



The fate of secondary metabolites in plants growing on Cd-, As-, and Pb-contaminated soils—a comprehensive review

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Abstract

The study used scattered literature to summarize the effects of excess Cd, As, and Pb from contaminated soils on plant secondary metabolites/bioactive compounds (non-nutrient organic substances). Hence, we provided a systematic overview involving the sources and forms of Cd, As, and Pb in soils, plant uptake, mechanisms governing the interaction of these risk elements during the formation of secondary metabolites, and subsequent effects. The biogeochemical characteristics of soils are directly responsible for the mobility and bioavailability of risk elements, which include pH, redox potential, dissolved organic carbon, clay content, Fe/Mn/Al oxides, and microbial transformations. The radial risk element flow in plant systems is restricted by the apoplastic barrier (e.g., Casparian strip) and chelation (phytochelatins and vacuole sequestration) in roots. However, bioaccumulation is primarily a function of risk element concentration and plant genotype. The translocation of risk elements to the shoot via the xylem and phloem is well-mediated by transporter proteins. Besides the dysfunction of growth, photosynthesis, and respiration, excess Cd, As, and Pb in plants trigger the production of secondary metabolites with antioxidant properties to counteract the toxic effects. Eventually, this affects the quantity and quality of secondary metabolites (including phenolics, flavonoids, and terpenes) and adversely influences their antioxidant, anti-inflammatory, antidiabetic, anticoagulant, and lipid-lowering properties. The mechanisms governing the translocation of Cd, As, and Pb are vital for regulating risk element accumulation in plants and subsequent effects on secondary metabolites.

Keywords Antioxidant · Bioavailability · Biogeochemical property · Mobility · Risk element · Secondary metabolites · Translocation

Introduction

Plants possess unique strategies to remain cellularly and physiologically unaffected during harsh environmental effects, e.g., high/low temperatures and excess risk elements (Cd, As, and Pb). To achieve adaption to fluctuating environmental effects, plants exhibit a series of metabolic mechanisms that generate secondary metabolites (Arnold et al. 2019; Movahedi et al. 2021).

Plant secondary metabolites are non-nutrient bioactive substances manufactured via the metabolic pathway under biotic (e.g., fungi, viruses, and insects attack) and abiotic (e.g., UV radiation, salinity, light intensity, temperature changes, drought, and metals) stresses (Zheljazkov et al. 2006; Teoh 2015). Hence, climatic changes can influence the production of secondary metabolites in plants (Kroymann 2011; Arnold et al. 2019). In principle, secondary metabolites are manufactured by plants under environmental stress for structural and functional stability via signaling processes and pathways (Edreva et al. 2008). For instance, orchinol (a type of phenanthrene), primarily produced as an adaptive approach by orchids, is directly associated with pathogen attacks (Stoessl and Arditti 1984). Plant secondary metabolites offer enormous health benefits to consumers (Table 1). Different plants (e.g., poplar, orchids, and artemisia species) can produce a wide range of secondary metabolites, including alkaloids, anthocyanins, bibenzyls, flavonoids, phenols, polysaccharides, and stilbenes (Harper 1998; Teoh 2015).

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Table 1 Different types of plant secondary metabolites and their importance to consumers

Plant species (scientific name)	Phytochemicals/bioactive compounds	Empirical formula	Economic importance	Reference
Orchids, e.g., <i>Orechis militaris</i> L., <i>Loroglossum hircinum</i> L., <i>Gastrodia elata</i> Blume, <i>Dendrobium</i> sp.	(a) Orchinol and Loroglossol. (b) Hydrocarbons, e.g., ethylene ($H_2C=CH_2$), and alkaloids, terpenes, stilbenes, bibenzyls, phenanthrenes, coumarins, and flavonoids	-	1) Prevent angiogenesis, tumor spread, and promote programmed cell death of cancer cells. 2) Protect nerve cells against chemicals and oxygen deprivation (stroke), promote nerve cell regeneration, and protect the skin from ultraviolet damage. 3) Protect the liver against poisons such as carbon tetrachloride (CCl ₄)	Teoh (2015)
Artemisia, e.g., <i>Artemisia annua</i> L	Terpene, e.g., artemisinin ($C_{47}H_{51}NO_{14}$)	$C_{15}H_{22}O_5$	Use as a fever medicine. Life-saving terpene and plactaxol (a diterpene), effective against ovarian, breast, colon, non-small-cell lung cancer, and malignant melanoma	Harper (1998)
<i>Ephemerantha lonchophylla</i> (Hook. f.)	Ephemeranthone, e.g., Denbinobin (1) and 3-methylgigantol	$C_{18}H_{16}O_5$	Displays anticancer activity. Denbinobin shows a significant reduction in tumor metastasis, orthotopic tumor volume, and spleen enlargement	Chen et al. (2010)
<i>Alnus maximowiczii</i> Callier, <i>Betulla striata</i> (Thunb.), <i>Dendrobium chrysanthum</i> Wall, <i>Ephemerantha lonchophylla</i> (Hook. f.)	Phenanthrene	$C_{14}H_{10}$	Natural phenanthrenes are cytotoxic against specific human cancer cell lines and possess anti-allergic, antimicrobial, anti-inflammatory, antioxidant, antiplatelet (antithrombotic), and spasmolytic properties	Kovács et al. (2008)
<i>Salix purpurea</i> subsp. <i>angustior</i> Lautenschl	(a) Flavonoid, (b) isoflavonoid, and phenylpropanoid	(a) C ₆ -C ₃ -C ₆ compounds. (b) $C_{15}H_{10}O_2$	Use to cure rheumatic pains	Aliferis et al. (2015)
Poplar species, e.g., <i>Populus trichocarpa</i> , <i>Populus tremula</i> , <i>Populus alba</i> , <i>Populus tomentosa</i> , <i>Populus deltoides</i>	Fatty acid and terpenoid derivatives, shikimate-phenylpropanoid, phenolic glycosides, and terpene		The therapeutic effects of terpenes have been focused on their anticancer effects because the derivative Taxol is one of the most widely used anticancer compounds	Movahedi et al. (2021)

These compounds exhibit antioxidant, antimicrobial, anti-inflammatory, antidiabetic, and anticoagulant properties. For example, some phenanthrene and stilbenoids possess cytotoxic properties, prevent angiogenesis (formation of new blood vessels) and tumor spread, and inhibit cancer cell replication, e.g., in human colon carcinoma cell lines (Kovács et al. 2008; De Luca et al. 2012; Vukmirovic et al. 2018). Recently, secondary metabolites from different plant species possessing antiviral properties have exhibited the potential for treating SARS-CoV-2 — severe acute respiratory syndrome coronavirus-2 (Bhuiyan et al. 2020). Elevated concentrations of Cd, As, and Pb from natural (geogenic-geochemical composition of source rock) and anthropogenic sources (e.g., industrial and mining processes) in soils can pose a threat to plants (Edreva et al. 2008). These elements are toxic to plants with no relevance to growth and development. The uptake, translocation, and accumulation of elements in plants depend on species and ecotype, plant organ, climatic conditions, and different seasons (Kabata-Pendias and Pendias 2001). Risk elements mostly remain in the plant's root/rhizome system (belowground biomass). However, As and Cd are relatively easily transported to aboveground biomass, e.g., the leaf (Szákóvá et al. 2018). The elements accumulated in edible organs of crops or spontaneous plants represent the main entry point in the food chain. Exposure to excess risk elements alters plant physiology, e.g., the rate of photosynthesis, respiration, enzymatic activities, and element distribution at the cellular level (Rout and Das 2003).

Abiotic stress, e.g., As, Cd, and Pb, can trigger the production of bioactive substances by changing aspects of secondary metabolism (Kováčik and Klejdus 2008; Nasim and Dhir 2010). Risk element stress on medicinal and other plants can also suppress secondary metabolite production (García-Calderón et al. 2015). High-risk elements in plant use for medicines can stimulate the production of bioactive compounds. Oxidative stress, induced by risk elements, initiates pathways that affect specific secondary metabolite production (Yadav 2010). Meanwhile, apoplastic barrier (e.g., Casparian strip), vacuolar sequestration, and phytochelatins in roots and other compartments of plants can maintain an adequate amount of essential metal ions (e.g., Zn) and reduce the damaging effects of non-essential ones (Yamaguchi et al. 2011). However, during an excess of risk elements, plants generate harmful oxygen species/singlets (e.g., superoxide (O_2^-) and hydrogen peroxide (H_2O_2)), which eventually lead to stress (Huang et al. 2019). Low molecular weight substances, enzymes, and many secondary metabolites (e.g., flavonoids, phenylpropanoids, and phenolic acid) serve as effective antioxidants (Kumar and Pandey 2013). Studies (e.g., Michalak 2006; Kumar et al. 2013) indicate that phenolics can form chelates with metals or scavenge ROS.

