

REVIEW

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Phytoremediation and ethnomedicinal potential of *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera belonging to the Scrophulariaceae family: a review

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Abstract

A number of species have developed detoxification strategies that allow them to accumulate high amounts of heavy metals in their tissues and grow despite a high heavy metal (HM) concentration in soils. Thus, they are considered hyperaccumulator or accumulator species, attractive for phytoremediation purposes. Families reported to contain a high number of hyperaccumulator species are Asteraceae, Euphorbiaceae, Rubiaceae, Fabaceae, Scrophulariaceae, Myrtaceae, Proteaceae, Caryophyllaceae, and Tiliaceae. Indeed, the family Scrophulariaceae has a large extension, with *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* being some of the best-known genera containing species used for medicinal purposes. This review focuses on identifying the species used in folk medicine that belong to these four genera and can accumulate high concentrations of heavy metals (HMs). Additionally, the human health risks related to the consumption of HM hyperaccumulator species are discussed, as well as the feasibility of plant tissue culture to provide safe vegetal material for medicinal uses or to estimate the intrinsic potential of species for phytoremediation purposes. The following species have demonstrated the ability to accumulate HMs and grow in mine or HM-polluted soils, as well as use in traditional medicine: *Buddleja asiatica*, *B. cordata*, *B. davidii*, *B. lindleyana*, *B. macrostachya*, *B. paniculata*, *B. scordioides*, *Eremophila latrobei*, *Scrophularia canina* subsp. *bicolor*, *S. ningpoensis*, *S. striata*, *Verbascum bombyciferum*, *V. olympicum*, *V. phrygium*, and *V. thapsus*. In some of these species, antioxidant machinery has been proven to participate as a defense strategy against exposure to high HM concentrations. Consuming plants that accumulate high amounts of HMs has been described as a potential risk to human health. Plant tissue culture has also been established in a few of these species, whether to propagate or use them as a bioactive phytochemical source. Promoting safety and quality control related to the HM concentrations in the tissues of these plants used by populations for curative purposes is necessary. Further research must be carried out on several species for phytoremediation purposes.

Keywords Secondary metabolite, Antioxidant, Plant tissue culture, Phenolic compounds, Heavy metal detoxification mechanisms

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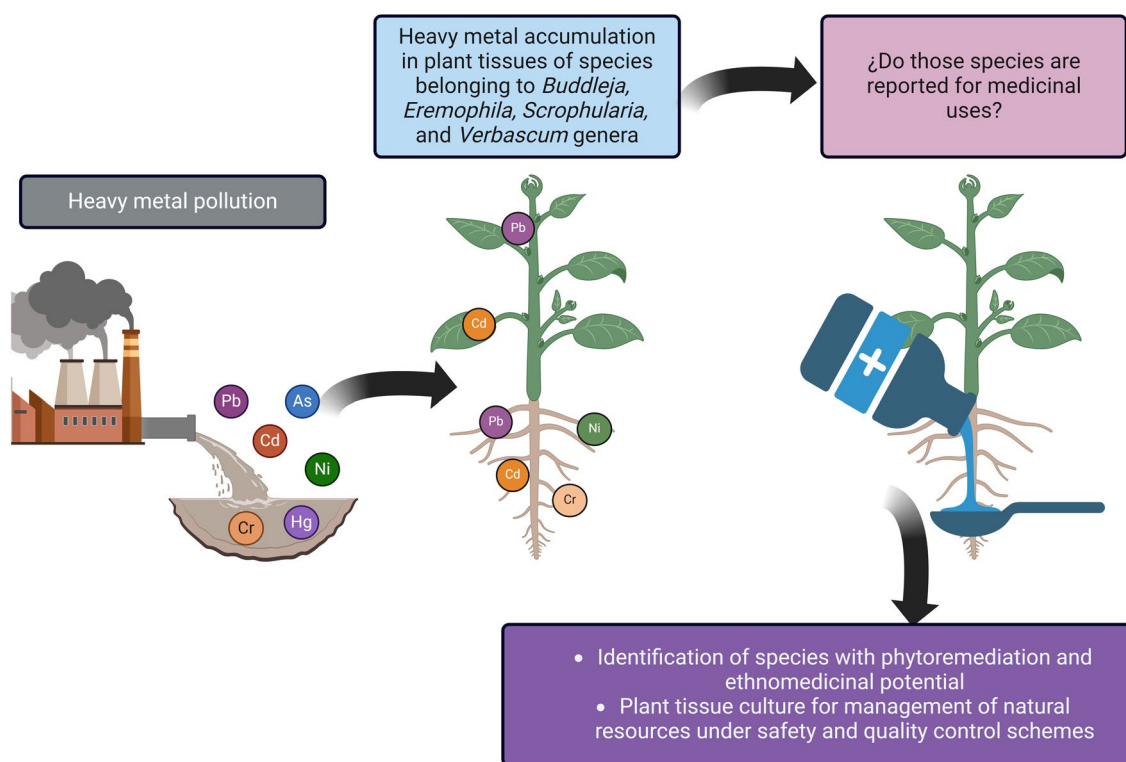
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Graphical abstract



Background

Plants acquire several heavy metals (HMs) from soils that are essential nutrients for their growth and development, such as Cu, Zn, Mn, Co, and Fe [22]; although some HMs are not essential for plants, e.g., Pb and Cd, they can also be uptaken [167]. In both cases, that is, regardless of whether they are essential nutrients, if HMs are present in soil at high levels, they become toxic [22, 167]. At the cellular and molecular levels, HMs may cause the inactivation of enzymes, the denaturation of proteins, the removal or replacement of metals necessary for biomolecules, damage to the structure and the peroxidation of membrane lipids, interruption of oxidation–reduction homeostasis by reactive oxygen species (ROS), and the formation of free radicals [119, 179]. At the same time, these processes are conducive to the activation of antioxidant enzymatic and non-enzymatic machinery and secondary metabolism as a plant defense strategy [30]. If ROS cannot be scavenged, oxidative cellular stress occurs, damaging proteins, lipids, and nucleic acid biomolecules [66, 68, 137].

Anthropogenic activities have caused a surplus of HMs in the atmosphere, and, consequently, they can be

uptaken by and bioaccumulated in plants, animals, and humans [20, 115]. As organisms cannot carry out the necessary processes to excrete HM at excessive levels, it is bioaccumulated in a high concentration in tissues. Thus, HMs become toxic [115]. HMs such as Pb, Hg, As, Cu, Zn, and Cd are highly toxic to humans. They have been related to several diseases and health problems, e.g., auditive loss, intellectual incapacity, behavior alterations, nervous system dysfunction, and cancer [89, 97, 112] (Fig. 1). In plants, HM toxicity manifests as negative changes in physiological processes, such as photosynthesis, cellular respiration, nitrogen metabolism, and mineral nutrition; additionally, decreased biomass and even death can occur [107]. From an ecological perspective, HM toxicity leads to productivity loss, vegetation disappearance, and decreased biodiversity [77].

Nevertheless, some plant species, classified as accumulators or hyperaccumulators, have developed detoxification strategies that enable them to accumulate high amounts of HMs in their tissues and grow despite elevated HM concentrations [88, 100]. Hyperaccumulator species possess an enhanced ability to

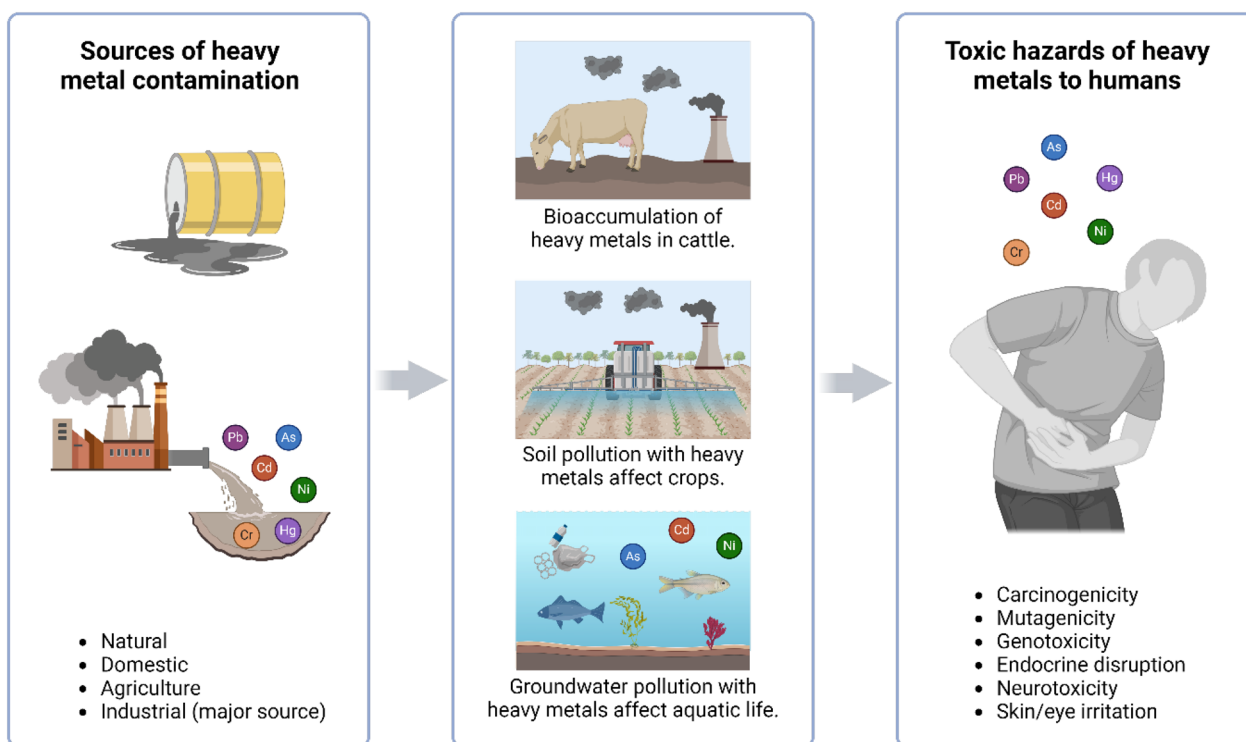


Fig. 1 Source, accumulation, and toxic hazards of heavy metals. Created with BioRender.com from templates (by Samara Ona)

absorb HMs through roots, a highly efficient ability to translocate from roots to shoots, an excellent ability to convert HMs into non-toxic compounds or mitigate their harmful effects, and an outstanding ability to accumulate high amounts of HMs in their leaves [100, 116, 179]. By 2015, 450 hyperaccumulator species had been identified, with a large number of them belonging to the Brassicaceae family. Other families reported to contain a high number of hyperaccumulator species are Asteraceae, Euphorbiaceae, Rubiaceae, Fabaceae, Scrophulariaceae, Myrtaceae, Proteaceae, Caryophyllaceae, and Tiliaceae [160].

Hyperaccumulator plants are suitable for phytoremediation because they reduce high concentrations of HMs and consequently decrease their environmental toxicity [8, 136]. Phytoremediation is a technology that employs biological, chemical, and physics processes by using plants to immobilize and store HMs [97, 146]. Although phytoremediation includes several technologies, such as phytostabilization, phytovolatilization, rizofiltration, phytodegradation, and phytoextraction [42, 89, 101, 117], the latter requires hyperaccumulator species and represents an easy, fast, and environmentally friendly technique for eliminating HMs [22]. From an ecological perspective, the hyperaccumulation ability has gained an outstanding role in some plants in

terms of avoiding herbivory and promoting allelopathy and biotic interactions [97, 131, 162].

The human consumption of accumulator or hyperaccumulator plants has been a concern of the scientific community due to the potential health risks. Plants are recognized in traditional medicine as remedies or alternatives to proper health care, and this practice has gained attention in recent years due to the assumed safety of the use of plants, attributed to the fact that they are natural products [83, 159]. Traditional medicine through herbal remedies is spreading worldwide due to the population's belief that plants possess efficacy and few side effects compared with conventional medicine [184]. Almost 80% of the world's population consumes, directly and indirectly, medicinal plants, which are of importance in rural areas where health facilities are scarce. Medicinal plants are mainly used for skin diseases, gastrointestinal disorders, malaria, infections, and respiratory problems [150]. Traditional herbal formulations used in China and India were analyzed to estimate HM concentrations, and the results showed that they contained Pb, Cd, and Hg at high concentrations [147]. Meanwhile, in the case of *Annona muricata* (guanabana), a plant used for cancer treatment, seven of the most widely used commercial formulations containing this species were determined to be within the permissible limits for HMs [80]. The

identification of medicinal plants that can accumulate HMs in their tissues is a priority. The Scrophulariaceae family is highly acclaimed in traditional medicine because several species are used to alleviate many health disorders; in some species, their therapeutic uses are credited with antioxidant, anti-inflammatory, antimicrobial, and cytotoxic pharmacological activities. The most representative genera of this family are *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* [184]. As the Scrophulariaceae family has been reported to be among the families that contain a high number of hyperaccumulator species [160] and is suitable for medicinal purposes [184], the present work was carried out to identify, through a documental investigation, the capability of medicinal species reported from the four genera of the Scrophulariaceae family to accumulate HMs in high amounts. Thus, data were compiled and summarized. Relevant data up until February 2024 were collected from different databases, such as Scifinder (<https://scifinder.cas.org/scifinder/login>), phytochemistry-related research, PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), and Web of Knowledge (<http://www.webofknowledge.com>), for ethnobotanical, biological, and biotechnological related research. In addition, the potential risk to human health following the consumption of these species and the importance of biotechnology in their sustainable and safe management are discussed.

