cd-doses and/or Cd load to the exposed plants, wherein a very low concentration of Cd can be toxic and detrimentally influence plant developmental processes and productivity.

Lead toxicity

Lead (Pb) toxicity is considered as the second most hazardous element after As, which comprises 0.002% of Earth's crust and it does not show any potential benefit in biological systems [19]. The additives in pigment and gasoline, effluents of storage battery industries, melting and manufacturing factories, activities related to metal plating, and vehicle wastes are the potential sources for adding Pb to soils and environments (Figure 2) [19]. Pb toxicity causes cellular injury and damage in plants from growing to mature stages. A series of morphological, physiological, biochemical, and molecular alterations occur in plants under Pb toxicity [20]. Pb-toxicity considerably changes the photosynthetic apparatus and declines chlorophyll pigment content leading to a decline in carbon metabolism efficiency in plants [19]. The crop yield component and productivity significantly declined due to Pb toxicity in different rice genotypes [21], where yield reduction was 46.27% to 69.12%. Weekly 25 μg kg^{-1} Pb exposure with human body weight is considered the threshold level [22]. Pb has no beneficial significance in plants, soils, and environments. Recently, Pb toxicity severely exposed to environments from the effluents of storage batteries. The translocation of toxic Pb from the environment to crop grains [19], indicates that Pb toxicity rapidly spreads from the environment to food chains. Pb toxicity is not only harmful to plants and soils but also significantly impairs soil microbial community structures [23].

Arsenic toxicity

Arsenic (As) is naturally producing metalloids that are nonessential for the plant developmental process. As is toxic for plants, humans, and the environment. Soil and water are the major sources of As hazard. As is a naturally occurring poison universally present in the Earth's crust, and is used in antifungal wood preservation processes, as an element of industrial manufacture, pesticides, and fireworks materials (Figure 2) [24]. The root is the first sensing organ that is initially affected by As exposure [25]. As uptake and transportation several plant organs significantly inhibit plant growth, development, and total biomass yield [26]. As toxicity alters the plant metabolism process it leads to inhibition of cell proliferation and even plant death [27]. The process of symbiosis is crucial for biological 'N_2' fixation and is an alternative source of 'N_2' source in plants. Unfortunately, toxicity negatively affects rhizobium bacteria, root nodule formation, and the ultimate naturally plant-microbe-based N supply system [25]. Recently, it has been reported that As toxicity declines grain yields up to 39% in rice.

Mercury toxicity

Mercury (Hg) is a toxic element. Hg hazard added to the environment through volcanic eruption, fuels or raw materials of batteries, electric materials, sludges, fertilizers, lime, and manures (Figure 2) [28, 29]. Hg exposure levels even at low concentrations (1.0 and 1.5 mg/L) can be toxic for plants that lead to disruption of cellular function, plant growth, and development [30]. Though the specific role of Hg in plant biological functions is still unclear [31], but it can cause trouble in plant physiological processes. El-Shehawi *et al* found that Hg causes sulfur (S) and iron (Fe) deficiency which induces oxidative stress in alfalfa [4]. The Hg toxicity (1.0 and 2.5 mg L^{-1}) declined root biomass yield by 50%, while shoot biomass declined by 50% at 0.5 mg L^{-1} Hg level [32].

Chromium toxicity

Chromium (Cr) is a non-essential toxic metal. Cr is added to the environment from the waste of leather factories, electroplating, paints, and dye industries, municipal trash, and uses of Cr-containing fertilizer [33]. Plants uptake Cr from soil contaminants that lead to a series of physiological and molecular alterations in plants [34]. Basit *et al.* [35] reported that excess accumulation of Cr significantly declines seed germination rate and plant growth which leads to plant biomass yield. Some other consecutive studies suggest that Cr toxicity considerately reduces photosynthetic pigments (Chl a, b, and total chl) content, which significantly reduces plant photosynthesis efficiency [33]. Excess accumulation of Cr negatively influences the activity of the cell cycle and causes an imbalance of elemental concentration, enzyme activity, and other metabolic processes, which leads to the induced generation of reactive oxygen species and oxidative stress in several plant species [36]. Recently, Saud et al [37], found that Cr toxicity declines seed germination rate, photosynthesis, plant growth, and yield. The shoot (38%) and root (37%) length of green gram declined in Cr toxicity treated Vigna radiate compared to control plants [38].