Several studies have described the effects of individual risk elements (Cd, As, and Pb) in soils and subsequent translocation in plants and metabolites. Meanwhile, most of these studies are site-specific. Therefore, we aim to compile and highlight the effects of elevated levels of Cd, As, and Pb in soils, uptake by plants, and their translocation to different aerial parts. Additionally, we collated vital literature to provide an in-depth overview and reliable inferences on the effects of As, Cd, and Pb after their uptake on plant secondary metabolites, as they show potency as herbal medication.

The next aspect of the study reviews Cd, As, and Pb uptake, translocation in plants, interactions with bioactive substances, and the potential effects on human health. Species of Cd, As, and Pb and their influence on secondary metabolites of plants are well-discussed. Commonalities and variabilities among different species of risk elements in plants may represent a prerequisite in determining the level of toxicity.

Soil-to-root pathway of risk elements

Natural processes (weathering of the parent material) and anthropogenic interferences (e.g., metallurgy, agricultural, and industrial activities) contribute primarily to the elevated Cd, As, and Pb levels in soils (Redondo-Gómez et al. 2010; Pourrut et al. 2011; Hu et al. 2018). However, anthropogenic accumulation produces the highest concentrations of risk elements in the soil than the former (Geiszinger et al. 2002).

The physicochemical forms of Cd, As, and Pb may exist in soils as inorganic species, organic complexes, adsorbed on solid phases, or constituents of solid phases, with varying solubility levels (Aydinalp and Marinova 2003). Plants absorb only the available fraction associated with the exchange complexes (organic and inorganic components) and soluble fractions in soil solution. Generally, the distribution and bioavailability of risk elements in the soil ecosystem are often well-governed by soil reaction (pH), redox condition, dissolved organic carbon (DOC), clay content, and oxides of Fe, Mn, and Al (Sungur et al. 2020).

Cadmium (Cd)

Cadmium toxicity in soils occurs via industrial (e.g., metallurgical activities and Zn refining) and agricultural practices, e.g., extensive herbicides and fertilizers (phosphate) applications (Redondo-Gómez et al. 2010). Although Cd-containing pesticides remained banned in Europe, Cd toxicity is possible by applying biosolids (e.g., sewage sludge) to arable fields (European Council Directive 1989).

Geochemically, the behavior of Cd in soils operates in a soluble and exchangeable portion, precipitated with carbonates, occluded in amorphous Fe/Mn oxides, complexed

with organic matter (OM), and residual form (Wiggenhauser et al. 2021). The soluble and exchangeable fractions of Cd are more bioaccessible to plants. Non-residual Cd: (CO_3^{2-} -bound, Fe–Mn oxides, and OM fractions) becomes bioaccessible with changing pH and redox potential E_h (Rinklebe and Shaheen 2014). Under oxidizing conditions, the decrease in sulfide (S^{2-}) produces protons, leading to increased solubility of Cd (Rinklebe and Shaheen 2014).

Cadmium can also form complexes with soil colloids. Soil acidity increases Cd desorption in colloids, allowing root uptake. The formation of $\text{Cd}(\text{OH})_2$ reduces the mobility of Cd at high alkaline pH, resulting in low plant accumulation (Gong et al. 2021). Soil E_h plays a vital role in Cd solubility. In flooded fields, E_h is again well-mediated by oxidized Fe^{III} , $\text{Mn}^{\text{III/VI}}$, NO_3^- , SO_4^{2-} , and other soil components useful in microbial respiration (Cui et al. 2020). In a reduction reaction, the ions/ionic compounds receive electrons to generate reduced substances, which result in decreased E_h (Lin et al. 2021). The decrease in E_h can lead to the reductive dissolution of Fe and Mn oxides, which release bonded Cd into soil solution and increase bioavailability (Shaheen et al. 2016; Wu et al. 2019). Conversely, reduced Cd can precipitate under sulfide conditions, decreasing solubility and bioavailability (Rinklebe et al. 2016). E_h may increase, which can cause the

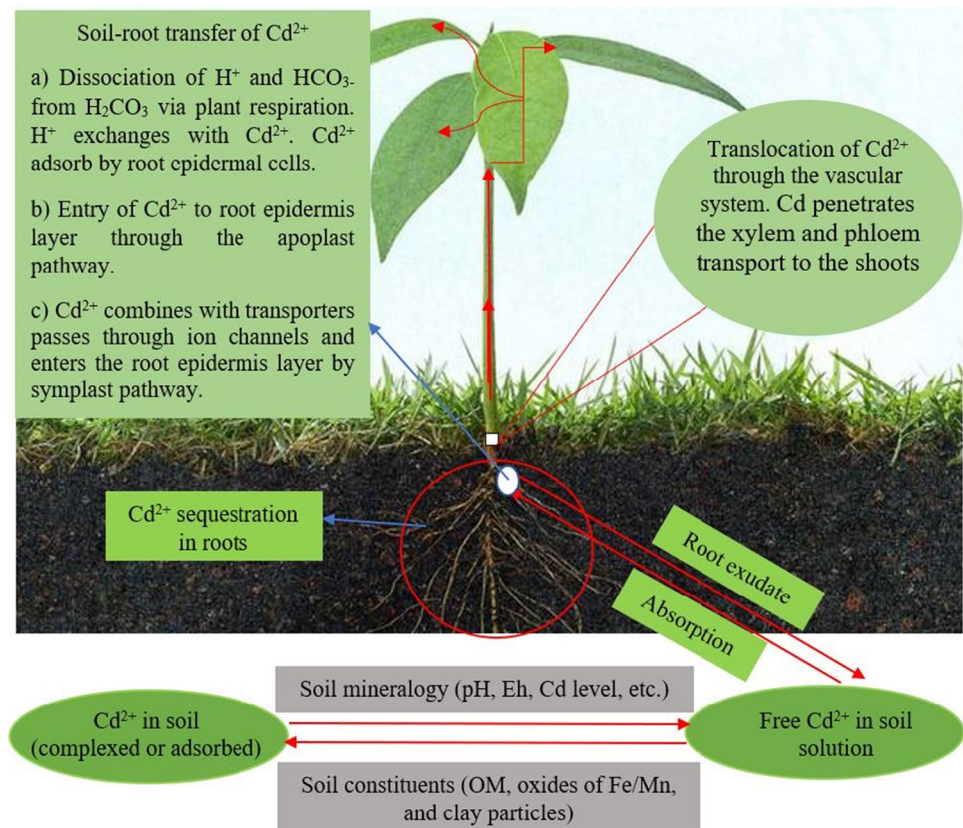
dissolution of CdS and release of Cd^{2+} in well-drained soils (Rinklebe et al. 2016; Shaheen and Rinklebe 2017).

As Cd adsorbent in soils, OM can immobilize Cd, reduce phytoavailability, and decrease the uptake of Cd. For example, Ali et al. (2020) recorded a decreased Cd accumulation in the roots, straws, and grains of *Oryza sativa* in the presence of OM. Organic acids, as negative anions, react with Cd^{2+} and can immobilize Cd, thus reducing its phytoavailability (Li et al. 2019a, b). However, in soils managed for wet cultivation (e.g., Entisols and Inceptisols), OM as chelates can enhance the phytoavailability of Cd (Subašić et al. 2022). It indicates that remediation of Cd-contaminated soils with OM should be well-managed. The application of OM should be well-controlled to prevent further contamination by other risk elements.

Cadmium uptake by plants depends directly on soil properties, plant type, chemical properties of Cd, mobility, and immobilization by root exudates in the rhizosphere (Fig. 1). The chelation of Cd can affect pH and E_h in the rhizosphere and subsequently influence the mobility of Cd within the soil. For example, an arbuscular mycorrhizal association can reduce the toxicity of Cd^{2+} in the rhizosphere by inducing alkalinity, which can immobilize Cd^{2+} (Janousková and Pavlíková 2010).

Root exudates (e.g., oxalic, fumaric, malic, and acetic acids) have different detoxification mechanisms for plants

Fig. 1 Schematic diagram showing uptake and translocation of Cd by plants under different soil physicochemical properties. Here Cd uptake is mediated by many transporters, NRAMP families, P-type ATPases, and ABC transporters. The absorption of Cd from soil and its distribution between roots and shoots is a regulated process involving metal transporters of the root cell, plasma membrane, xylem, phloem loading/unloading, and leaf/shoot sequestration and detoxification. NRAMP natural resistance-associated macrophage protein; ABC ATP-binding cassette; E_h redox potential; OM organic matter (adapted and modified from Shahid et al. 2016)



to alleviate the toxicity of free Cd^{2+} through organic complexation (Lapie et al. 2019). Metal chelators and many other organic acids also play essential roles in reducing Cd toxicity in some organelles (e.g., via glutathione in the vacuole) and macromolecules (Shahid et al. 2016). Hence, chelation performs a vital function in the tolerance of plants to Cd toxicity.