Hyperaccumulator strategies to counteract HM toxicity

According to the tolerance and limitation strategy used to counteract HM toxicity, plants can be categorized into indicator, excluder, accumulator, and hyperaccumulator species [43]. Indicator plants absorb and translocate HMs to their organs in direct proportion to the HM soil concentration [191]. Excluders restrict HM absorption and transport [191]. Accumulators store (mainly in roots) higher concentrations of HMs than those found in soil and do not show symptoms of toxicity [43, 165]. Hyperaccumulators maintain a greater HM concentration in aerial biomass, between 10- and 500-folds more than that observed in plants grown in unpolluted soils, and they do not exhibit symptoms of toxicity due to the ability to detoxify the effects of HMs [124, 162].

Hyperaccumulator attribution depends on the type of HM or metalloid, e.g., cadmium hyperaccumulator species must concentrate at least 100 mg kg⁻¹ of Cd; 1000 mg kg⁻¹ of As, Co, Cr, Cu, Ni, Pb, and Se; and 10,000 mg kg⁻¹ of Mn and Zn [131, 162, 177]. Hyperaccumulator species can be classified as “obligate” or “facultative”. Obligate hyperaccumulators are found in metalliferous soils, while facultative hyperaccumulators are species with unusual capabilities because they

grow in nonmetalliferous soil [131]. Nearly 450 species belonging to over 45 taxonomic families have been categorized as hyperaccumulator species of different HMs, such as Cd, Cu, Co, Mn, Ni, Pb, Se, Ti, and Zn [100, 129, 131]. In fact, of the total number of hyperaccumulators reported, 25% belong to the Brassicaceae family [47], while other families reported to contain a high number of hyperaccumulator species are Asteraceae, Euphorbiaceae, Rubiaceae, Fabaceae, Scrophulariaceae, Myrtaceae, Proteaceae, Caryophyllaceae, and Tiliaceae [160]. Furthermore, the most important hyperaccumulator species categorized by taxonomic family and element are as follows: Asteraceae for Cu, Co, and Ni; Brassicaceae for Cd, Ni, Pb, and Ti; Crassulaceae for Cd and Zn; Fabaceae for Cu and Se; and Lamiaceae for Cu and Co [131].

From a physiological perspective, the hyperaccumulation process is based on the detoxification mechanisms of HMs, which include a high rate of HM absorption by roots, quick translocation to shoots (Fig. 2), enhanced conversion of HMs to non-toxic compounds through sequestration and compartmentalization, ROS scavenging (Fig. 3), and an outstanding ability to accumulate high amounts of HMs in leaves, all of which are significantly improved compared with those of non-hyperaccumulator species [100, 116, 179]. From cellular and molecular perspectives, these improvements are related to the alteration of gene expression, which could result in the constitutive overexpression of genes associated with various physiological processes, such as those pertaining to the membrane transporters responsible for HM uptake, the translocation and sequestration of HMs, and antioxidant machinery [67, 88, 100, 124, 162].

HM absorption

The bioavailability of HMs in soils is the primary determinant of HM uptake by roots. Under metal deficiency, plants can secrete exudates from roots to increase the absorption of metals; this is mainly related to micronutrient metals, such as Fe, Mn, Cu, and Zn [27]. Root exudates may act as ligands that chelate HMs, as well as influence the pH and Eh conditions in the rhizosphere, consequently affecting the mobility and bioavailability of HMs and, thus, promoting their mobilization in the cell wall [88, 100, 119]. The root exudate composition depends on the stress that occurs, and, in the case of stress conditions caused by HMs, low-molecular-weight exudates (e.g., organic acids, amino acids, phenolic compounds, and sugars) are mainly involved in the absorption of metals [27, 88, 173]. After HMs mobilize to the cell wall, where they can be bound and absorbed by plants through metal membrane transporter proteins, which constitute uptake systems [100, 119]. However, a higher abundance of metal protein transporters has been

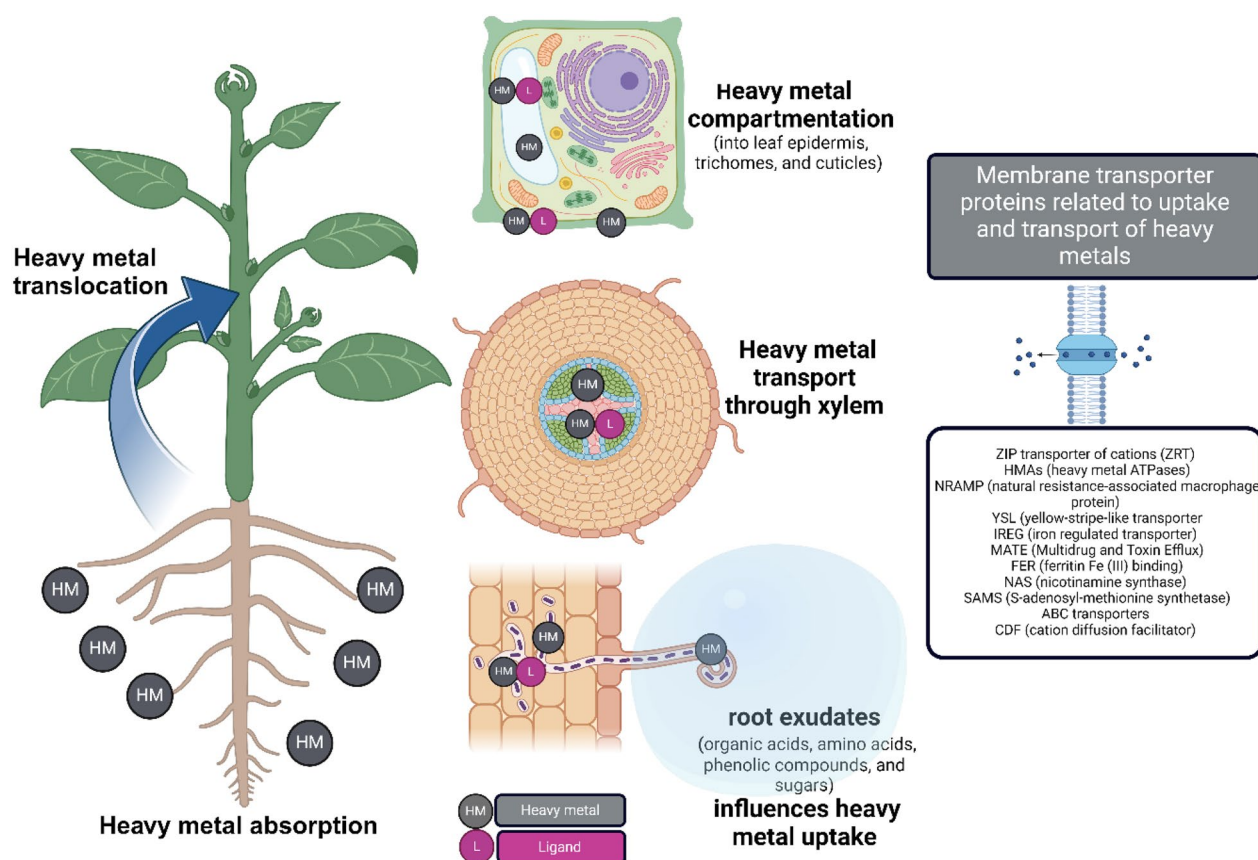


Fig. 2 Heavy metal (HM) absorption by roots and translocation to shoots as HM-detoxifying mechanism in hyperaccumulator plants. Created with BioRender.com

found in HM accumulator species than in non-accumulator species [119]. In addition, the ability to secrete root exudates that increase the solubility, availability, and uptake of HMs is an indication of metal absorption in HM accumulator species [119]. In the hyperaccumulator plant *Sedum alfredii*, Cd stress conditions changed the composition of root exudates, and it was argued that trehalose, erythritol, naphthalene, D-pinitol, and n-octacosane possibly influence Cd stabilization. At the same time, glycine, phosphoric acid, tetradecanoic acid, oxalic acid, and threonic acid could be related to Cd mobilization [92]. Additionally, under Pb enrichment conditions, the exudates of this hyperaccumulator species changed, causing an increase in amino acids (L-alanine and L-proline), organic acids (oxalic and glyceric acids), and some phenolic compounds (4-methylphenol and 2-methoxyphenol) [93]. In *Erigeron annuus*, a hyperaccumulator species, Cd stress promoted the secretion of carbohydrates, lipids, lignins, proteins, aromatic structures, and phenolic compounds such as tannins. Carbohydrates, aromatic structures, and tannins were suggested to be crucial for cadmium tolerance, as they were detected as

new molecules produced under Cd stress; meanwhile, in the control treatment, they were not detected [186]. In the As hyperaccumulator species *Pteris vittata*, the constitutive overexpression of the inorganic phosphate transporter resulted in a higher abundance of protein transporters than in the As non-accumulator *P. tremula* species [125].

HM translocation from roots to shoots

Hyperaccumulator species are characterized by the ability to quickly translocate HMs from roots to shoots via active loading into the xylem. In contrast, accumulator species convert metal ions into non-toxic compounds by binding them to ligands to restrict them in the cytoplasm or vacuoles of root cells [100, 123, 162]; however, it seems that, for hyperaccumulator species, the latter is also important for all trace metals [162]. In hyperaccumulator species, metal ions move into the xylem via symplastic movement; membrane transporter proteins enable this movement [165]. These proteins are abundant because of the constitutive overexpression of genes

Heavy metal conversion to non-toxic compounds

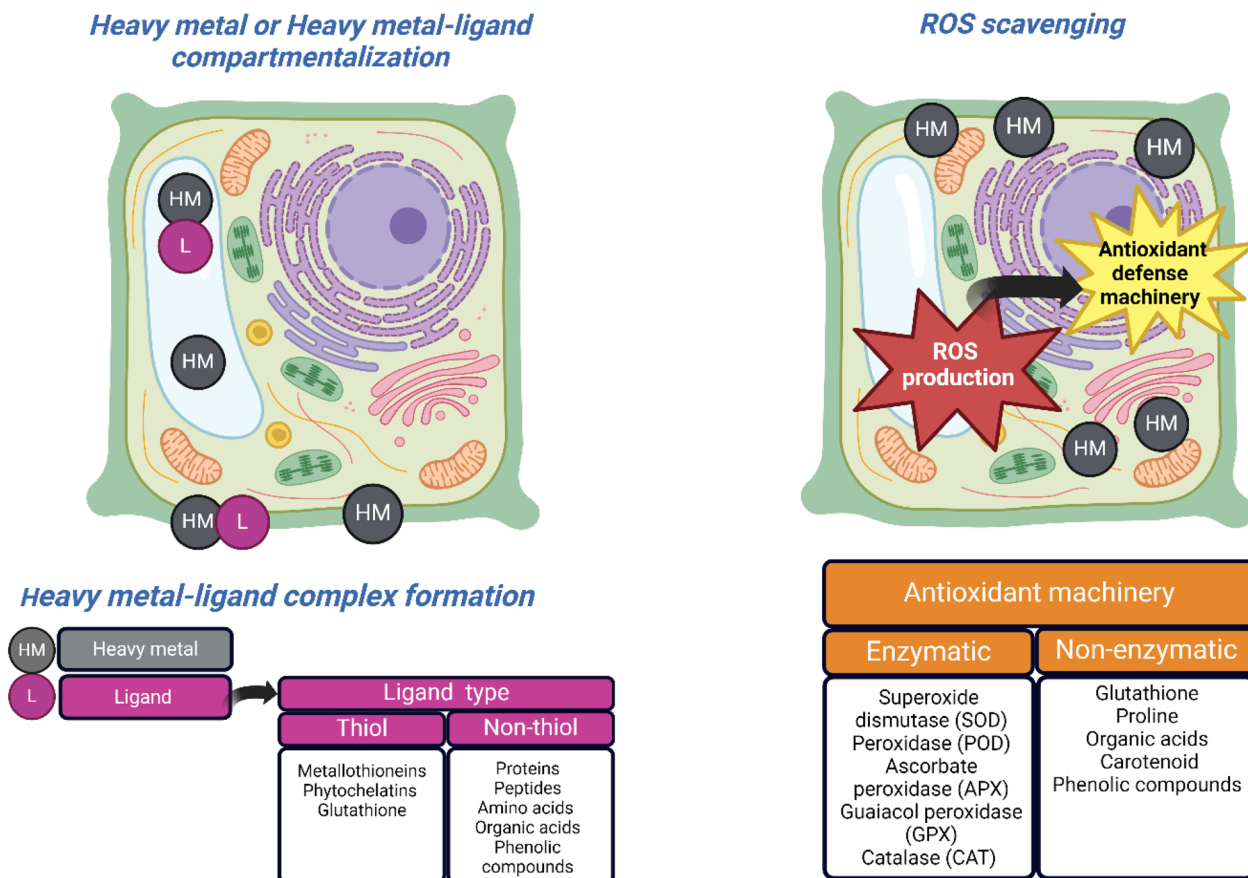


Fig. 3 Heavy metal (HM) conversion to non-toxic compounds and reactive oxygen species (ROS) scavenging as HM-detoxifying mechanism in hyperaccumulator plants. Created with BioRender.com

implied in loading and unloading metals in the xylem [162]. The xylem can transport metal ions or bind them to ligands [171].