GLUTATHIONE-INVOLVING HEAVY METAL DETOXIFICATION AND TOLERANCE IN PLANTS

Glutathione (GSH) is an excellent source of thiol in cells that are located in several cellular organelles such as vacuole (VC), mitochondria (Mt), chloroplast (ChP), and endoplasmic reticulum (EPR). The thiol group of GSH forms a bond with HMs. GSH is involved in the

HMs detoxification process by mitigating the H_2O_2 level in the cells. During the HMs-induced ROS scavenging system the GSH is changed to its oxidized form (GSSG) which is one of the key processes of the redox signaling process (Figure 3). GSH plays as role of antioxidant and is involved in ROS homeostasis and detoxification processes foreign toxic metals (xenobiotics including major HMs) that lead to enhanced HMs tolerance in plant cells (Figure 3 and Table 2). The toxic metal and xenobiotic conjugate with GSH by the activity of glutathione S-transferase (GST), and subsequently transport metals to VC. Another process is chelation, where GSH plays a role as a precursor of phytochelatins (PCs) synthesis. In another process enzyme PCS coordinates the binding process of thiol group and PCs.

GSH supplementation enhances HM's stress tolerance through the regulation of antioxidant systems [44]. Several studies have indicated that exogenous supplementation of GSH enhances antioxidant enzyme activity that helps to enhance HMs toxicity tolerance in plants. Daud *et al*. [45], found GSH supplementation (50 μM) declines leaf Cd content and increases SOD, APX, POD, and GR activity in Mexican cotton. Khan *et al.* [46], reported that exogenous application of GSH (50 μM) mitigates Pb-induced physiological and metabolic impairments by reducing oxidative stress markers (MDA and H_2O_2) levels and increasing SOD, CAT, POD, APX, and GR activity in *Gossypium hirsutum*.

The potential of GSH-derived PCS and its biosynthesis-related genes have a pivotal role in HM stress tolerance in a series of plant species. The PCs are synthesized by the phytochelatins synthase (PCS) gene that responds under HMs stress. Overexpression of *BnPCS1* lines showed better growth and biomass yield, along with exhibiting higher Cd accumulation and translocation compared to WT, which led to Cd stress tolerance [47]. The *PCS* genes are well distributed in diverse plant species and *AtPCS1*, *OsPCS1*, *TaPCS1*, and *BjPCS1* are well characterized in *Arabidopsis*, rice, and wheat [2]. These genes are involved in diverse metal toxicity tolerance *(*Table 2*)*. Exogenous supplementation of sulfur was reported to enhance GSH concentration along with their corresponding genes *MsGS* and *MsPCS1* in roots, which leads to Cd toxicity tolerance in alfalfa plants [6]. Recently, Rahman *et al*. [10], found that GSH triggers the PC accumulation, and Hg responsive upregulation of the *MsPCS1* gene helps to enhance Cd tolerance in alfalfa. With the above advancement of GSH-related research in HMs toxicity stress it is clear that GSH is potentially involved in HMs detoxification and tolerance processes, which lead to enhanced endogenous GSH and PC biosynthesis and plant fitness under diverse HMs stress.