Free Cd^{2+} uptake into the root epidermal layer undergoes a series of interactions. At the plasma membranes of root cells, H_2CO_3 dissociates to release H^+ and HCO_3^- in the course plant's respiration (Yamaguchi et al. 2011). Hydrogen ions swiftly shift for Cd^{2+} adsorption in root epidermal cells and subsequently to the epidermis layer via the apoplast pathway. Cadmium ion enters plant cells in Ca^{2+} , Fe^{2+} , and Zn^{2+} channels (Sadana et al. 2003). However, this is more restricted to specific areas of Cd concentration in soils, where the physiology of the root system remains unaffected. Cadmium combines with transporter proteins for Zn^{2+} and Ca^{2+} as it passes through the corresponding ion channels for these molecules and enters the layer of the root epidermis through the symplast pathway. Other viable absorption channels of Cd^{2+} include diffusion to the root surface (Shaaria et al. 2021).

Inside the root, phytochelatins form chelates with Cd^{2+} through phytochelatin synthases to resist transfer to the shoot (Bayçu 2002). However, many transporters regulate Cd uptakes, e.g., P-type ATPase, natural resistance-associated macrophage protein (NRAMP), Ca^{2+} /cation antiporter (CaCA), and lysosomal cystine transporter (LCT) (Mao et al. 2021). Identifying Cd uptake mechanisms and transporters will enhance the fast and effective elimination of Cd contamination in soils.

Arsenic (As)

The various forms of As in soils include free ionic species, precipitated as solids, adsorbed on organic or inorganic constituents, and exchangeable and structural composition of primary and secondary minerals (Shahid et al. 2014; Joseph et al. 2015). Inorganic species of As (i.e., As^{III} and As^{V}) are present in different forms, e.g., fully protonated As or arsenous acids (Sadiq 1997). The primary and thermodynamically stable forms of $\text{As}^{\text{III/V}}$ in soils include hydrogen arsenate (HAsO_4^{2-}), dihydrogen arsenate (H_2AsO_4^-), and arsenous acid (H_3AsO_3). The presence of As in an inorganic form can depend on pH and redox potential (E_h), and among these, H_2AsO_4^- frequently occurs in aerobic soils (Warren and Alloway 2003). The arsenate form (AsO_4^{3-}) of As is more stable and adsorbed quickly to clay minerals and Fe/Mn (hydro)oxides (Khalid et al. 2017a). However, arsenite ($\text{As}(\text{OH})_3^0$) occurs primarily under reduced soil conditions and is more soluble, mobile, and toxic (Khalid et al. 2017a). For example, As mainly exists as arsenate (V) in oxic soil

conditions as its main chemical species. Arsenic presents in an anionic form in combination with oxygen, unlike cationic elements (e.g., Cd and Zn) that exist in an independent anionic form (Masscheleyn et al. 1991). Thus, inorganic As species in soils are considered more toxic than their organic counterparts because of their higher solubility, mobility, and rapid absorption. Organic As species in the natural environment include the following: monomethylarsonite (MMA^{III}), monomethylarsonate (MMA^{V}), dimethyl-arsenite (DMA^{III}), dimethylarsinate (DMA^{V}), arsenocholine, arsenosugars, arsenobetaine, trimethylarsine oxide, and tetramethyl-arsonium ions (Joseph et al. 2015; Fig. 2).

The soil reaction (pH) represents a key variable governing the chemical distribution of metals in soils (Shahid et al. 2012; Khalid et al. 2017b). The biogeochemical behavior of As in the soil–plant system depends mainly on soil pH (Khalid et al. 2017a). Under acidic soil conditions, e.g., below a pH of 5.5, As is highly mobile and phytoavailable (Signes-Pastor et al. 2007). Admittedly, this is due to the transformation of As into a more soluble As fraction (As^{III}) at low soil pH. A relative abundance of inorganic As species — As^{III} and As^{V} — varies with soil pH, usually 8–9 and 3–5, respectively (Adra et al. 2016). Again, the pH dependence of $\text{As}^{\text{III/V}}$ adsorption differs in Fe and Al (oxy)hydroxides. The difference in sorption behavior is especially critical at acidic pH. Retention of As^{V} in ferrihydrite usually occurs at pH 3–5, and for As^{III} is at pH 8–9 (Dixit and Hering 2003). Iron oxyhydroxides are generally considered superior As adsorbents than Al hydroxides, with maximum As^{V} adsorption on amorphous Al hydroxide at pH 4–4.5 (Anderson et al. 1976). Soil redox status has a significant effect on As speciation and geochemical behavior. Usually, the solubility of As increases at a decreasing E_h rate. For example, in an oxidation state, As^{V} predominates (Khalid et al. 2017a). However, As^{V} eventually is converted to As^{III} at a low E_h value-reduction state (Gorny et al. 2015). Thus, the alteration of oxidation and reduction states of As affect the As solubility greatly. The solubility of As in soils is partly a function of E_h .

The mobility of As in soils increases with an increasing level of DOC, and vice versa in the case of adsorption (Mombo et al. 2016). Soil colloids and metal oxides are crucial adsorption sites for As and amorphous Fe hydroxides (Armendariz et al. 2016). In the process of oxidizing Fe, amorphous Fe oxides form. Arsenic is easily and quickly absorbed to amorphous Fe by ligand exchange of As for the OH and OH_2 groups (Finnegan and Chen 2012). Hence, it is vital to consider the bound form of As and the total concentration to assess the status of soil contamination. Other competing ionic species, such as P and Si, affect the mobility of As and bioavailability in soils (Armendariz et al. 2016; Chandrakar et al. 2016).

The mobility, bioavailability, and toxicity of As in the soil–plant system greatly depend on As oxidation states

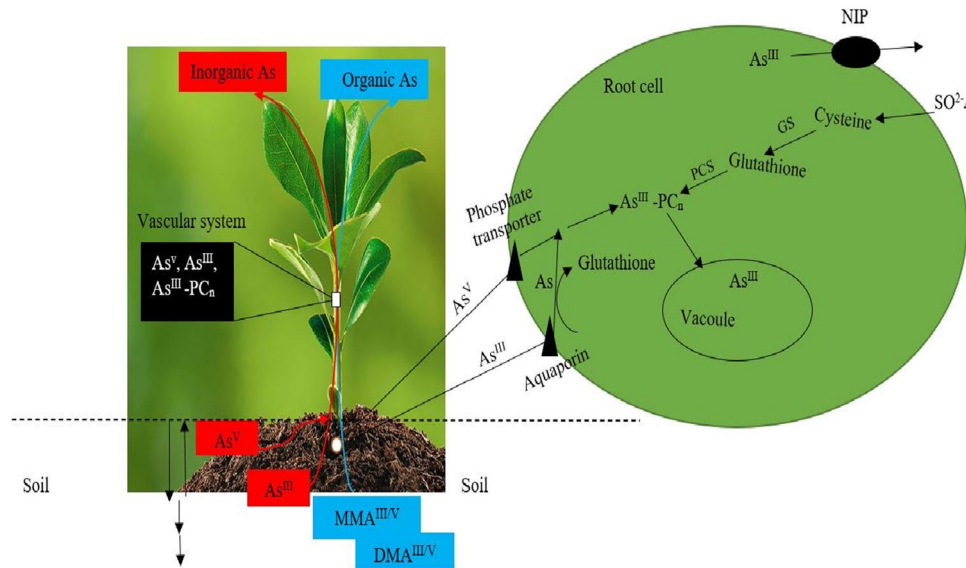


Fig. 2 Diagrammatic representation of uptake pathway, detoxification, and transport of arsenic in the root cell and vascular system of plants. Arsenite— As^{III} , arsenate— As^{V} , monomethylarsenite— $\text{MMA}^{\text{III/V}}$, and dimethylarsenite— $\text{DMA}^{\text{III/V}}$. Cysteine is synthesized from sulfate and is transformed into glutathione by glutathione synthetase (GS). Phytochelatin synthase (PCS) produces phytochelatin

from glutathione. Arsenite binds to phytochelatin ($\text{As}^{\text{III}}\text{-PC}_n$) and is transported into vacuoles or to the shoot-like arsenite or as a phytochelatin-arsenite complex. Efflux of arsenite from the cell can also be performed by Nodulin-26-like intrinsic protein (NIP) aquaporins. Aquaporin contributes to As uptake. Arsenate reductase (AS) reduces arsenate to arsenite by using glutathione as a reductant

(Shahid et al. 2013). Both As^{V} and As^{III} are highly soluble in H_2O and may change valency states depending on the pH (Parvin et al. 2022) and E_h (Marin et al. 1993). In reducing environments, As remains as As^{III} , while H_3AsO_3 is the predominant species. Arsenic in aerated soils often occurs as H_2AsO_4^- (acid soils) or HASO_4^{2-} (neutral species and base form) (Moreno-Jiménez et al. 2012). However, in anaerobic soil, HAS_3O_3 predominates where As availability is higher, and As^{III} becomes more weakly retained than the As^{V} . Changes in environmental conditions can affect the occurrence of As at different oxidation states. The biogeochemical characteristics of As are not entirely dependent on the total concentration (a constituent of stable minerals) in soils (Rafiq et al. 2017) and are generally not bioavailable. The uptake of As by plant species depends on the concentration and its speciation in soils, depending on the exchangeable (bioavailable) level (Martínez-Sánchez et al. 2011; Rafiq et al. 2017).