HM sequestration and compartmentalization

The conversion of HMs into non-toxic compounds is the most critical detoxifying mechanism in hyperaccumulator species. It depends on how fast HMs can be chelated with ligands or the sequestration of a significant amount of metal ions from the cytoplasm into the vacuoles or cell walls (Fig. 3) of leaf epidermis, trichomes, and cuticles [162]. In plants, most metal ions are bound to proteins or ligands [145]. Type thiol ligands comprise metallothioneins (MTs), phytochelatins (PCs), and glutathione (GSH), while non-thiol ligands include proteins, peptides, amino acids, and organic acids; this latter type has been found to be significant in hyperaccumulator species [14].

MTs are proteins induced in plants under abiotic stress, including stress caused by HM pollution, and there is evidence of their role in HM tolerance [43, 88]. They help counteract HM damage by scavenging ROS, activating the transcription of genes, regulating metalloenzymes [139], helping to repair the plasma membrane [43], and forming metal ion complexes with the thiol groups of cysteines [88]. PCs are peptides synthesized from glutathione by the glutamyl cysteine dipeptidyl transpeptidase enzyme (also known as phytochelatin synthase) [66, 104]. The expression of genes that code for PCs is constitutive, although it can be induced by different metals [156]. The overexpression of such genes has been observed to be an indication of the tolerance and accumulation of HMs [158]. GSH has been determined to play an outstanding role in maintaining ROS homeostasis as a strategy for detoxifying the effects of HMs [52].

Nicotianamine (NA) is a precursor of ligands in grass plants known as phytosiderophores; it is formed by the

condensation of three molecules of S-adenosyl-methionine (SAM), catalyzed by the enzyme nicotianamine synthase (NAS). NA forms complexes with bivalent cations [130] and is involved in Fe homeostasis [34], as well as Fe elimination to prevent oxidative damage to cells under Fe-excess conditions [34].

Histidine is an amino acid that forms Ni, Zn, and Cd complexes. It is considered one of the most essential amino acids for hyperaccumulation [171]. In *Alyssum lesbiacum*, a nickel hyperaccumulator species, the constitutive overexpression of the TP-PRT1 gene leads to enhanced histidine production compared with that in *A. montanum* [130].

Citrate, malate, and oxalate are organic acids that transport HMs through the xylem and sequester HMs into the vacuole [156]. A higher constitutive production of organic acids has been found in hyperaccumulator species than in non-hyperaccumulator species [162].

HMs or HM–ligand chelates can be mobilized in cell walls and vacuoles [130]. In the case of cell wall mobilization, many of them accumulate between the plasma membrane and the cell wall [86] because the latter provides polygalacturonic acid, which acts as a cation exchanger, where HMs can bind to carboxyl groups [43]. The vacuole is the main organelle in cells that stores toxic compounds and compartmentalizes metal ions [111]. The acidic environment of vacuoles favors the formation of organic metal–acid complexes, which facilitate the sequestration of metals in vacuoles by organic acids [162]. In excess HMs, PCs may accumulate in vacuoles, which can be considered an indicator of HM stress [156]. If the final location of HMs or HM–ligands is the vacuoles, then this indicates the involvement of some vacuolar membrane transporter proteins [88]. Pb is a metal that can be localized in cell walls, intercellular spaces, and vacuoles, as observed in the roots of *Symphyotrichum drummondii*. In contrast, in the accumulator plant *Sedum alfredii*, little Pb mobility was detected in the vascular bundles, but more Pb was observed in the cell walls [66]. Approximately 70% of Zn is stored in the vacuoles of the epidermis of the mature leaves of *Noccaea caerulescens*, a Cd/Zn hyperaccumulator species (Lateinmaier 2013).

Some membrane transporter protein genes that have been found to be related to the uptake and translocation process in hyperaccumulator species are those belonging to the ZIP transporter of cations (ZRT), HMAs (heavy metal ATPases), NRAMP (natural resistance-associated macrophage protein), YSL (yellow stripe-like transporter), IREG (iron-regulated transporter), MATE (multidrug and toxin efflux), FER (ferritin Fe (III) binding), NAS (nicotianamine synthase),

SAMS (S-adenosyl-methionine synthetase), ABC transporters, and CDF (cation diffusion facilitator) [88, 100, 123].

The ZIP gene families are involved in the transport of cations such as Fe, Mn, and Zn. In *Arabidopsis*, 18 genes encoding ZIPs involved in Zn mobilization have been found [100]. The efficient translocation of HMs from roots to shoots is due to the overexpression of membrane transport genes encoding P1B-type ATPases, known as HMAs; HMA4 is overexpressed in Zn and Cd hyperaccumulator plants. The FDR3 gene belongs to the MATE family and is expressed in the roots of *Thlaspi caerulescens* and *A. halleri* [130]. The Cd/Zn hyperaccumulator *T. caerulescens* showed increased root-to-shoot translocation and reduced sequestration in root vacuoles compared with the non-accumulator *Thlaspi arvense* (Lateinmaier 2013).

YSL metal transporter plays a crucial role in Fe homeostasis, as well as in long-distance transport of metal–NA transport. In the roots and shoots of *Noccaea caerulescens*, members of the family TcYSL3 and TcYSL5 participated in the loading and translocation of metal–NA complexes [151].

The transport of HMs takes place in xylem flow from roots to shoots and photosynthetic leaves, passing through an interaction with cell walls and the removal of xylem sap, as in the hyperaccumulator *Solanum nigrum*, which transports Cd, Co, and Zn from roots to shoots and then distributes them in the shoots through the phloem [120].

If the final location of HMs or HM–ligand is the vacuoles, then this indicates the involvement of some vacuolar membrane transporter proteins, such as those of the ZIP protein family, ABC transporters, HMAs, NRAMP, and CDF transporters [88, 123]. PC–HM complexes can be transported into vacuoles by metal/H⁺ antiporters or ABC transporters [43]. NRAMP mobilizes ions such as Cu, Mn, Co, Fe, and Cd; NRAMP3 and NRAMP4 are localized in the tonoplast and control Fe export in germinating seed vacuoles [123].

ROS scavenging

Under high-concentration HM exposure, ROS production is induced. ROS include superoxide O₂^{•−}, hydroxyl radical OH[•], oxygen O₂^{•−}, and hydrogen peroxide H₂O₂. These molecules act as signals to activate plant defense mechanisms, and, in turn, they must be scavenged due to their high reactivity [30, 68]. The antioxidant machinery of plants that scavenge ROS comprises enzymatic and non-enzymatic mechanisms (Fig. 3). In hyperaccumulator species, enhanced antioxidant machinery has been observed compared with that in non-hyperaccumulator species [96]. The former includes the

activity of superoxide dismutase (SOD), peroxidase (POD), ascorbate peroxidase (APX), guaiacol peroxidase (GPX), and catalase (CAT) enzymes. SOD is the first enzyme that counteracts ROS, and it catalyzes the reaction O_2^- to H_2O_2 ; afterward, this H_2O_2 product is used as a substrate for the CAT, APX, and GPX peroxidase enzymes to produce H_2O [69]. H_2O_2 elimination is crucial because it can diffuse between cell membranes. Although H_2O_2 is considered to have low toxicity, its interaction with transition metals can lead to the formation of OH^- radicals, which are highly reactive molecules that can cause severe damage to cells [143]. Non-enzymatic mechanisms include organic compounds able to scavenge ROS, such as GSH; ascorbic acid; α -tocopherol; osmolytes, such as proline; non-protein amino acids; and secondary metabolites, e.g., phenolic compounds and carotenoids [30]. All these compounds contribute to the adaptation and survival of plants under stress conditions by representing a strategy that balances ROS production [39, 180]. Ascorbic acid can donate electrons in several enzymatic and non-enzymatic reactions. Meanwhile, GSH is a precursor of PCs and regenerates other antioxidants (e.g., ascorbic acid) [61]. Ascorbic acid and GSH are potential water-soluble antioxidants because both are powerful ROS scavengers and donate electrons to the peroxidase enzymes APX and GSH, respectively [52, 61].

Secondary metabolites

Secondary metabolites are a defense mechanism in plants; under biotic or abiotic stress, their biosynthesis and accumulation may prevent and reduce damage [105]. This is largely attributed to the antioxidant effect, where carotenoids, saponins, and phenolic compounds are highlighted [23, 39]. Phenolic compounds' antioxidant capacity has been related to their roles as hydrogen or electron donors, in metal chelation, and in the prevention of free radical formation [174]. In addition, it was found that HMs interact with enzymes that produce phenolic compounds, and, consequently, the accumulation of phenolic compounds could be observed [150]. One of the most abundant secondary metabolites is phenolic compounds, as they are involved in lignin biosynthesis [33]. Excess copper increased the stimulation of the enzyme cinnamyl alcohol dehydrogenase (CAD), which increased lignin formation and, thus, played an important role in the tolerance to excess HMs [87].

However, GPX also contributes to lignin biosynthesis by constituting a physical barrier against HMs [128]. Compared with a control, the accumulation of Cd, Cu, and Pb in *Zea mays* increased the content of total phenolic compounds, mainly rutin and chlorogenic acid; the latter is a potent antioxidant and is increased by the presence of HMs [85]. In *Kandelia obovata*, Cd tolerance

was evaluated, and, at a higher concentration (20 mg/kg), the content of phenolic compounds in roots (36.6%) and leaves (18.2%) increased compared with that in a control. This increase in phenolic compounds in both organs indicates the ability to translocate and chelate HMs. In addition, SKDH (Shikimate 5-dehydrogenase) and CAD enzymes related to lignin production increased, suggesting that the cell wall's resistance increases the physical barrier against HMs [40].

Phytoremediation and ethnomedicine of *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera, belonging to *Scrophulariaceae*

The family Scrophulariaceae has a large extension, represented by 220 genera and 4800 species. Some of the best-known genera are *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* because they include several species used for medicinal purposes [122, 184]. However, as the Scrophulariaceae family has been reported to be among the families that contain a significant number of hyperaccumulator species [160] and is suitable for medicinal purposes [184], the following analysis focuses on the species within this family that possess the ability to tolerate or accumulate HMs (Table 1); additionally, their antioxidant machinery as a detoxifying mechanism (Table 2) and their medicinal uses (Table 3) are examined.