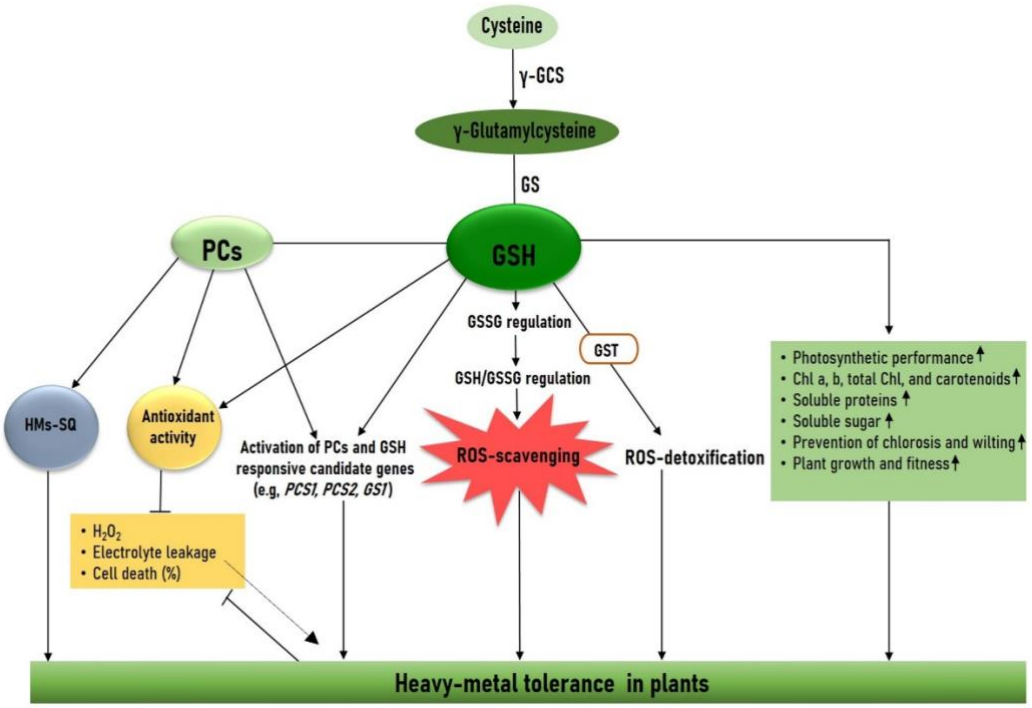

Figure 3. Glutathione involving HMs tolerance in plants. Abbreviation, γ -GCS, γ -glutamylcysteine synthetase; GS, glutathione synthetase; GSH, glutathione, PCs, phytochelatins, GSSG, glutathione disulfide; GST, glutathione S-transferase; HMs, heavy metals; SQ, sequestration, PCS, phytochelatins synthase; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide; Chl, chlorophyll.

Table 2. Glutathione and phytochelatins responsive key genes involved in HMs detoxification and tolerance in plants.

Plant species	Key gene	Gene roles under HMs	Ref.
Triticum aestivum L.	*TaGST*	*TaGST* showed growth and tolerance against stress As toxicity	[40]
Beta vulgaris subsp. vulgaris	*BvPCS3, BvHIPP32, BvGST23*	*BvHIPP32* retained the excess Cd in the root cell wall; *BvGST23* stimulated GSH-related antioxidants, and ROS detoxification in Cd-exposed plants	[9]
Hibiscus cannabinus L. cv. Fuhong 992	*HcTrx*	Exogenous GSH eliminated ROS and activated antioxidant defense; *HcTrx* overexpression lines improved chlorophyll levels and enhanced Cr tolerance	[48]
Solanum lycopersicum	*UGT*	GSH triggers the degradation and metabolism of residual fungicides by *UGT* genes	[49]
Medicago sativa L.	*MsGS, MsPCS1*	*MsGS, MsPCS1* enhanced exogenous GSH and PCs accumulation and Cd tolerance	[6]
Brassica juncea L.	*AtPCS1*	*AtPCS1* encoding PCS showed tolerance to Cd and As	[50]
Arabidopsis thaliana L.	*AsPCS1, GSH1*	*AsPCS1* and *GSH1* enhanced total PCs and GSH production, which led to Cd and As tolerance	[51]
Oryza sativa L.	*OsPCS1, OsPCS2*	Between two homologues, *OsPCS2* controlled PCs synthesis that led to As tolerance in rice	[52]
Brassica juncea L.	*GSH2*	Overexpression of GS lines enhanced GSH, PCs, thiol, S, and Ca, which led to Cd tolerance	[53]
Arabidopsis thaliana L..	*VsPCS1*	Overexpression of *VsPCS1* Increased PCs synthesis and Cd tolerance	[54]

Abbreviations: GSH, glutathione; PCs, phytochelatins; UGT, UDP-glycosyltransferase; GS, glutathione synthetase, PCS, phytochelatin synthase

CONCLUSION AND FURTHER PROSPECTS

HMs toxicity is now a global problem for agricultural plants, soils, the environment, and human health. Therefore, eco-friendly, and cost-effective strategies of HMs toxicity mitigation and stress tolerance are highly demandable. This study provides an updated understanding of major heavy metal toxicity impacts on agricultural plants. Further, this study suggests the potential role of GSH and PCs and their corresponding candidate genes which help to mitigate and tolerate distinct heavy metals in plants. A glutathione-

based heavy metal mitigation approach proves effective by harnessing the natural detoxification properties of glutathione. By cultivating crops rich in glutathione or its precursors, such as certain members of the Brassicaceae family, the plants actively absorb heavy metals from the soil. Glutathione, present within the plant cells, binds to the heavy metals, facilitating their sequestration and subsequent transport to vacuoles for storage or root exudation. Additionally, fostering plant-microbe interactions, particularly with mycorrhizal fungi, enhances glutathione production, contributing to an increased capacity for heavy metal detoxification. This update study might be helpful to plant breeders or farmers for enhancing HMs stress tolerance in diverse crop plants under toxic environments. However, with the progress of the study GSH-induced regulation of candidate genes, proteins, and metabolites have not been well established. Therefore, multiomics-assisted agriculture crop improvement would be a promising area of research along will open a new avenue of HMs-tolerant crop production for smart and sustainable plant production for global food security.

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AUTHORS CONTRIBUTION

SKR conceived the research plan and wrote the manuscript. MN and FR supported to figure drawing and edited the manuscript. All the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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