Arsenic enters plants mainly in an inorganic form (As^{III} or As^{V}) through transporter proteins likely governed by the concentration gradient of As between growth media and plant cells (Neidhardt et al. 2015; Fig. 2). Both As^{V} and phosphate use the same transporters to cross the plasma membrane of the root cell, e.g., in *Brassica napus* L. and *Brassica juncea* (L.) Czern. (Niazi et al. 2017). Arsenic transporters play crucial roles in As uptake, translocation, and detoxification. Several As transporters associated with its accumulation in grains; that is, Carey et al. (2010)

reported phloem transport of 55 and 90% of As^{III} and DMA , respectively, in *Oryza sativa* L. grains.

Microbes are vital in the transformation of As species in soils. Environmental microbes have the potential to produce highly toxic As^{III} by the process of biomethylation of As^{III} or reducing As^{V} . Microbes have evolved detoxification mechanisms, among which oxidation of As^{III} to much less toxic As^{V} by the *ArsH* oxidase used in some bacteria (Chen et al. 2015). In As -contaminated soils, organoarsenicals (e.g., MMA , DMA , TMA , TMAO , and TETRA) usually represent a minor component or are not detected in soils (Geislinger et al. 2002). Arsenic reduction, methylation, and demethylation can occur depending on the type, condition, and microbes of the soil. Under anaerobic conditions, organoarsenicals reduce to volatile arsine, including monomethylarsine (MMA^{III}), dimethylarsine (DMA^{III}), and trimethylarsine (TMA^{III}) (Zhang et al. 2021). Microbial As methylation is an effective method for As detoxification in micro-organisms and an ideal bioremediation method. However, approaches to recycle volatile or collect methyl As should be developed.

Lead (Pb)

Soil contaminated with Pb oxide results from anthropogenic inputs of leaded fuels, old Pb plumbing pipes, and metallurgy (Retief and Cilliers 2006; Pourrut et al. 2011) and accumulates in the upper soil layers in decreasing concentration with

depth (Cecchi et al. 2008). For example, in an abandoned Pb smelter in Příbram, the Czech Republic, the concentration of Pb in the arable layers was up to 2500 mg kg⁻¹ and 400 mg kg⁻¹ in the subsoils (Šichorová et al. 2004). Lead in soils exists as a free metal ion, mostly complexed with inorganic components (e.g., PbCO₃²⁻, PbHCO₃³⁻, PbSO₄²⁻, and PbCl₂⁻), or occurs as organic ligands (e.g., humic and amino acids). Ionic Pb, Pb^{II}, Pb oxides and hydroxides, and Pb-metal oxyanion complexes are the general forms released into soils. The most stable forms of Pb are Pb^{II} and Pb-hydroxy complexes. The dominant insoluble Pb compounds are Pb-phosphates, Pb carbonates (at pH > 6), and Pb-(hydr) oxides (Yan et al. 2012).

Under anaerobic conditions, volatile organo-Pb (tetramethyl Pb) can form from microbial alkylation (Aten et al. 1980). In addition to the inorganic compounds of Pb, several organo-Pb compounds, such as tetraethyl Pb, are formed. Organo-Pb compounds of commercial and toxicological value are predominantly limited to the alkyl (methyl and ethyl) Pb compounds and their salts (e.g., diethyl-Pb-dichloride, dimethyl-diethyl-Pb, and trimethyl-Pb-chloride). In nature, Pb usually occurs as a mineral combined with other elements, such as S (e.g., PbS and PbSO₄) or oxygen (PbCO₃) (Wang and Mulligan 2006). Lead (Pb) in soils, in the context of species, solubility, mobility, and bioavailability undergo complex relationships engineered by some biogeochemical factors. The uptake of Pb by plants depends individually or collectively on soil pH, E_h , mineralogy, Pb concentration, organic and inorganic ligand, cation levels, biological and microbial conditions, and plant species (Kopittke et al. 2007; Rizwan et al. 2018). Due to the strong binding of Pb with organic and colloidal materials, only small amounts of Pb in the soil solution are phytoavailable (Punamiya et al. 2010). The bioavailability of Pb directly depends on its speciation and concentration of free Pb ions (Uzu et al. 2009). A significant plant uptake route for many cationic metals (especially free metal ions) is through the soil solution in dissolved form (Punamiya et al. 2010).

Concentrations of free Pb²⁺ in soils depend on both adsorption or desorption processes in which they participate (Vega et al. 2010; Campillo-Cora et al. 2020). By using surface complexation models, Gustafsson et al. (2011) determined that free Pb adsorption is dominated by OM at soil pH < 6, whereas adsorption in Fe oxides is more prevalent at pH > 6. Soil pH remains vital in determining the free Pb²⁺ activity in soil solution, as Pb adsorption and most precipitation reactions often are favored by high acidic pH. An increase in pH induces increases in the negative charge of OM that binds with the cationic charge of metals, e.g., Pb, Zn, and Cd. Dissolved OM also controls Pb solubility in soils, forming organo-Pb complexes that increase Pb solubility at high alkaline pH (Sauve et al. 1998). Water-soluble and potentially leachable Pb in non-acid soils often occurs as Pb-DOM complexes (Weng et al.

2002; Ashworth and Alloway 2008). In many contaminated soils, mineral components of Pb, for example, litharge (PbO), hydrocerussite (Pb₃(CO₃)₂(OH)₂), and cerussite (PbCO₃), are stable to limit Pb solubility (Cabała et al. 2020) and pyromorphite (Pb₅(PO₄)₃Cl), form under high phosphate concentration (Scheckel et al. 2005).

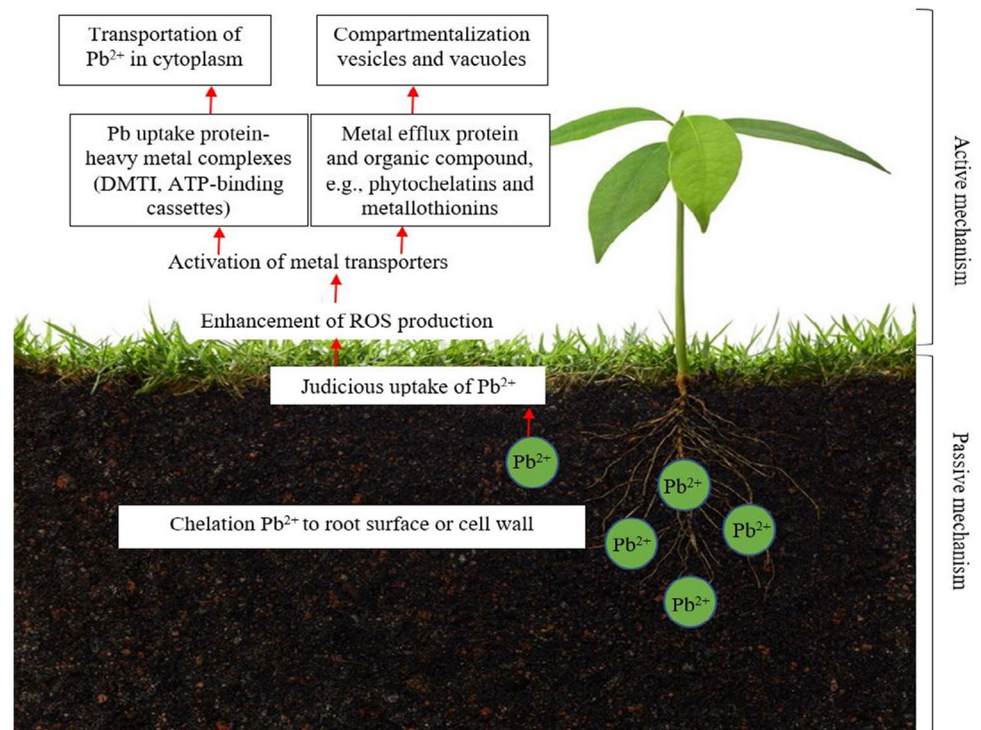
Lead is absorbed in the soil solution by plants through the roots and enters the food chain (Sharma and Dubey 2005; Uzu et al. 2009). Absorption of Pb by roots occurs through the apoplastic pathway or permeable channels of Ca²⁺, further transported by symplastic movement (Fig. 3). Part of Pb in soil solution is adsorbed on roots and bound to carboxyl groups of mucilage uronic acid or directly by polysaccharides on the surface of the cell of the rhizoderm by root exudation (Seregin and Ivanov 2001). There is also possible adsorption of Pb ions on the surfaces of the root, which eventually diffuse into root cells, such as in the cases of *Lactuca sativa* L. and *Vigna unguiculata* L. Walp. (Kopittke et al. 2007; Uzu et al. 2009). Additionally, Pb may enter roots in several ways, predominantly through ionic channels. The protective effect of Ca²⁺ on Pb²⁺ toxicity relates to its inhibition of the metal accumulation in the root tip, a potential target site of Pb²⁺ toxicity (Kim et al. 2002).