Buddleja genus

Buddleja comprises nearly 125 species, exhibiting wide diversity in terms of inflorescence and flowers; a wide distribution; and growth in tropical, subtropical, and temperate zones. They are mainly found in Asia, Africa, and America [37, 56]. The main centers of diversity in America are the Andes, Brazil, Mexico, and Central America [56], reporting about 50 native species [172]. Some species are used in traditional medicine, such as *B. americana*, *B. asiatica*, *B. cordata*, *B. crispa*, *B. davidii*, *B. globosa*, *B. japonica*, *B. lindleyana*, *B. madagascariensis*, *B. officinalis*, *B. parviflora*, *B. perfoliata*, *B. saligna*, *B. scordioides*, *B. sessiliflora*, and *B. yunnanensis*, and some of them are used to treat diseases or illness, such as ulcers, conjunctivitis, skin disorders, infections, hemorrhages, gastrointestinal disorders, and heart disorders, as well as having analgesic effects [56, 84]. The secondary metabolites to which their medicinal properties are attributed correspond to monoterpenes, sesquiterpenes, diterpenes, triterpenes, iridoids, steroids, saponins, flavonoids, and phenylpropanoids [56, 84]. The species of this genus tend to grow on roadsides, in abandoned areas, and in contaminated soils [63]. Some species can accumulate or tolerate HMs, such as *B. asiatica*, *B. cordata*, *B. davidii*, *B. lindleyana*, *B. macrostachya*, *B. paniculata*, and *B.*

Table 1 Phytoremediation potential of species belonging to the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera

Species	Growth conditions	Heavy metal concentration			Observations related to phytoremediation		References
		Heavy metal	HM source in mg kg ⁻¹ , mg L ⁻¹ , or μM	Aerial part, mg kg ⁻¹ (organ)	Root, mg kg ⁻¹		
<i>Buddleja</i> genus <i>B. asiatica</i>	Wild plants extracted from Bo Ngam Pb mine, Thailand	Pb	85,640 mg kg ⁻¹	2187 (leaf)	1765	Pb hyperaccumulator	[135]
			206,153 mg kg ⁻¹	4336 (leaf)	2655	Pb hyperaccumulator	[175]
	Wild plants extracted from Bo Ngam Pb mine, Thailand, propagated via stem cutting and grown in hydroponic culture for 15 d	Cd	0.5 mg L ⁻¹	10 (shoot)	463		
		Pb	20 mg L ⁻¹	572 (shoot)	21,667		
		Zn	20 mg L ⁻¹	100 (shoot)	2178		
	Wild plants extracted from Bo Ngam Pb mine, Thailand, grown for 3 months in pots containing soil from Bo Ngam Pb mine, Thailand	Pb	89,084 mg kg ⁻¹	399 (shoot)	3326		
	Plants were collected at Honghe University, China; propagated; and transplanted to soil enriched with Cd	Cd	200 mg kg ⁻¹	28 (leaf); 26 (stem)	76	Cd-hypertolerant	[63]
<i>B. cordata</i>	Wild plants grown in a Cr salt-producing factory, China	Cd	5 mg kg ⁻¹	0.46 (shoot)	0.71	Ability to accumulate HMs	[180]
		Cr	846 mg kg ⁻¹	31 (shoot)	571		
		Cu	141 mg kg ⁻¹	30 (shoot)	240		
		Hg	0.02 mg kg ⁻¹	0.04 (shoot)	0.01		
		Ni	99 mg kg ⁻¹	4 (shoot)	30		
		Pb	70 mg kg ⁻¹	7 (shoot)	23		
		Zn	208 mg kg ⁻¹	103 (shoot)	715		
	Wild plants grown in ultramafic soil in Guanajuato, Mexico	Ca	9 mg kg ⁻¹	6889 (leaf)		Ability to grow in ultramafic soil	[114]
		Co	60 mg kg ⁻¹	1.2 (leaf)			
		Fe	47 mg kg ⁻¹	1788 (leaf)			
		Mg	32 mg kg ⁻¹	4481 (leaf)			
		Mn	736 mg kg ⁻¹	22 (leaf)			
		Ni	274 mg kg ⁻¹	10 (leaf)			
		Zn	53 mg kg ⁻¹	13.6 (leaf)			

Table 1 (continued)

Species	Growth conditions	Heavy metal concentration			Observations related to phytoremediation		References
		Heavy metal	HM source in mg kg ⁻¹ , mg L ⁻¹ , or μM	Aerial part, mg kg ⁻¹ (organ)	Root, mg kg ⁻¹		
<i>B. davidii</i>	Wild plants grown in Sb deposit area in Hunan, China	Sb	5950 mg kg ⁻¹	NR	42	Sb-tolerant	[126]
		Bi	1672 mg kg ⁻¹	NR	2877	High tolerance to Bi	[176]
	Wild plants grown near Pb–Zn mine, China	Cd	13 mg kg ⁻¹	18 (leaf); 8 (stem)	15	Ability to grow in the Pb–Zn mine	[191]
		Cr	102 mg kg ⁻¹	2 (leaf); 6 (stem)	17		
		Cu	278 mg kg ⁻¹	36 (leaf); 12 (stem)	28		
<i>B. lindleyana</i>	Wild plants grown in coalmine wasteland, China	Ni	34 mg kg ⁻¹	5 (leaf); 5 (stem)	9	Good adaptability to grow in substrate of mine containing HMs	[190]
		Pb	3839 mg kg ⁻¹	35 (leaf); 45 (stem)	178		
		Zn	2190 mg kg ⁻¹	1709 (leaf); 711 (stem)	1423		
		Cd	3 mg kg ⁻¹	17 (shoot)	17		
		Cr	168 mg kg ⁻¹	184 (shoot)	160		
		Cu	456 mg kg ⁻¹	495 (shoot)	709		
		Mn	447 mg kg ⁻¹	1029 (shoot)	2230		
		Pb	68 mg kg ⁻¹	123 (shoot)	322		
		Zn	87 mg kg ⁻¹	1404 (shoot)	2293		
		Cd	200 mg kg ⁻¹	5 (leaf); 32 (stem)	184		
<i>B. macrostachya</i>	Seedlings grown in pots for 90 days					Cd-hypertolerant	[63]
<i>B. paniculata</i>	Plant purchased, propagated via stem cutting, and grown in hydroponic culture for 15 d	Cd	0.5 mg L ⁻¹	6 (shoot)	354	Pb hyperaccumulator	[175]
		Pb	20 mg L ⁻¹	132 (shoot)	13,517		
		Zn	20 mg L ⁻¹	129 (shoot)	13,517		
		Pb	89,084 mg kg ⁻¹	353 (shoot)	2510		
<i>B. scandioides</i>	Wild plants grown in mine in Zacatecas, Mexico					Tolerant to and accumulates Pb	[144]
<i>Eremophila</i> genus							

Table 1 (continued)

Species	Growth conditions	Heavy metal concentration			Observations related to phytoremediation	References	
		Heavy metal	HM source in mg kg ⁻¹ , mg L ⁻¹ , or μM	Aerial part, mg kg ⁻¹ (organ)			Root, mg kg ⁻¹
<i>E. latrobei</i>	Wild plants grown in Pb–Zn gossans, northwest Queensland, Australia	Ag	0.9 mg kg ⁻¹	0.07 (shoot)	NR	Ability to grow in Pb–Zn gossans [91]	
		Cd	3.7 mg kg ⁻¹	4 (shoot)	NR		
		Co	84 mg kg ⁻¹	0.6 (shoot)	NR		
		Cu	570 mg kg ⁻¹	15 (shoot)	NR		
		Ni	33 mg kg ⁻¹	2.8 (shoot)	NR		
		Pb	1000 mg kg ⁻¹	7.3 (shoot)	NR		
<i>Scrophularia</i> genus	Wild plants grown in Campo Pisano, Italy	Pb	3258 mg kg ⁻¹	119 (shoot)	NR	Tolerant to high Pb and Zn concentrations [35]	
		Zn	12,038 mg kg ⁻¹	1190 (shoot)	NR		
		Pb	2723 mg kg ⁻¹ + zeolite	240 (shoot)*	2936		Pb accumulation [26]
		Zn	11,472 mg kg ⁻¹ + zeolite	1100 (shoot)*	5968		
		Mn	1000 mg kg ⁻¹ *	175 (leaf); 50 (stem)*	25*		Shoots accumulate HMs, especially high amounts of Fe [64]
		Fe	35,000 mg kg ⁻¹ *	1250 (leaf); 500 (stem)*	250*		
<i>S. ningpoensis</i>	Wild plants grown in Daozhen, China	Co	16 mg kg ⁻¹ *	0.6 (leaf); 0.4 (stem)*	0.3*		
		Zn	5 mg kg ⁻¹ *	0.4 (leaf); 0.2 (stem)*	0.17*		
		As	25 mg kg ⁻¹ *	1.25 (leaf); 0.5 (stem)*	0.25*		
		Pb	65 mg kg ⁻¹ *	15 (leaf); 0.25 (stem)*	0.1*		
		Fe	9198 mg kg ⁻¹	215 (shoot)	ND	Pb phytostabilizer [118]	
		Pb	6847 mg kg ⁻¹	6270 (shoot)	577		
<i>S. scoparia</i>	Wild plants grown in Pb–Zn mine in Hamedan, Iran	Zn	3638 mg kg ⁻¹	68 (shoot)	341		
		Mn	751 mg kg ⁻¹	386 (shoot)	36		
<i>Verbascum</i> genus	Wild plants grown in Brusa, Turkey	Cd	0.8 mg kg ⁻¹	1.2 (shoot)	0.65	Bioindicator and accumulator of Cd, Cu, Cr, Ni, and Pb [19]	
		Cr	71.0 mg kg ⁻¹	94.1 (shoot)	36.75		
		Cu	46.5 mg kg ⁻¹	21.0 (shoot)	2.19		
		Fe	37.5 mg kg ⁻¹	30 (shoot)	16.7		
		Ni	20.0 mg kg ⁻¹	23.4 (shoot)	11.4		
		Pb	22.0 mg kg ⁻¹	41.2 (shoot)	35.0		
		Zn	14.6 mg kg ⁻¹	22.2 (shoot)	8.3		

Table 1 (continued)

Species	Growth conditions	Heavy metal concentration			Observations related to phyto remediation		References
		Heavy metal	HM source in mg kg ⁻¹ , mg L ⁻¹ , or μM	Aerial part, mg kg ⁻¹ (organ)	Root, mg kg ⁻¹		
<i>V. olympicum</i>	Seeds were collected from the alpine belt of Uludag Mountain, Turkey, and grown in pots with Cd solution for 7 days	Cd	250 μM	580 (leaf)	4857	Accumulates and tolerant to Cd	[18]
<i>V. phnygium</i>	Mature seeds were collected from Murat Dağı Mountain, Turkey, and grown in pots with Zn solution for 7 days	Zn	30 mg L ⁻¹	2181 (leaf)	17,044	Plant highly tolerant to Zn	[3]
<i>V. thapsus</i>	Wild plants grown in Gümüşköy Ag deposit, Turkey	As	12,685 mg kg ⁻¹	3551 (shoot)	10,400	Could be used to remediate soils and areas contaminated by As and Ag	[182]
		Ag	38,26 mg kg ⁻¹	11.2 (shoot)	10.5		
		Pb	5213 mg kg ⁻¹	537 (shoot)	643		
		Ti	29 mg kg ⁻¹	65	194		
		Cu	375 mg L ⁻¹	493	448		
	Seeds were prepared from the Pakan Bazır Company and grown in hydroponic culture for 14 d					Could be used for remediation of soil contaminated by Ti	[148]
						Could be used as a plant species for Cu phytoextraction, is a Cu hyperaccumulator	[82]

In most cases, data shown in this table were rounded off from those described in the corresponding reference
ND not detected; NR not reported
*The data shown are an approximation according to visual observation of histogram graphic's references

Table 2 Activity of enzymes and changes in non-enzymatic antioxidant machinery of species belonging to *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbasicum* genera in response to HM exposure

Species	HM	Organ	Activity of antioxidant enzymes				GPX	Non-enzymatic antioxidant responses	References
			SOD	CAT	POD	APX			
<i>B. asiatica</i>	Cd exposure for 90 d	Leaves	25, 50, and 200 μM Cd decreased SOD activity (392 vs. 300, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)*	100 μM Cd increased CAT activity (0.7 U vs. 0.9, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)*	25 μM Cd increased POD activity (100 vs. 137, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)*				[63]
		Leaves	SOD activity was not affected by Cd treatment	CAT activity decreased by 100 μM Cd treatment (0.6 vs. 0.2, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)*	200 μM Cd increased POD activity (1000 vs. 2002, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)*				
<i>B. macrostachya</i>	Cd exposure for 3 d	Roots	400 μM Cd increased SOD activity (2.7 vs. 5.7, $\text{U g}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)	400 μM Cd increased SOD activity (18.3 vs. 36.4, $\mu\text{mol H}_2\text{O}_2 \text{mg}^{-1} \text{min}^{-1}$, control vs. Cd treatment, respectively)				400 μM Cd increased TAL and PAL activities. Salicylic acid, p-coumaric acid, ferulic acid, echinacoside, and acteoside concentrations increased	[31]
		Shoots	250 mg L^{-1} Pb increased SOD activity	250 mg L^{-1} Pb increased CAT activity	250 mg L^{-1} Pb increased POD activity			Increased concentrations of catechin, vitexin, rutin, quercetin, genistein, myricetin, resveratrol, luteolin, naringenin, and kaempferol flavonoids	
<i>S. striata</i>	Pb exposure for 3 d	Roots	250 mg L^{-1} Pb decreased SOD activity	250 mg L^{-1} Pb increased CAT activity	250 mg L^{-1} Pb decreased POD activity			Increased concentrations of catechin, genistein, diosmin, myricetin, resveratrol, daidzein, and luteolin flavonoids	[45]
		Shoots	250 mg L^{-1} Pb decreased SOD activity	250 mg L^{-1} Pb increased CAT activity	250 mg L^{-1} Pb decreased POD activity			Increased concentrations of catechin, genistein, diosmin, myricetin, resveratrol, daidzein, and luteolin flavonoids	

Table 2 (continued)

Species	HM	Organ	Activity of antioxidant enzymes				Non-enzymatic antioxidant responses		References
			SOD	CAT	POD	APX	GPX		
<i>V. ol ympicum</i>	Cu exposure for 7 d	Leaves	500 µM Cu increased SOD activity (40 vs. 100, U mg ⁻¹ , control vs. Cu treatment, respectively)*	250 µM Cu increased CAT activity (0.8 vs. 2.3, U mg ⁻¹ , control vs. Cu treatment, respectively)*		500 µM Cu increased APX activity (1.2 vs. 2.5, U mg ⁻¹ , control vs. Cu treatment, respectively)		[4]	
		Roots	Cu 500 µM increased SOD activity (20 vs. 120, U mg ⁻¹ , control vs. Cu treatment, respectively)*	Cu 250 µM increased CAT activity (1 vs. 2.8, U mg ⁻¹ , control vs. Cu treatment, respectively)*		Cu 500 µM increased APX activity (0.4 vs. 1.7, U mg ⁻¹ , control vs. Cu treatment, respectively)*			
	Cd exposure for 7 d	Leaves	250 µM Cd increased SOD activity (40 vs. 170 U mg ⁻¹ , control vs. Cd treatment, respectively)*	250 µM Cd increased CAT activity (0.7 vs. 3.2, U mg ⁻¹ , control vs. Cd treatment, respectively)*		250 µM Cd increased APX activity (1.2 vs. 3.1, U mg ⁻¹ , control vs. Cd treatment, respectively)		[18]	
		Roots	250 µM Cd increased SOD activity (20 vs. 88 U mg ⁻¹ , control vs. Cd treatment, respectively)*	250 µM Cd increased CAT activity (1 vs. 3.2 U mg ⁻¹ , control vs. Cd treatment, respectively)*		250 µM Cd increased APX activity (0.5 vs. 2, U mg ⁻¹ , control vs. Cd treatment, respectively)*			
<i>V. thapsus</i>	Cu exposure for 14 d	Leaves	375 mg L ⁻¹ Cu increased SOD activity (50 vs. 90 U mg ⁻¹ , control vs. Cu treatment, respectively)*	375 mg L ⁻¹ Cu increased CAT activity (1 vs. 2 U mg ⁻¹ , control vs. Cu treatment, respectively)*		375 mg L ⁻¹ Cu increased APX activity (1.5 vs. 2.4 U mg ⁻¹ , control vs. Cu treatment, respectively)*		[82]	
		Roots	375 mg L ⁻¹ Cu increased SOD activity (40 vs. 78 U mg ⁻¹ , control vs. Cu treatment, respectively)*	375 mg L ⁻¹ Cu increased CAT activity (0.8 vs. 1.8 U mg ⁻¹ , control vs. Cu treatment, respectively)*		375 mg L ⁻¹ Cu increased APX activity (1.5 vs. 2.3 U mg ⁻¹ , control vs. Cu treatment, respectively)*			

The mg⁻¹ or g⁻¹ data shown for enzyme activity are expressed regarding protein reported in the corresponding reference. In most cases, data shown in this table were rounded off from those described in the corresponding reference

PAL phenylalanine ammonia-lyase; TAL tyrosine ammonia-lyase

*The data shown are an approximation according to visual observation of histogram graphic's references

Table 3 Medicinal use and secondary metabolites of species of the *Buddleia*, *Eremophila*, *Scrophularia*, and *Verbasicum* genera with phyto remediation potential

Species	Ethnomedicinal use	Secondary metabolite		References
		Phenolic compounds	Terpenes	
<i>B. asiatica</i>	Used for skin diseases, weight loss, abortion, head tumors, pain, fever, and diarrhea Acts as an abortifacient and has antitumor, antifungal, and antimalarial effects	Acteoside* Apigenin Diosmin Isoacteoside Linarin** Luteolin Rutin	6-O-(3",4"-Dimethoxycinnamoyl) catalpol Ajugol Alpha amyirin Aucubin Buddlin Catalpol Lignoceric acid Methyl catalpol Mimengoside A Stigmasterol β-caryophyllene oxide β-sitosterol β-sitosterol-O-glucoside	Bhattacharay [32] Chen et al. [38] El-Domiaty et al., [51] Houghton and Mensah [73] Mohamed et al. [106]
			1-Hydroxycycloclorenone 6α-Hydroxyisocapnell-9-en-8-one Buddledin A Cycloclorenone Isocapnell-9-en-8-one Steroids sitosterol Stigmasterol	[55] [56]
<i>B. cordata</i>	Used against gastrointestinal infections, liver disorders, nasal hemorrhages, muscle cramps, rheumatism, and headache; as diuretic; and in kidney treatment	Hydroxycinnamic acids (caffeic, p-coumaric, sinapic, and ferulic acids) Linarin** Sesamin Vanillic acid Verbascoside*		
<i>B. davidii</i>	Antifungal, wound-healing, and ulcer treatment	Acetylmaritinoside Angoroside C Balanophonin Buddlenol A-F Calceolarioside A Campneoside II Forsythoside B Isomartynoside Jionoside D Linarin** Martynoside Plantainoside C Poliumoside Quercitin Syringaresinol	Ajugol Benzoyl catalpol Buddledins A-E Buddlejoside A13 Buddlejoside A14 Buddlejoside A15 Buddlejoside A16 Dihydrobuddledin A Dimethoxycinnamoyl catalpol p-Methoxycinnamoyl catalpol	[1] [74] [84] [184]

Table 3 (continued)

Species	Ethnomedicinal use	Secondary metabolite		References
		Phenolic compounds	Terpenes	
<i>B. lindleyana</i>	Rheumatism and cough. Acts against blood stasis	Acteoside* Apigenin Linarin** Luteolin Quercetin Rutin	13, 28-Epoxy-23-hydroxy-3 β -acetoxo-olean-11-ene 13, 28-Epoxy-23-hydroxy-11-oleanene-3-one 13, 28-Epoxy-21 β , 23-dihydroxy-11-oleanene-3-one Buddlejasaponin IV _b Buddlintriterpene A Buddlintriterpene B Clinoposaponin III Desrhamnoverbascosaponin Mimengoside I Mulleinsaponin I Mulleinsaponin VII Oleanane Saikosaponin M	[133, 134] [187]
			6- α -L-(2''-Caffeoyl)rhamnopyranosylcatalpol 6- α -L-(4''-O-trans-p-Coumaroyl)rhamnopyranosylcatalpol Buddlejasaponin I Buddlejasaponin Ia Buddlemacroside A Mimengoside C	
<i>B. macrostachya</i>	Used to treat sores and inflammation, hepatitis, conjunctivitis, and keratitis	8-Hydroxylinalool 3-O- α -D-glucopyranoside 9-O- α -L-Rhamnopyranosyl-4-hydroxy-cinnamic acid Acacetin-7-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside Acteoside* Apigenin Darendoside A Decaffeoylacteoside Echipsurosides A Martynoside Salidroside		[71, 72]
<i>B. paniculata</i>	Activity against <i>Streptococcus mutans</i> causing dental caries			[154]

Table 3 (continued)

Species	Ethnomedicinal use	Secondary metabolite	Terpenes	References
<i>B. scordiodides</i>	Diarrhea, headache, and wounds	Phenolic compounds		
		4,5-Dicaffeoylquinic acid 4-Hydroxybenzoic acid Acacetin** Apigenin Caffeic acid Chlorogenic acid Coumaric acid Eriodictyol Ferulic acid Isoquercitrin Kaempferol Luteolin Mangiferin Naringenin Naringin Neohesperidin Protocatechuic acid Quercetin Quercitrin Quinic acid Rosmarinic acid Rutin Shikimic acid Sinapic acid Syringic acid Syringin Vanillic acid Verbascoside*	3,23,28-Trihydroxyoleana-11,13(18)-diene Buddlejasaponin O-methyl catalpol Saikogenin A	[24] [48] [56]
<i>E. latrobei</i>	Anti-inflammatory, used in aromatherapy and fumigations; for respiratory discomfort and treatment of scabies; and as antibiotic		(-)-10,11-Dehydroeupingalone (-)-Ngaione (+/-)-Myoporone 4-Hydroxydihydromiodesmone 9-Hydroxy-5,9-dihydromyomontanone Bicydogermiacrene E-Caryophyllene Endo-fenchyl acetate Methoxymyodesert-3-ene Muuroa-4,10(14)-dien-1-β-ol Phytol t-Muurolol α-Fenchene α-Pinene β-Santalene	[138] [153]

Table 3 (continued)

Species	Ethnomedicinal use	Secondary metabolite	Terpenes	References
<i>S. canina</i> subsp. <i>bicolor</i>		Phenolic compounds		
		Verbascoside*	(E)-phytol 8-Epiloganic acid 8-O-Acetylharpagide Aucubin Harpagide	[170]
<i>S. ningpoensis</i>	Used for hypertension, cancer, and diabetes. It is often used for treatment of polydipsia, fever, gingivitis, tonsillitis, laryngitis, carbuncle, acute lymphadenitis, intestinal dryness, and constipation	Acetylangeloside C	14-Deoxy-12(R)-sulfo and rographolide	[132] [181]
		Acteoside*	Eucalyptolic acid	
		Angoroside C	Lupaneol	
		Cistanoside D	Oleanolic acid	
		Cistanoside F	Scrokoelzside A	
		Decaffeoylacteoside	Sitosterol	
		Liquiritigenin	Sugiol	
		Nepitrin	Ursodeoxycholic acid	
		Ningposide A	Ursolic acid	
		Ningposide B	β-daucosterol	
		Ningposide C		
		Pedicularioside A		
		Rhamnopyranosyl vanilloyl		
		Scrophuloside B1		
		Scrophuside		
		Sibirioside A		
		Trans-cistanoside D		
<i>S. striata</i>	Plant used to control infections; heal wounds; and treat eye and ear infections, skin burns, infectious, pain, gastrointestinal disorders, colds, and hemorrhoids	Catechin	1-Octen-3-ol	[152]
		Diosmin	Benzaldehyde	[2]
		Hydroxycinnamic acids (caffeic, p-coumaric, sinapic, and ferulic acids)	Linalool	[122]
		Kaempferol		
		Luteolin		
		Myricetin		
		Nepitrin		
		Quercetin		
		Resveratrol		
		Rutin		
		Verbascoside*		

Table 3 (continued)

Species	Ethnomedicinal use	Secondary metabolite	Terpenes	References
<i>V. bombyciferum</i>	For bronchitis and tuberculosis prevention. Acts as antiseptic, astringent, and antimicrobial	Phenolic compounds		
		(+)-Catechin 3,5- Dicafeoylquinic acid 3-Caffeoylquinic acid 5-Caffeoylquinic acid Caffeic acid Ferulic acid Gallic acid Hyperoside Isogentisin (–)-Epicatechin Kaempferol-3- glucoside Naringin p-Coumaric acid Quercetin Quercitrin Resveratrol Rutin Shikimic acid Syringic acid Trans-cinnamic acid Vanillic acid	6-O-β-D-Glucopyranosylaucubin 8-O-Acetylharpagide Ajugol Aucubin Catalpol Harpagide Harpagoside	[5] [15] [13] [185]
<i>V. cheiranthifolium</i>	Used for respiratory and skin disorders, abdominal and rheumatic pain, earache, hemorrhoids, and diarrhea	Apigenin Apigenin glucoside Chlorogenic acid Luteolin-7-O-glucoside Quercetin Rutin Verbascoside*		[163] [44]
<i>V. olympicum</i>	Used for asthma and cough prevention and acts as antimicrobial		6-O-β-D-Glucopyranosylaucubin 8-O-Acetylharpagide Ajugol Ajugoside Aucubin Geniposidic acid Harpagide Harpagoside Laterioside Sinuatol	[50] [13] [185]

Table 3 (continued)

Species	Ethnomedicinal use	Secondary metabolite		References
		Phenolic compounds	Terpenes	
<i>V. thapsus</i>	Used as analgesic, anti-inflammatory, antiseptic, spasmolytic, astringent, diuretic, emollient, to treat expectorant piles, bruises, and frostbite	3'Methylghercitin Hesperidin Verbascoside* Verbascosaponin	6,10,14-Trimethyl-2- pentadecanone Ajugol Aucubin Catalpol Geosmin Harpagoside Linalool Saikogenin A Sitosterol (E)-phytol α-bisabolol	Turker et al. [166] [108] [46]

* Verbascoside is synonym of acteoside
**Linarin is synonym of acacetin.