Although Pb uptake is a non-selective phenomenon, it nevertheless depends on the functioning of an H⁺/ATPase pump to maintain a negative membrane potential in rhizoderm cells (Wang et al. 2007). However, Ca²⁺-permeable channels represent one of the main pathways Pb enters roots (Demidchik et al. 2018). Studies on transgenic plants have shown the penetration of Pb in roots through different non-selective pathways, e.g., cyclic nucleotide-gated ion channels (Eapen and D'Souza 2005). The restrictive transport of Pb²⁺ into the root system indicates that remediation requires a critical selection of plants (hyperaccumulators — above-ground accumulators of metals), uptake high levels of Pb, and translocate to aerial plant parts with no or minimal toxicity. After Pb adsorption on the rhizoderm, root entry can occur passively and follow the translocation of the H₂O stream (Kopittke et al. 2007). Non-uniform Pb absorption along the gradient of plant apical roots offers another option for root uptake (Seregin et al. 2004). High Pb concentrations in root apical meristem where root cells are young, with thin cell walls, facilitate Pb root uptake (Seregin et al. 2004). The low rhizodermic pH of the apical area increases Pb solubility in soil solution.

Translocation and speciation of Cd, As, and Pb in plant tissues

The epidermal cell layer in plant species is a well-elaborated system considered an absorbing tissue for ion uptake and membrane transporters. After passing through all blockages

Fig. 3 Schematic representation of the transfer of Pb^{2+} from the soils to the root and further translocation in plant parts. Translocation of Pb^{2+} metal ions occurs by apoplastic movement resulting in the deposition of metal ions in the endodermis and is further transported by symplastic movement. *DMTI* divalent metal (ion) transporter 1, *ROS* reactive oxygen species



on the root surface, metals end up in the root cortex, including the apoplast barrier (in the endodermis). Metal ions enter the symplast, the stele, and the xylem (Broadley et al. 2007; Akhter et al. 2014). Eventually, after a series of passages, metals are loaded into stems.

Transport of Cd in plant tissues

After passing through all barriers from root surfaces over the root cortex, including apoplastic space, e.g., the apical parts where Casparian bands are less developed, Cd^{2+} enters the symplast and transported to the stele and xylem elements (Redjala et al. 2009; Akhter et al. 2014).

The loading of Cd^{2+} in the xylem of roots represents one of the vital processes in Cd transport involved in differential Cd accumulation in hyperaccumulating plants (Verbruggen et al. 2009a; Yamaguchi et al. 2011). Translocation of Cd^{2+} primarily is a function of the retention in roots and loading activity in the xylem (forms part of apoplasmic space) (Verbruggen et al. 2009b). Retention occurs through Cd-chelating molecules, such as apoplastic barriers, phytochelatins, and vacuole sequestration. Competition between sequestration in root cells, e.g., transport from the symplast to the stele and xylem loading, enables most higher plants to accumulate many Cd^{2+} in roots compared to shoots (Yamaguchi et al. 2011). However, plant hyperaccumulators mostly accumulate a higher concentration of metals in the aboveground parts than in their roots (Verbruggen et al. 2009a). In plant xylem sap, Cd^{2+} has the potential to form complexes with

ligands (Ana et al. 2014). These complexes, with free Cd^{2+} , are transported to the aerial parts of the plant with the flow of xylem sap driven by transpiration. Hyperaccumulation of As defined as a concentration above (in $mg\ kg^{-1}$) 1000 was in ferns growing on industrially polluted soils (Reeves 2006), 8350 for *Pityrogramma calomelanos* L. (Visoottiviset et al. 2002), and 22,630 also for *Pteris vittata* L. (Ma et al. 2001). Several species of the Brassicaceae family, such as *Thlaspi caerulescens* J., accumulated $3000\ mg\ kg^{-1}$ (Reeves et al. 2001). Free Cd^{2+} also interacts with the cell walls of xylem vessels and partly adsorbs on them or can migrate through the cell walls of the xylem to stem and leaf cells, mainly under the influence of transpiration flow (Sterckeman and Thomine 2020).

Additionally, Cd^{2+} can re-enter the apoplast before loading into xylem vessels upon reaching the stele (Hu et al. 2009; Sterckeman and Thomine 2020). For instance, Akhter et al. (2014) recorded high Cd concentration in the walls of xylem vessels in *Hordeum vulgare* L. Furthermore, Cd^{2+} in stele can coordinate with S and acetate ligands. The process suggests the possibility of Cd^{2+} complexation with phytochelatins (heavy-metal-binding peptide) and carboxylic acids in vacuoles and subsequent binding to cell walls. Chelation and sequestration of metals by particular ligands are approaches plants use to cope with stress. Higher plants respond to heavy metals by synthesizing phytochelatins and related cysteine. For example, phytochelatin synthases and γ -glutamylcysteine (γ -Glu-Cys) catalyze the synthesis of heavy metal binding (Yadav 2010).

The tendency to move Cd^{2+} from the xylem parenchyma to xylem vessels depends on the activities of transporters (Mori et al. 2009). A difference in the ability of transporters to load Cd^{2+} into the xylem is vital in determining the differences between Cd concentrations in the xylem sap (Mori et al. 2009). Yamaguchi et al. (2011) detected the differences in Cd^{2+} uptake into stem xylem in cultivars of *Solanum torvum* Sw reflected differences in membrane transporters. Mendoza-Cózatl et al. (2008) identified high concentrations of phytochelatins, glutathione, and Cd^{2+} in the phloem sap of *B. napus*. Thus, the phloem is also a conduit for long-distance source-to-sink transport of Cd^{2+} . Identified transporters/protein-regulated Cd include the P-type ATPase family and HMA subfamily (heavy metal ATPases), involved in the transmembrane transfer of ions belonging to the symplastic pathway (Maccaferri et al. 2019).

Cadmium forms chelate with organic ligands in the leaf and migrate within cells (Yamaguchi et al. 2011). Free ions of the complexes enter the cell vacuole for storage as chelates. In the shoot, Cd^{2+} distributes in the various units of the cell and tissues (Sterckeman and Thomine 2020). Additionally, part of this Cd^{2+} redistributes to other organs (e.g., the reproductive parts) and through the phloem into the root system. Excess Cd can also preferentially excrete via the leaf surface (e.g., through hydathodes) to avoid toxicity (Dong et al. 2019).

Transport of As species in plant tissues

Transports of different As species from roots have been well-studied among plants (Zhao et al. 2009; Huang et al. 2011). Xylem tissues are directly involved in the root translocation of As and subsequent distribution among various plant tissues (Kumar et al. 2015). Arsenate is reduced to As^{III} in the plant cell with the assistance of As reductase (Yoshinaga et al. 2011). For example, As hyperaccumulating plant species, *P. vittata* can accumulate As^{V} and transport more As^{III} through the xylem with less tendency for As^{III} -thiol complex formation (Zhou et al. 2000).

Arsenite efflux mainly occurs via aquaporin channels through the epidermal cells (Fig. 2). Typical protein-coding in the transport of As^{III} and As-related substances includes Nodulin 26-like intrinsic protein, OsNIP2;1- Si-influx transporters mostly in *O. sativa* As-transport (Yan et al. 2021), and other transporters in the aquaporin family (Bienert et al. 2008). Additionally, the ability to load As directly into the xylem affects the shoot accumulation in many plants. The uptake rate of methylated organic As species is slower than those of inorganic As species (Agre and Kozono 2003). Meanwhile, the translocation of methylated As species from root to shoot via the xylem is fast (Raab et al. 2007a; Shaikoor et al. 2015). Moreover, in xylem and phloem tissues,

methylated As species are often more mobile than their inorganic counterparts (Carey et al. 2010).

Some organic As species get transported from soil to the xylem stream through the Si influx and efflux transporters (Li et al. 2009; Mitani-Ueno et al. 2011). Influx Si (e.g., Lsi1) transporter allows the bidirectional (inclusion and exclusion) flux of Si and As^{III} between soil and plant roots cells, while Lsi2, an efflux, involves in the exclusion of Si/ As^{III} into the stele and xylem tissues (Khalid et al. 2017a; Yibin et al. 2019). A hydroponic experiment conducted by Raab et al. (2007b), using over 40 species of *Zea mays* L., showed that the transport of DMA^{V} from root to shoot was about 10 and 3 times greater than MMA^{V} and As^{V} , respectively. Thus, As species in plants reflect differential transport mechanisms.

Trivalent As is considered more toxic than As^{V} as it reacts like a soft metal with thiols (Ramírez-Solis 2004; Fig. 2). Arsenite may form relatively weak bonds with monothiols, and high intracellular concentrations of As^{III} can deplete glutathione cells. It forms strong bonds with dithiols in small molecules, e.g., lipoic acid cofactor, and with vicinal thiols in proteins, leading to the inactivation of various enzymes and receptors (Ramírez-Solis 2004). In contrast to As^{V} , a negatively charged oxyanion in solution, As^{III} , is the neutral undissociated acid $\text{As}(\text{OH})_3$ at physiological pH.

Meanwhile, the transports of these substrates across the aquaporins operate mainly by two pores, the conserved asparagine-proline-alanine boxes and aromatic/arginine (Maurel et al. 2008). Nodulin-26-like intrinsic protein (NIP) aquaporins can also perform the efflux of As from plant cells. All NIPs have different pore structures at arginine selective filters. NIPs are into subgroups: (1) archetype nodulin-26 (permeable to $\text{C}_3\text{H}_8\text{O}_3$, $\text{C}_3\text{H}_6\text{O}_3$, and H_2O), (2) a pore size larger than archetype nodulin-26 (permeable to large solutes, e.g., CH_3NO , H_3BO_3 , and $\text{CH}_4\text{N}_2\text{O}$ but less permeable to H_2O) (Wallace et al. 2006), and (3) finally for the transport of silicic acid ($\text{Si}(\text{OH})_4$). The As^{III} species is permeable to all NIP subgroups and transported by Si influx and efflux transporters (Panda et al. 2010).

Arsenic accumulation also depends on plant species. For example, Tremlová et al. (2017) observed a higher accumulation of As by *Equisetum fluviatile* L. than by *Juncus filiformis* L. living under similar conditions. The difference in As accumulation probably depends on different regulations of the phosphate transporters or the aquaglyceroporins involved in the cellular uptake of both As species. According to Tlustoš et al. (2002), radish has As^{III} dominated in roots, while As^{V} translocates to the leaves. Arsenic speciation in the phloem of many plants and its role in As accumulation remain largely uncharacterized.

The translocation efficiency of As from roots to shoots affects the tolerance of plants and determines the ability of hyperaccumulators to accumulate As (Verbruggen

et al. 2009a). The reduction of As^V to As^{III} efficiently in hyperaccumulator plants is often reported. Thus, As^{III} predominates in root-to-shoot transport, whether there is As^V or As^{III} supply to the plants (Raab et al. 2007a, b). It is, therefore, convenient to know the predominant As species to select the most suitable plant accumulator for effective phytoremediation.

Transport of Pb in plant tissues

Lead accumulates primarily in root cells because of the blockage by Casparian strips (Dogan et al. 2018). Unlike As, Pb shows a more translocation restriction phenomenon. Thus, a higher fraction of accumulated Pb remains in roots compared to the aerial plant parts (Kiran and Prasad 2017). And this is in support of negative charges that exist on root cell walls that trap Pb ions (Pourrut et al. 2011; Tariq 2018). Thus, hyperaccumulation of Pb is often restricted in many plants and generally dominates in the root (Probst et al. 2009; Fahr et al. 2013). A comparative analysis of different fruiting parts of plants indicated that root edibles accumulate the highest Pb concentration in aboveground organs (Fahr et al. 2013).

Deposition of Pb in various organelles of plants and vascular tissues in the root system of plants confirms the retention of Pb in this section (Yuan et al. 2015; Li et al. 2016). However, the translocation of Pb to aboveground biomass is concentration and duration dependent, e.g., in *B. juncea* and *Neyraudia reynaudiana* (Kunth) (Zhou et al. 2016; Kohli et al. 2018). Root retention of Pb partly involves the binding of Pb to ion exchange on the cell wall and extracellular precipitation in the form of Pb CO₃²⁻. Meanwhile, the un-precipitated Pb ions intermittently are transported to other parts of cells via pleiotropic drug resistance, mitochondrial inner membrane protein, and ATP-binding cassette transporters (Lee et al. 2005; Fig. 3). The synthesis of phytochelatins, peptides, and organic acids forms chelates with Pb upon entry into root cells to tolerate and toxify Pb (Hall 2002; Patra et al. 2004). Active efflux of Pb across the plasma membrane is known to be mediated by specific transporters (Kaur et al. 2013; Jiang et al. 2017). Other transporters contribute to Pb resistance by regulating the transport of Pb outside cells, e.g., leucine-rich repeat protein (Zhu et al. 2013).

In leaf tissues, Pb is well-reflected near the xylem, phloem, sclerenchyma, and mesophyll cells; indication of transport to the aerial parts requires translocation via xylem vessels (Verbruggen et al. 2009b). Again, Pb can form complexes with minerals (e.g., P, Ca, and S) (Zheng et al. 2012) and organic or amino acids while passing through the xylem tissues (Maestri et al. 2010). Lead translocation could occur through the phloem (Rascio and Navari-Izzo 2011), confirmed through an X-ray mapping.

In this case, a high fraction of Pb deposition occurred near the xylem and phloem cells of Pb-treated *Prosopis* sp. (Arias et al. 2010).

Interaction of risk elements with plant physiological and metabolic processes

Excess As, Cd, and Pb can change the expression of vital enzymes in the respiratory process and eventually lead to physiological changes in plants. In addition, stress from risk elements can also result in reduced shoot length and biomass, decreased respiratory rate, and reduced crop quality. Plant physiological disorders under risk element stresses can increase ROS. Examples of ROS include free oxygen radicals — superoxide (O²⁻), hydroxyl (OH), and hydrogen peroxide (H₂O₂); peroxy radical (ROO); and non-radicals — H₂O₂, ¹O₂, and ozone (O₃) (Riley 1994; Okem et al. 2015). Reactive oxygen species are dangerous for plant metabolism and cause detrimental effects on vital macromolecules, e.g., proteins, carbohydrates, lipids, and DNA (Singh et al. 2017; Talukdar 2017).

Meanwhile, plants undergo a series of internal modifications that include metabolic secretion to protect them from the toxicity of risk elements (Michalak 2006; Okem et al. 2015). These mechanisms, e.g., production and accumulation of antioxidant enzymes, free-proline, glutathione, and phenolics, protect plants from free radicals and prevent biomolecule damage (Michalak 2006; Bhattacharya et al. 2010). Phenolic compounds have antioxidative and metal-chelating properties and, thus, play a vital role in protecting plants against metal-induced stresses (Tatipamula and Kukavic 2021). The concentration of metals is a function of the level of phenolics (Melato et al. 2012). Hence, high-risk element concentrations enhance the production of phenolic compounds. Meanwhile, an increased amount of cell wall-bound phenolics signifies a mechanism for detoxification.

Phenolics and other plant secondary metabolites have pharmaceutical significance due to their properties (Dai and Mumper 2010; Melato et al. 2012). Thus, a high accumulation of risk elements can affect the quality, quantity, or composition of phytochemicals, questioning the effectiveness of medicinal plant/herb products. For example, excess treatments with Cd, Pb, and Cu altered the chemical composition of essential oils of *Ocimum basilicum* L. (Prasad et al. 2011) and dill and reduced the menthol content in peppermint oil (Zheljazkov et al. 2006). Meanwhile, many plants have different levels of toxicity to stress from metals. According to Stancheva et al. (2005), different levels of (in mg kg⁻¹) Cd — 3, Pb — 80, and Zn — 340 only resulted in sage biomass inhibition, but essential oil yield and quality remained unaffected.

Formation of secondary metabolites under risk element stress

Plant secondary metabolite formations are plant/stress-specific. Meanwhile, secondary metabolites are known to develop from primary metabolites (precursors) in plants (Aharoni and Galili 2011). At molecular, anatomical, and morphological levels in plants, varieties of tolerance or adaptation mechanisms develop, including interrelated gene networking (Goharrizi et al. 2022). Different plants exhibit varying biosynthesis pathways during secondary metabolite formation. For instance, putative transcription factors in the formation of glandular secretory trichomes and the biosynthesis of artemisinin include ENHANCER OF GLABRA3 (Aa-EGL3) and TRANSPARENT TESTA GLABRA1 (Aa-TTG1) (Guerriero et al. 2018).

Risk element uptake by plants affects photosynthetic pigments, sugars, proteins, and non-protein production. Reactive oxygen species in plants are part of the metabolism of chloroplasts, mitochondria, and peroxisomes. However, high exposure to risk elements can overwhelm the systems protecting the plants and result in oxidative

stress. Oxidative stress then results from an imbalance between the production and accumulation of reactive oxygen species.