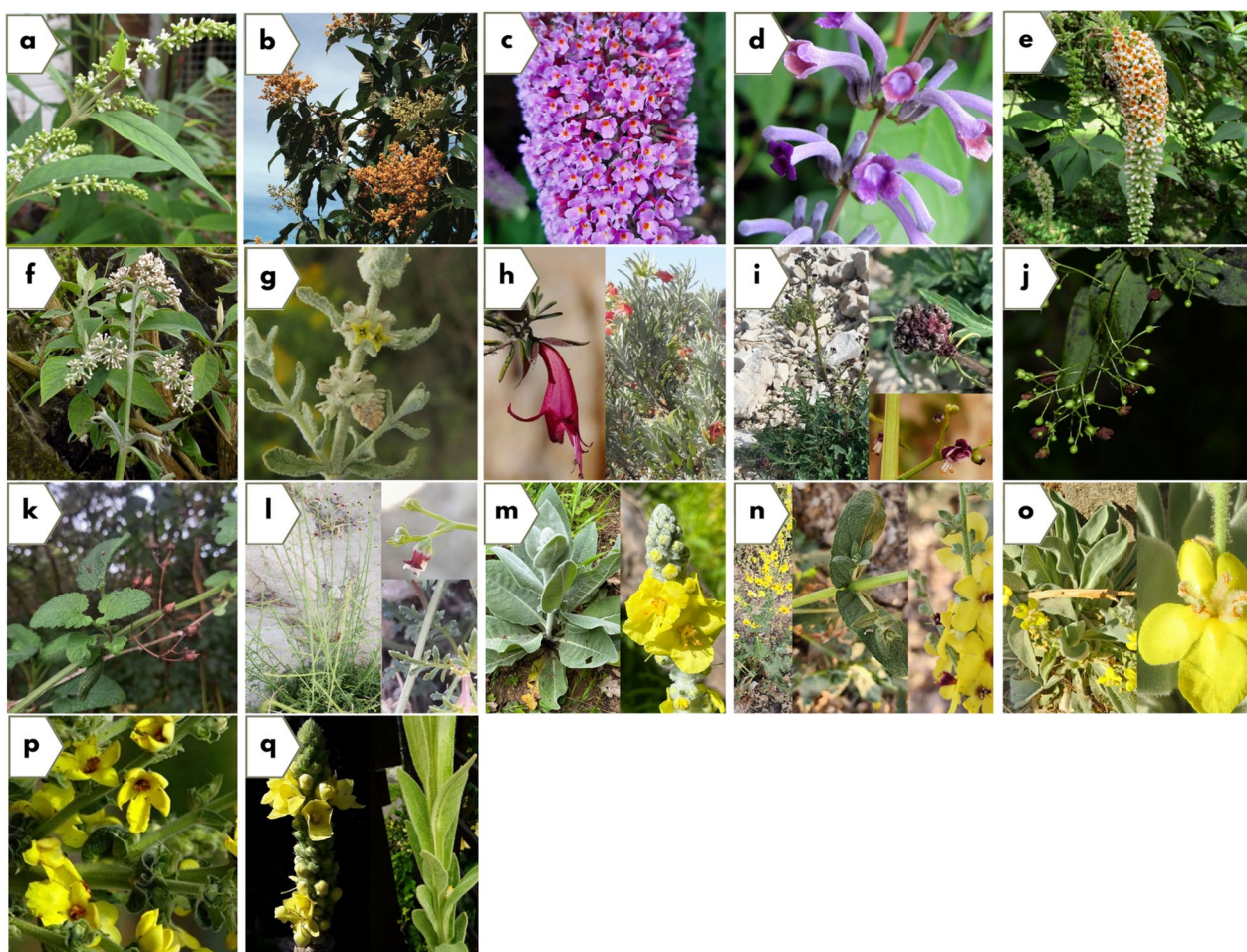


Fig. 4 Medicinal species of the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera with phytoremediation potential. **a** *B. asiatica*, **b** *B. cordata*, **c** *B. davidii*, **d** *B. lindleyana*, **e** *B. macrostachya*, **f** *B. paniculata*, **g** *B. scordioides*, **h** *E. latrobei*, **i** *S. canina* subsp. *bicolor*, **j** *S. ningpoensis*, **k** *S. scoparia*, **l** *S. striata*, **m** *V. bombyciferum*, **n** *V. cheiranthifolium*, **o** *V. olympicum*, **p** *V. phrygium*, **q** *V. thapsus*. Created with Canva.com. Images sources from: **a-f** <https://www.treesandshrubsonline.org/>; **g-i, l-o, q** <https://identify.plantnet.org/es/>; **j** <https://www.gbif.org/es/>; **k** <https://observation.org/>; **p** <https://turkiyecicek.wordpress.com/2016/04/09/verbascum-phrygium-scrphulariaceae-siracaotugiller-2/>

scordioides (Fig. 4a–g) (Table 1), and they have also been reported to have medicinal uses (Table 3).

It was found that wild plants of *B. asiatica* (Fig. 4a), extracted from the Bo Ngam Pb mine in Thailand, accumulated a large amount of Pb in their shoots (Table 1); therefore, they could be considered as Pb hyperaccumulators [135]. In addition, *B. asiatica* propagated, from those wild plants, showed a substantial accumulation of Pb, Cd, and Zn in their roots after a specific period of incubation in the Bo Ngam Pb mine substrate, under hydroponic conditions [175]. This species was argued to have potential for use in soil phytoremediation, as well as in revegetating contaminated soils and in improving natural revegetation because it is a perennial plant that may avoid annual reseeding [135, 175]. *B. asiatica* collected at Honghe University, China, was propagated and exposed

to Cd; it showed restricted Cd accumulation in shoots, lower than that in roots. For this reason, it was considered to be Cd-hypertolerant [63] (Table 1). Wild plants grown in a Cr salt-producing factory in China showed the ability to accumulate several HMs (Cd, Cr, Cu, Hg, Ni, Pb, and Zn) [180] (Table 1).

B. cordata (Fig. 4b) can grow under adverse conditions, including unfertile soils [62, 114]. It was found that leaf litter samples of this species, grown near polluted areas around Mexico City, contributed to the mobilization of metals, such as Al, Cd, Cu, Fe, Mn, Zn and Pb, based on phenolic compounds; the authors discussed the idea that these compounds may act as chelators [127]. This species accumulated Ca, Co, Fe, Mg, Mn, Ni, and Zn in its leaves when it grew in ultramafic soil in Guanajuato, México [114] (Table 1).

B. davidii (Fig. 4c) can grow at sites contaminated with an ample variety of HMs, such as the Sb deposit in China, where this species was found to be tolerant to the high concentrations of Sb in the soil [126] (Table 1); it was also found to be Bi-tolerant (Table 1) through Bi exclusion [176]. This species grew near the Pb–Zn mine in China, showing an abundant biomass production and the accumulation of Cd, Cr, Cu, Ni, Pb, and Zn [191] (Table 1).

B. lindleyana (Fig. 4d) can grow in coal mine tailings containing Cd, Cr, Cu, Mn, Pb, and Zn, accumulating mainly Mn and Zn in its roots (Table 1), thus indicating the adaptability of this species to grow in mine substrate containing heavy metals. Therefore, it could be used for phytoremediation [190].

B. macrostachya (Fig. 4e) seedlings grown in pots for 90 days showed a restricted Cd accumulation capacity in aerial organs compared with in roots, and they were considered hypertolerant to Cd [63] (Table 1).

B. paniculata (Fig. 4f) grew rapidly and densely in and easily adapted to soil from Bo Ngam Pb mine, Thailand, as well under hydroponic culture conditions, where the species accumulated significantly higher concentrations in roots than in shoots [175] (Table 1); therefore, they could be considered Pb hyperaccumulator [175].

B. scordiodoides (Fig. 4g) could grow in a mine in Zacatecas, Mexico, where it was able to tolerate and accumulate Pb (Table 1), thus being a plant that could be used in mine tailings and to remediate lead-contaminated soils; it could also grow in temperate and arid climates, as it tolerates different climates [144].

Eremophila genus

The *Eremophila* genus comprises approximately 230 species, presenting gray leaves that provide protection from intense light. The species of this genus are perennial shrubs and trees that can be found in arid and semi-arid regions of Australia, and many of them are used in traditional medicine by Australian Aborigines to relieve the common cold, cough, chest pain, and fever [60, 153]. In recent years in Australia, there has been increasing awareness of the traditional medicine of the Aboriginal population because 84% of the *Eremophila* plants are not found anywhere else in the world. So, plants of this genus have been examined in many investigations to determine their chemical composition, which has been found to consist of unique and structurally diverse metabolites, especially sesquiterpenoids and diterpenoids [60, 90]. Some species used for medicinal purposes are *E. alternifolia*, *E. duttonii*, *E. glabra*, *E. latrobei*, *E. maculata*, *E. microtheca*, *E. neglecta*, *E. serrulata*, and *E. sturtii* [60, 153]. Extracts from the species of this genus have been tested for antiviral, antibacterial, and anti-cancer activities; among the metabolites of interest are

serrulatane- and viscidane-type diterpenoids, which have antimalarial, anti-inflammatory, antidiabetic, and antibacterial properties [60, 153].

E. latrobei (Fig. 4h) has been reported to show the ability to grow in Pb–Zn gossans, northwest Queensland, Australia; it excludes Pb from its foliage (Table 1), making it ideal for revegetating Pb-contaminated sites in arid areas [91].

Scrophularia genus

The name *Scrophularia* comes from “scrofula”, a type of tuberculosis, because some species belonging to this genus have been used to treat tuberculosis [94]. Plants of this genus grow in central Europe, North America, and Asia [109]. It is one of the largest genera of the Scrophulariaceae family and consists of about 350 species of medicinal plants that are widely used in China, Korea, and Japan for gastrointestinal disorders, inflammation, fever, and cancer [99, 122]. Among the secondary metabolites characterizing this genus are phenylethanoids, flavonoids, iridoids, triterpenes, alkaloids, and essential oils [122]. Among the biological activities of the genus are the anti-inflammatory effects of *S. auriculata*, *S. buergeriana*, *S. dentata*, *S. frutescens*, *S. ningpoensis* and *S. striata*; *S. amplexicaulis* showed antimicrobial activity against *Staphylococcus aureus*, *S. cryptophila* inhibited the growth of *Trypanosoma brucei*, *S. deserti* was effective against *Brucella melitensis*, and *S. frutescens* was effective against Gram-positive bacteria [122]. Other species used for medicinal purposes include *S. aquatica*, *S. dentata*, *S. nodosa*, *S. lucida*, *S. chrysanthemifolia*, and *S. canina* subsp. *bicolor*, whose roots and aerial parts are highlighted as sources of vegetal material [122].

In Campo Pisano, Italy, wild plants of *S. canina* subsp. *bicolor* (Fig. 4i), a species native to the Mediterranean, could tolerate high concentrations of Pb and Zn, accumulating them at higher concentrations in roots than in shoots (Table 1), and they produced high biomass [35]. This species could be used to restore vegetation cover, reduce metal concentrations at contaminated sites, and reduce metal transport by erosion [26]. Furthermore, using amendments such as zeolite (Table 1) could contribute to the survival of plants, as a 39% reduction in Pb was observed compared with 15% in control soil [26].

S. ningpoensis (Fig. 4j), wild plants grown in Daozhen, China, showed different abilities to accumulate Mn, Fe, Co, Zn, As, and Pb in roots, stems, and leaves. Higher concentrations of HMs were observed in the leaves, followed by the stems, while the roots displayed the lowest concentrations; these organs exhibited highly notable differences in As and Pb (Table 1). Additionally, a health risk assessment indicated that consuming the leaves and

stems of this species could pose a risk approximately ten times higher than that of consuming the roots [64].