The main effects of risk element-induced oxidative stress in cells ignite the enzymatic response and metabolite production (Fig. 4). For example, Cd, a non-redox metal, can indirectly increase the production of reactive oxygen species (ROS) in plants, which elevates free oxygen radicals. In a proteomic analysis of alfalfa stem exposed to Cd, Gutsch et al. (2018) observed that an abundance of peroxidases and their corresponding genes remained upregulated after stress treatment. Additionally, soybean and lupin exposed to 15–25 mg Cd kg⁻¹ and 150–350 mg Pb kg⁻¹ induced phenylalanine ammonia-lyase activities. However, the increase did not correlate with the induction of gene expression and lignin accumulation in lupin (Pawlak-Sprada et al. 2011). Thus, this indicates the presence of transcriptional and posttranscriptional regulation and involvement of activated phenylpropanoid pathway in the synthesis of secondary metabolites than lignin building blocks.

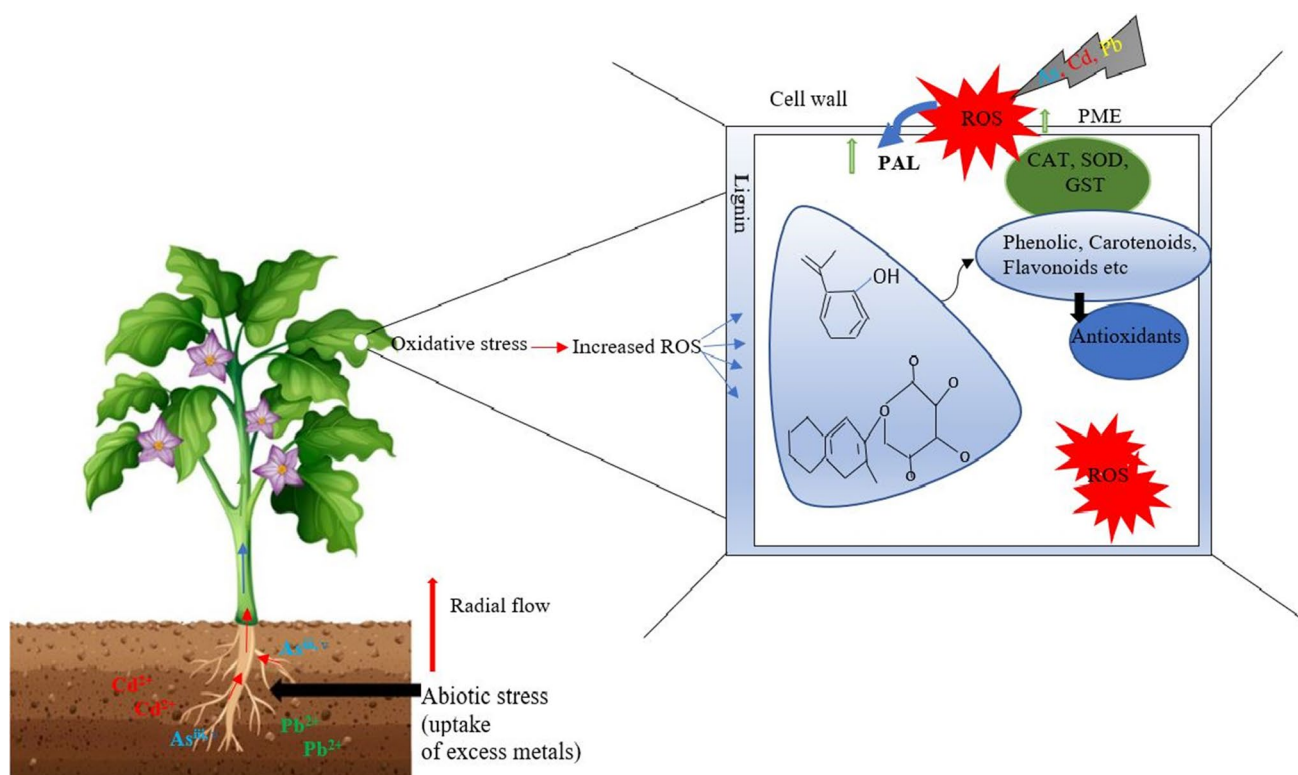


Fig. 4 Processes involved in the formation of plant secondary metabolite under heavy metal stress. The stress triggers a ROS burst, which exerts an induction on phenylalanine ammonia-lyase (PAL) (stress-responsive enzymes). The phenylpropanoid pathway is boosted with the subsequent production of, e.g., phenolic acids and flavonoids. These secondary metabolites, together with the enzymatic antioxidant

system, contribute to counterbalancing ROS. At the cell, an increased lignification is observed, as well as a modification of the pectins (increase in acidic pectins) which can sequester risk elements through the “box” structure. *PME*: pectin methylesterase; *SOD*: superoxide dismutase; *GST*: glutathione-*S*-transferase; *CAT*: catalase (adapted and modified from Berni et al. 2018)

Impact of excess Cd, As, and Pb on secondary plant metabolites

Plants exposed to excess Cd, As, and Pb exhibit a marked effect on metabolic activities. Excess Pb destroys chloroplast ultrastructure, prevents electron and nutrient transport, and seizes CO₂ entry by stomatal closure (Srivastava et al. 2014; Kumar et al. 2015).

Cadmium Cadmium phytotoxicity has inhibitory effects on the metabolism of some micro-nutrients, photosynthesis, disturbs transpiration, and fixation of CO₂ (Prasad 2005). Under an increasing concentration of Cd, different plant species exhibit differential accumulations of specific metabolites. For example, a high Cd load of 83 mg kg⁻¹ caused an increase in proline levels in *Drimys elata* Jacq. (Okem et al. 2015). In *D. elata* bulbs, Okem et al. (2015) reported a reduction in chlorophyll, phenolic, and flavonoid concentrations under increasing Cd loads. Reduced chlorophyll content under Cd stress affects plant physiology, as photosynthetic electron transport processes are altered, suppressing energy transformation (Paunov et al. 2018) and microbial activities.

The low phenolic and flavonoid levels can partly result from the sudden halt of electron transport. Meanwhile, decreased secondary metabolite levels under the risk element stress of plants result in poor antimicrobial activity (Ibrahim et al. 2017).

Under the same loads of excess risk elements, plants exert differential accumulation and production of specific metabolites. In the analysis of metabolic profiles of two *Cynodon dactylon* L. genotypes exposed to the same level of Cd stress, Xie et al. (2014) recorded different levels of amino acids (glutamic acid, gulonic acid, glycine, norvaline, proline, serine, and threonine), organic acids (citric, glyceric, malic, and oxoglutaric acids), and sugars (galactose, talose, and xylulose). The differential accumulations indicate different tolerance to Cd by the two genotypes, especially in the case of proline production. Notably, the reduction of some acids during Cd stress, e.g., aspartic acid, regardless of plant species and genotype, partly relates to the buffering effects through modulations of other amino acids (Chaffei et al. 2004; Xu et al. 2012).

In plants, proline production represents the most common stress marker, vital in alleviating Cd toxicity (Kishor et al. 2005; Liang et al. 2013). During risk element detoxification, proline scavenges ROS and forms chelates, which increase glutathione and protect antioxidant enzyme activities (Perveen et al. 2012). Proline synthesis often occurs in plants' leaves as organs for the photoactivation of vital enzymes (Arora and Saradhi 1995). Additionally, proline can act as an osmoprotectant when plants are stressed. In this case, proline offsets water deficit during metal stress in many plants by

stomatal closure. Notable, this inactivates processes: metal translocation and transpiration (Liang et al. 2013). Hence, what then becomes the fate of plants and other metabolites on increasing loads of risk elements? However, increased or decreased metabolites under stress from risk elements are a symptom of damage. Thus, metabolites need critical elemental analysis before use. Consumable metabolites can contain <0.3 mg kg⁻¹ Cd, according to WHO (2007), to avoid detrimental health effects on humans.

Stress induced by, e.g., drought and risk elements in plants can regulate the biosynthesis of amino acids (Curtis et al. 2018). The biosynthesis and accumulation of asparagine, an amino acid derivative, represent an example of a Cd stress plant (Okem et al. 2015). Asparagine provides a high N:C used by plants as an N storage compound to ensure future recovery (Chaffei et al. 2004). Meanwhile, high asparagine can participate in detoxification processes or the biosynthetic way of chelating peptides (Costa and Spitz 1997). Some secondary metabolites are involved in stress defense, e.g., isoprenoids, phenylpropanoids, alkaloids, or polypeptide pathways (Dixon 2001). Xu et al. (2012) found an accumulation of branched-chain amino acids (e.g., isoleucine and valine) in *Solanum nigrum* L. roots under high Cd accumulation and tolerance. However, under Cd stress, isoleucine and valine contents can increase for Cd-sensitive plants but unchanged for Cd-tolerant (Okem et al. 2015), suggesting that two different stress defense pathways exist in different genotypes. According to Mahajan et al. (2020), Cd increases diosgenin content in *Trigonella foenum-graecum* L. The accumulation of sesquiterpenoids (lubimin and 3-hydroxylubimin) is high in *Datura stramonium* L. treated with Cd salts (Furze et al., 1991).