S. scoparia (Fig. 4k), a wild plant that grows in the Pb–Zn mine in Hamedan, Iran, showed Pb accumulation in shoots (Table 1); however, it had a translocation factor of 0.09 and a bioconcentration factor of 1.43, indicating that it could be used for phytostabilization when Pb is present in the soil. Plants showing translocation and bioconcentration factor values greater than 1 have the potential to be used for phytoextraction purposes, while those with values lower than 1 are more suitable for phytostabilization [118].

S. striata (Fig. 4l) has been reported to show a remarkable bioaccumulation of Pb [45]. The antioxidant enzymatic machinery in this species was analyzed under Pb and Cd stress conditions, showing significant enzyme activity [31, 45].

Verbascum genus

The *Verbascum* genus consists of about 360 species; plants of this genus contain secondary metabolites, such as flavonoids, iridoids, phenylethanoids, steroids, saponins, and neolignan glycosides [76, 184]. The species of this genus are commonly known as mullein, and their leaves and flowers have been used for their expectorant and antitussive properties to treat lung discomfort and bronchitis, inflammatory diseases, tuberculosis, spasms, diarrhea, headache, and migraine by different populations in Europe, Asia, Africa, and North America [184]; depending on the species, the roots are also used for medicinal purposes [161]. Other uses reported for species belonging to this genus are antiseptic, astringent, emollient, narcotic, sedative, diuretic, and antimalarial uses, with several biological effects being demonstrated, such as antioxidant, antimicrobial, antiviral, antimalarial, anti-inflammatory, anticancer, and cytotoxic effects [15, 163]. The species of this genus grow in a wide variety of habitats, such as rocky mountains, open forests, roadsides, meadows, and HM-polluted areas [3].

However, mullein's properties are also used in veterinary medicine to treat cow skin and pig gastrointestinal diseases [76]. Some species described as having medicinal properties are *V. bombyciferum*, *V. cheiranthifolium*, *V. chionophyllum*, *V. chrysochaete*, *V. cilicicum*, *V. densiflorum*, *V. dudleyanum*, *V. lasianthum*, *V. latisepalum*, *V. phlomoides*, *V. pumilum*, *V. pycnostachyum*, *V. salvifolium*, *V. splendidum*, *V. symes*, and *V. thapsus* [15, 161, 163]; some of them have also been examined for their responses to HM exposure (Table 1).

V. bombyciferum (Fig. 4m) is a plant that grows on roadsides and in garbage dumps. It is considered an ornamental plant that helps revegetate destroyed areas due to its high biomass production. This species could be used

to monitor the presence of Cd, Ni, Pb, and Zn, as it can accumulate these HMs [19] (Table 1).

V. cheiranthifolium (Fig. 4n) grown in an HM-polluted Keban mining district in Elazig, Turkey, showed the ability to accumulate high levels of Cu, Pb, Zn, and Cd HMs in its twigs and roots. It is considered a hyperaccumulator species [142].

In other studies, the seeds of *V. bombyciferum* and *V. olympicum* (Fig. 4o), both being species endemic to Turkey, were tested for the effects of various HM concentrations (Cu, Cr, Ni, Cd, and Zn), and they showed a reduction in the percentage of seed germination depending on the type of HM [65]. In *V. olympicum*, increasing the HM concentration decreased the seed germination percentage. In contrast, *V. bombyciferum* showed reduced germination only in response to Cd and Cr; however, no germination occurred under high concentrations (> 500 μ M Cd, Cu, or Ni; 250 μ M Cr; and 1250 μ M Zn). Although, in general terms, root growth was lower in both species than in the control, shoot growth was not inhibited; thus, the authors argued a tolerance limit for seed germination at a 500 μ M concentration of these HMs [65].

V. phrygium (Fig. 4p) mature seeds were collected from Murat Dağı Mountain, Turkey, and grown for 7 days in pots with a Zn solution, and they showed a high tolerance to this HM [3] (Table 1).

V. thapsus (Fig. 4q) is a species that was found to be able to grow in Gümüşköy Ag deposit, Turkey [148, 182], and its seeds were found to germinate in a hydroponic substrate enriched with Cu [82]; the authors of those works determined that this species could be used to remediate soils and areas contaminated by As, Ag, and Ti, as well as being a potential Cu hyperaccumulator (Table 1).

Of all the species described above, only a few have been investigated in terms of the effect of HM exposure on antioxidant machinery, such as *B. asiatica*, *B. macrostachya*, *S. striata*, *V. olympicum*, and *V. thapsus* (Table 2). In general terms, the activity of SOD, CAT, POD, APX, or GPX increased in shoots or roots under HM exposure, and only *S. striata* was analyzed in terms of the antioxidant non-enzymatic response. In this species, PAL (phenylalanine ammonia-lyase) and TAL (tyrosine ammonia lyase) activities increased, along with the concentration of several phenolic compounds (Table 2).

In addition, these species, which have proven their potential to accumulate HMs in their organs (Table 1), have been documented for different medicinal uses, mainly related to inflammation, illness, and infectious disease processes, among others, where phenolic compounds and terpenes have also been identified (Table 3). The verbascoside (synonym acteoside) phenylpropanoid is mainly found in *Buddleja*, *Scrophularia*, and

Verbascum species, while ajugol, aucubin, and catalpol terpenoids have been observed in *Buddleja* and *Verbascum* species (Table 3). In addition, several species of *Buddleja*, *Scrophularia*, and *Verbascum* have been reported to contain flavonoids, notably linarin (synonym acacetin), apigenin, or quercetin (Table 3). All of these phytochemicals have proven their pharmacological effects. Verbascoside is a bioactive phytochemical with an anti-inflammatory effect that inhibits histamine and arachidonic acid release from mast cells [13], and it protects pancreatic β -cells against endoplasmic reticulum stress in clonal and human β -cells by modulating the activation of protein kinase RNA-like endoplasmic reticulum kinase, thus increasing the viability of and insulin content in these cells [58]. This compound can also reduce acute kidney injury due to its anti-inflammatory and antioxidant effects, which decrease the markers of serum creatinine, blood urea nitrogen, and renal glutathione [140]. Quercetin is a phytochemical used in the treatment of diarrhea [10] and against dengue virus, and it acts by protecting infected LLC-MK2 cells from released virion [11]. Additionally, it has been reported to be a musculotropic agent because it limits the availability of Ca^{2+} involved in excitation–contraction coupling [10]. Apigenin is a bioactive metabolite with anticancer properties; it reduces the growth of lung, breast, colon, blood, prostate, cervical, and stomach tumor cells by causing apoptosis via caspase-dependent routes. It demonstrated cardiovascular activity in a rat model by preventing hemodynamic perturbations and re-establishing the function of the left ventricle in the rat [110]. Ajugol attenuated renal injury in multiple myeloma by blocking LILRB4 signaling and reducing PFKFB3 expression and the infiltration of inflammatory cells; it was thus considered to have anticancer potential [178]. Aucubin has shown potential anti-inflammatory activity against pathological illness, diabetes, gastric mucosal lesions, and epilepsy. The oral administration of aucubin to hyperglycemic mice decreased the expression of p-I κ B α and inhibited the expression of inflammatory cytokines (IL-1 β , IL-8, IL-10, and TNF- α), while its intragastric administration to mice with gastric mucosal lesions reduced IL-6 and TNF- α levels.

In mice with pilocarpine-induced epilepsy, aucubin decreased proinflammatory cytokine levels [81]. Catalpol was shown to reduce atherosclerotic lesions in a rabbit model, showing a decrease in triglyceride, high cholesterol, and LDL cholesterol levels [188].

Biotechnology as a tool for obtaining medicinal plants and identifying phytoremediation species

One of the primary methods of obtaining medicinal plants is to extract them from their wild habitat for sale on the market [147]. However, the high demand for natural products has led to over-extraction, resulting in the decline of plant species and habitat destruction, pushing many plants to the verge of extinction [6]. In recent decades, the extraction of medicinal plants has increased in Europe, North America, and Asia because the demand for plant resources has increased between 8 and 15% annually [41].

In addition, when wild medicinal plants are sold on the market, no quality or safety processes are carried out, and neither botanical identity nor purity studies are carried out because of cost limitations [147]. Indeed, the quality and safety of medicinal plants are important issues for the industry, as they are raw materials used for herbal products, which is why regulatory values have been set for herbal products and medicinal plants [147]. Due to the increasing HM pollution in the environment, medicinal plants may accumulate HMs; thus, research on determining their concentration of HMs should be carried out before they are marketed [57]. Some examples of medicinal plants and market samples of products of plant origin that accumulate HMs are sweet pyra (*Amaranthus dubius*), maguey (*Agave amaniensis*), chamomile (*Matricaria chamomilla*), basil (*Ocimum tenuiflorum*), and black elderberry (*Sambucus nigra*) [113].

An alternative to the growing problems of the contamination and extraction of plant resources is plant tissue culture (PTC), which can be used to propagate plants (e.g., medicinal or phytoaccumulator species) on a large scale, produce disease-free plants, obtain varieties tolerant to environmental stress conditions, improve plants, and produce bioactive secondary metabolites [75]. Furthermore, it has advantages such as geographic, environmental, and seasonal independence; uniform yields; and relative quality control [53]. PTC also serves as a tool to investigate the accumulation and translocation of HMs, as it also allows for testing the effects of HMs under controlled conditions, including the cellular and molecular detoxifying mechanisms of HMs [36].

Most of the works reported in the literature aiming to establish PTC for testing species belonging to the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera have been conducted regarding the propagation of plants, with Murashige and Skoog and 3% (p/v) sucrose being the most common culture medium formulation (Table 4). In addition, it can be observed in all those reports that a plant growth regulator is crucial for inducing a morphogenetic response in explants (Table 4). Shoots used as explants are predominantly tested with

Table 4 Culture medium and plant growth regulator effects reported in explants of species belonging to the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera to establish plant tissue cultures

Species	Culture medium	Plant growth regulators (μM)			Morphogenetic response induced mainly in the explant	References
		Auxin	Cytokinin	Gibberellin		
<i>B. cordata</i>	MS 50% + 3% (p/v) sucrose	0.45 μM 2,4-D	2.32 μM Kin	4.34 or 8.67 μM GA ₃	Callus in leaves	[55]
			4.44 μM BA		Shoots in nodes	[54]
					Shoot elongation in nodes	
<i>B. incana</i>	WP 100% without carbon source	Without plant growth regulators			Rhizogenesis in elongated shoots	
					Shoots in shoots	[79]
<i>S. kakudensis</i>	MS 100% + 3% (p/v) sucrose	0.5 mg L ⁻¹ (~2.85 μM) IAA	2 mg L ⁻¹ (~8.84 μM) BA		Shoots in shoots	[99]
	MS 50% + 3% (p/v) sucrose	0.5 mg L ⁻¹ (~2.85 μM) IAA			Rhizogenesis in shoots	
<i>S. nodosa</i>	WP 100% without carbon source			0.72 mM GA ₃	Germination in seeds	[149]
	WP 100% + 3% (p/v) sucrose	0.5 mg L ⁻¹ (~2.26 μM) 2,4-D	0.1 mg L ⁻¹ (~0.46 μM) Kin		Callus in leaves and roots	
<i>S. takesimensis</i>	MS 100% + 3% (p/v) sucrose	Without plant growth regulators			Rhizogenesis in shoots	
		1 mg L ⁻¹ (~5.7 μM) IAA	3 mg L ⁻¹ (~13.26 μM) BA		Shoots in shoots	[155]
<i>S. takesimensis</i>	MS 100% + 3% (p/v) sucrose	1 mg L ⁻¹ (~4.9 μM) IBA			Rhizogenesis in shoots	
		1 mg L ⁻¹ (~5.7 μM) IAA	2 mg L ⁻¹ (~8.84 μM) BA		Shoots in leaves	[78]
<i>S. yoshimurae</i>	MS 100% + 3% (p/v) sucrose	1.07 μM NAA	4.44 μM BA		Shoots in shoot tips	[141]
					Shoots in stem node	
<i>V. eriophorum</i>	MS 50% + 3% (p/v) sucrose		0.5 mg L ⁻¹ (~2.21 μM) BA		Shoots in nodal segments	[183]
<i>V. phrygium</i>	MS 100% + 3% (p/v) sucrose	Without plant growth regulators			Germination in seeds	[3]
<i>V. thapsus</i>	MS with minimal organic compounds + 3% (p/v) sucrose	5.37 μM NAA or 0.45 μM 2,4-D	13.32 μM BA		Shoots in leaves	[166]
		5.37 μM NAA			Rhizogenesis in shoots	

2,4-D 2,4-dichlorophenoxyacetic acid; BA: N⁶-benzyladenine; GA₃ gibberellic acid; IAA indole-3-acetic acid; IBA indole-3-butyric acid; Kin kinetin (N⁶-furfurylaminopurine); MS Murashige and Skoog culture medium; NAA α-naphthaleneacetic acid auxin; WP woody plant culture medium

N⁶-benzyladenine (BA) cytokinin, with indole-3-acetic acid (IAA) or α-naphthaleneacetic acid auxin (NAA) (higher concentration of cytokinin regarding auxin) being used for their induction. Using IAA or indole-3-butyric acid (IBA) auxin in shoot explants generally promotes rhizogenesis, and testing 2,4-dichlorophenoxyacetic acid (2,4-D) auxin with kinetin (Kin) induces callus formation mainly in leaves (Table 4).