Arsenic The most dangerous biochemical effect of As at the subcellular level is the production of ROS. Under As stress, many plants show changes in metabolome and reduce trends within the chloroplast, e.g., fronds of the hyperaccumulator plant *Pteris cretica* L. (Zemanová et al. 2020). Melato et al. (2012) reported a decrease of > 35% in the length of *Chrysopogon zizanioides* L. plants treated with As compared to an identical plant without As stress. Total soluble phenolic content in *C. zizanioides* increased with an increasing concentrations of As, Cr, Cu, Ni, Pb, and Zn in the growth medium. During As uptake by plants, some of the As^V taken up by cells eventually convert to As^{III} employing arsenate reductase (Kalita et al. 2018). The As^{III} forms a complex with thiol groups in proteins, inhibiting arsenate reductase activities (Hu et al. 2020). Thus, excess As^{III} may probably be more deleterious to the quality of secondary metabolite. However, this is so far not well-studied.

Plants produce secondary metabolites as a response to adaptation. The accumulation of metabolites can represent a function of increasing environmental (abiotic) stress

conditions. For example, *Withania somnifera* L. plants tolerated high concentrations of trivalent/tetravalent As species until 5 and 10 days by increasing antioxidant enzymes and synthesis of thiols, especially in the roots (Siddiqui et al. 2015). Phenolics and flavonoids can scavenge active oxygen species due to their ability to donate H atoms or electrons (Okem et al. 2015). In a combined application of methyl jasmonate to As-stressed, *B. napus* increased leaf chlorophyll fluorescence, biomass production, and reduced malondialdehyde content, compared to the same plant under only As stress (Farooq Muhammad et al. 2016). Methyl jasmonate regulates plant defense against abiotic stress and produces antioxidants and secondary metabolites (Ahmed et al. 2015). Under induced methyl jasmonate, As-stressed *B. napus* cultivars observed enhanced phenylalanine ammonia-lyase, polyphenol peroxidase, and antioxidants (Farooq Muhammad et al. 2016). These compounds stimulate the phenylpropanoid pathway and produce derivatives such as phenols and flavonoids, which play a vital role in minimizing oxidative stress and As concentration in active reproductive parts, e.g., root and leaf (Wang et al. 2011).

Lead Lead toxicity inhibits ATP production, lipid peroxidation, and DNA damage by ROS over-production (Hou et al. 2018; Melato et al. 2012).

Plants exhibit defense mechanisms to cope under Pb stress, e.g., reduced uptake into cells, sequestration into vacuoles by forming complexes, binding by phytochelators, glutathione, and amino acids, including the synthesis of osmolytes (Yuan et al. 2015). Notwithstanding, Pb affects photosynthetic mechanisms by inhibiting enzyme activities such as δ -aminolaevulinic acid dehydratase (Gupta et al. 2009; Cenkci et al. 2010) involved in enzymatic pathways of photosynthetic pigments. Inhibition of chlorophyll biosynthesis leads to reductions in pigment contents and alteration in chlorophyll fluorescence (Hou et al. 2018). An increase in phenolic content in *Phaseolus vulgaris* (Wall.) with increasing Pb concentrations indicated the prevention of oxidative damage by scavenging active oxygen species and breaking the radical chain reactions during lipid peroxidation.

Metabolomics often is dedicated to a comprehensive analysis of organic metabolites within cells and tissues. Due to the beneficial properties of metabolites, the interest in characterization and quantification is pertinent, resulting in the identification and usage of different instrumental methods. Different physicochemical methods are applicable in analyzing plant metabolites (Table 2). Moreover, the application of elicitors in plant cultures triggers the large-scale production of secondary metabolites and is vital in the pharmaceutical and therapeutic industries. The selection of sites for unpolluted soils needs close monitoring to ensure the safety and efficacy of cultivated plants.

Conclusions

The study revealed that high levels of risk elements above permissible limits in soils affect the metabolic activities of plants, including the production of secondary metabolites after the uptake of Cd, As, and Pb. The accumulation of risk elements is associated with different plant tissues according to their functions: (i) absorbing tissues responsible for the entry of Cd, As, and Pb from soils through root rhizoderm; (ii) without competing ions, risk elements flow through soils into roots in all root zones. However, tissues functioning as barriers (e.g., Casparian strips) restrict the radial transport in roots. Meanwhile, these appear in mature cells, with modifications of cell walls for some metals; (iii) and finally, to the metal-accumulating and metal-containing tissues, plants uptake only accessible Cd, As, and Pb in exchange complexes (organic and inorganic components) and soluble fractions in the soil solution. However, the mobility and bioavailability of the risk elements to plants often get eased by factors such as pH, redox condition, DOC, clay content, and metal oxides.

Plants counteract the toxic effects of Cd, As, and Pb by engaging antioxidant enzymes and proline, glutathione, and phenolic compound production to protect them against free radicals and biomolecule damage. Phytotoxicity by risk elements has inhibitory effects on the metabolism of nutrient photosynthesis, disturbs transpiration, and fixation of CO₂. Excess risk elements cause chlorophyll reduction, increased free proline, and secondary metabolites (e.g., phenolics, flavonoids, alkaloids, and terpenes).

Decreased plant secondary metabolite contents result in poor antimicrobial activities of plants grown on risk element-contaminated sites. Risk element contamination of soils alters the physicochemical state of plants as they adapt to stress conditions. Eventually, excess risk elements affect the synthesis of secondary metabolites, consequently influencing the quality and efficacy of medicinal products by decreasing antimicrobial properties.

Knowledge gap

Limited information exists on specific physiological responses of medicinal plants to heavy metals in soils and the resulting changes in the efficacy of plant metabolites. With the increasing rate of metalliferous activities, many plants, including medicinal herbs, can accumulate a high concentration of metals. However, there are many existing gaps on the effects of other metal-(loid)s, e.g., Au, Ag, Ni, and Hg, with little or no detailed proteomic analysis of secondary metabolites and their derivatives developed

Table 2 The effect of risk elements on plant secondary metabolites and their respective analytical methods for their analysis

Plant	Metabolites	Risk elements	Plant part	Effect on metabolite	Analytical technique	Reference
<i>Chrysopsisgon zizantoides</i> L	Phenolic	As, Cr, Cu, Ni, Pb, and Zn	Leaves	Total soluble phenolics, free phenolic acids, and cell wall-bound phenolic content exhibited a linear correlation with increasing metal concentrations	Phenolic content estimation with Folin-Ciocalteu, a colorimetric method based, using gallic acid as a standard phenolic compound. Spectramax 190 microplate reader (Molecular Devices, Sunnyvale, USA)	Melato et al. (2012)
<i>Gynura procumbens</i> Lour	Phenolics, flavonoids, and total saponin content	Cd and Cu	A dry weight of leaves	Reduced production of total phenolics, flavonoids, and saponin under combined Cd and Cu treatment	Folin-Ciocalteu reagent (Kanto Chemical, Osaka, Japan) for determining the total phenolic content. Determination of total flavonoids using a spectrophotometer with rutin as a standard. Total saponin content determined in leaves using a vanillin-sulfuric acid colorimetric reaction	Ibrahim et al. (2017)
<i>Drimia elata</i> Jacq	Total phenolic and flavonoid contents	Cd and Al	Bulb samples	Reduction in chlorophyll, phenolic, and flavonoid contents in plants exposed to increasing concentrations of Cd and Al	Total phenolic determined using the Folin-Ciocalteu (Folin C) assay. Total flavonoid determined by vanillin assay	Okem et al. (2015)
<i>Andrographis paniculata</i> (Burm. Fil.)	Andrographolide	As	Stem	Andrographolide is high for tolerant plants. Metabolic changes significantly in control and As ₂ O ₃ -treated plant samples	HPLC analysis, 1D ¹ H NMR spectroscopy	Vijayakumar et al. (2017)
<i>Datura stramonium</i> L	Lubimin, 3-hydroxylubimin	Cd	Root	Increased content of metabolite	-	Furze et al. (1991)
<i>Phyllanthus amarus</i> Schum. and Thonn	Phyllanthin and hypophyllanthin	Cd	Root and shoot	Decreased content of metabolite	Scanning electron microscopic and thin-layer chromatography	Rai et al. (2005)

HPLC high-performance liquid chromatography

by plants in affected areas. Finally, the optimization of both As^{III} and As^V species determine the intensity of their deleterious effects on secondary metabolites, especially medicinal herbaceous plant species.

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Data availability The authors declare that data supporting the findings of this study are available within the article.

Declarations

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Consent to participate All authors have approved the final version of the manuscript and have given their consent for publication.

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