Some of the PTC reports on species of the *Buddleja* genus have focused on obtaining compounds of pharmacological importance and for the propagation of plants. For example, Estrada-Zúñiga et al. [55] established *B. cordata* callus cultures to obtain phenolic compounds such as verbascoside and linarin, which have therapeutic properties. They also used PTC to

propagate this species and evaluate the ability of the regenerated plantlet to produce verbascoside [54]. *B. incana* in vitro propagation has also been established because the wood of this species is used for the construction of houses and tools, as well as for medicinal purposes [79].

In *S. kakudensis*, cultivations were carried out to perform mass propagation (Table 4) and to determine the acacetin content through PTC, with acacetin being a secondary metabolite of interest due to it having biological properties such as anticancer, antioxidant, and anti-inflammatory properties [99]. Other studies were conducted to determine the number of secondary metabolites of interest; for example, in *S. nodosa*, PTC of seeds, leaves, and roots (Table 4) was used to

determine the number of iridoid glucosides [149]. At the same time, regarding *S. takemensis*, a protocol was established to conserve the species [155] and to understand the number of phenolic compounds from plants regenerated via PTC [78]. Similarly, micropropagation was carried out in *S. yoshimurae* to obtain plants [141].

Meanwhile, for plants of the genus *Verbascum*, a protocol has been established for the conservation of *V. eriphorum* [183] and *V. thapsus* (Table 4) [166]. PTC can also be used to investigate whether *V. phrygium* can be used in phytoremediation by evaluating growth parameters during in vitro germination [3].

Moreover, the bioactive secondary metabolites produced by PTC [75] can be used in bioactive nanomedicine through the formulation of nanotransporters or nanoparticles, which can be used in the treatment of cancer and diabetes, among others [10, 12]. To date, several types of nanocarriers and drugs have been incorporated into delivery systems, such as liposomes, ethosomes, polymersomes, nanoemulsions, solid lipid nanoparticles, and nanogels [12]. A form of drug and metabolite administration that is gaining attention is lipid particles, such as liposomes, because, in conjunction with phytochemicals, they can enhance pharmacological activity and reduce possible side effects; in fact, some liposomes delivering phytochemicals are already on the market, such as quercetin and resveratrol [10], with both compounds being produced by plants of the *Buddleja*, *Scrophularia*, and *Verbascum* genera (Table 3).

Discussion

Plants play an essential role in human health. They are a source of bioactive compounds, and approximately 25–50% of pharmaceutical products are estimated to come from plants. Nearly 80% of the world's population uses herbal medicine as a primary source of health care, particularly in developing countries [102]. In addition, non-communicable diseases such as cancer, diabetes, and cardiovascular disease are on the rise; therefore, the population uses medicinal plants as a joint treatment with modern medicine, resulting from the perception of minor adverse reactions and lower costs than allopathic medicines [98]. Indeed, the World Health Organization has emphasized raising awareness of the use of traditional medicine to improve health under efficacy, quality, and safety schemes [9]. Currently, pharmacopeias from Europe and the United States indicate that plants are compounds of high medicinal value. Their use is based on traditional medicine and information obtained from the study of bioactive compounds, making plants an important resource for the population [157].

Consuming HM hyperaccumulator or accumulator species may put human health at risk. Accelerated

industrialization has led to an increase in unprocessed metals that are discharged into air, water, and soil, which can bioaccumulate in food and water and have serious consequences for human health, such as cancer, mental illness, and impaired development and growth [103]. The present work allows for the identification of some medicinal species belonging to the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera that have the potential to accumulate HMs in their tissues. Phytoremediation research has been carried out in different territories around the world, notably in Australia, China, México, Iran, and Turkey (Fig. 5). However, it was found that the ability to accumulate high amounts of HMs depends on the species, the time of HM exposure, and the type and concentration of HM in the source; this was observed in different experiments carried out in *B. asiatica* by Rotkittikhun et al. [135] and Waranusantigul et al. [175] (Table 1). These authors argued that neither pot nor hydroponic experiments support data from field trial experiments, and, thus, they are not acceptable for assessments of the phytoextraction potential [135, 175]. Va der Ent et al. [168] suggested that the criteria used to categorize hyperaccumulator plants could be unnecessarily conservative and, thus, suggested the criterion for the hyperaccumulation of Cu, Co, and Cr to be lowered to 300 µg/g for dried plant leaves and the criterion for the hyperaccumulation of Zn to be lowered to 3000 µg/g for dried plant leaves. In terms of health risk, in *S. ningpoensis*, the accumulation observed in different organs (which did not meet the criteria considered for the categorization of hyperaccumulator or accumulator) indicates that consuming the leaves and stems of this species could pose a risk approximately 10 times higher than that of consuming the roots due to there being higher HM accumulation in the roots than in the shoots [64]. Dovlatbadi et al. [49] demonstrated the potential health risk of consuming agricultural products irrigated with wastewater effluents because of the bioaccumulation of HMs in crops. Moreover, the consumption of not only the species belonging to the Scrophulariaceae family analyzed in this work but also other species (as medicinal or food plants) that have been reported to be hyperaccumulator species (Table 5) may pose health risks. The quantity and quality of medicinal compounds in plants may change when they are exposed to heavy metals; thus, it is necessary to promote safety and quality control related to HM concentration in the tissues of plants used by populations for curative purposes [21, 83, 159], as a high percentage of the world's population uses herbal medicine [102]. In many countries, there is no quality control of medicinal products, except in Canada, Europe, Australia the USA, and Japan, where strict regulatory guidelines on herbal products are followed [9]. PTC may represent a feasible

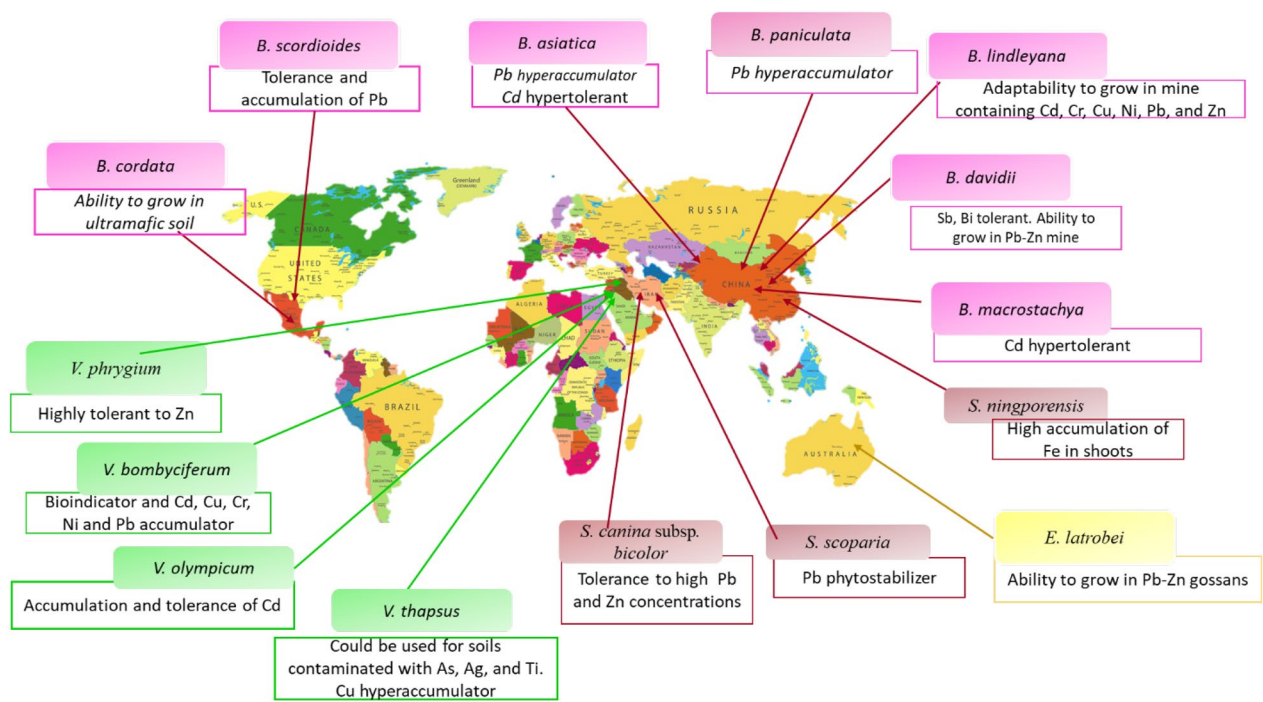


Fig. 5 Global distribution of phytoremediation research on various species within the genera *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum*. Created with Microsoft PowerPoint (map source: <https://reversite.com/full-mapa-del-mundo-con-nombres>)

Table 5 Examples of HM hyperaccumulator species belonging to Asteraceae, Brassicaceae, Euphorbiaceae, Fabaceae, and Lamiaceae families, with medicinal or edible uses

Family	Heavy metal	Hyperaccumulator species (common name)	Plant use	References
Asteraceae	Pb	<i>Brickellia veronicifolia</i> (peistó)	Medicinal	[70]
		<i>Baccharis latifolia</i> (chilca)	Medicinal	[28]
		<i>Bidens triplinervia</i> (acahual cimarrón)	Medicinal	[121]
		<i>Enydra fluctuans</i> (harkuch)	Medicinal and edible	
Brassicaceae	Ni	<i>Brassica juncea</i> (chestnut mustard)	Edible	[162]
		<i>B. carinata</i> (Ethiopian mustard)	Edible	[25]
		<i>Alyssum murale</i> (yellow tuft)	Edible	
Euphorbiaceae	Ni	<i>Phyllanthus orbicularis</i> (currant)	Medicinal	[29]
		<i>Jatropha curcas</i> (Barbados nut)	Medicinal	[59]
Fabaceae	Se	<i>Astragalus bisulcatus</i> (two-grooved milkvetch)	Medicinal	[7]
Lamiaceae	Pb	<i>Salvia sclarea</i> (clary sage)	Medicinal	[16]
		<i>Mentha × piperita</i> (peppermint)	Medicinal and edible	[17]
		<i>Lavandula vera</i> (lavender)	Medicinal and edible	

strategy for safely managing vegetal natural resources and obtaining many plants used for phytoremediation [53, 75].

Although several studies in the literature describe the complex detoxifying strategies that may be used in hyperaccumulator or accumulator species, only a few studies, mainly related to enzymatic antioxidant machinery, have determined them in species belonging to the *Buddeja*, *Eremophila*, *Scrophularia*, and *Verbascum*

genera (Table 2). Hence, further research must be carried out, such as studies on secondary metabolism because of its potential role in HM detoxification [39], as well as studies on the pharmacological activities that may be exerted by medicinal plants [164]. The presence of HMs in plants functions as an elicitation because the modification of secondary metabolism by molecules that cause stress represents a strategy for survival; thus, genes involved in the synthesis of secondary metabolites

are activated [113]. However, under a long period of HM exposure, secondary metabolite accumulation may decrease, as was observed in a *B. cordata* cell suspension culture, where the accumulation of total phenolic compounds significantly decreased after a long period of Cu, Fe, Mn, and Zn exposure [169]. As verbascoside, as well as linarin and quercetin, has been extensively reported in species of the *Buddleja*, *Scrophularia*, and *Verbascum* genera (Table 3), it may be that it contributes to enhancing the antioxidant non-enzymatic machinery of species able to counteract the harmful effects of HMs, thus allowing for the accumulation of high amounts of HMs in their tissues. Different experimental models have demonstrated that verbascoside exerts antioxidant activity based on free radical scavenging or Cu and Fe chelation because it mediates oxidation [13, 189]. This compound provides protection against the DNA damage caused by hydroxyl radicals induced by Fe, as it can form complexes with HMs [13]. Meanwhile, it has been reported that the structure of flavonoids allows them to easily chelate metal ions, thereby forming complex compounds [95].

Conclusion

Several species belonging to the *Buddleja*, *Eremophila*, *Scrophularia*, and *Verbascum* genera, such as *B. asiatica* (Pb hyperaccumulator), *B. cordata*, *B. davidii*, *B. lindleyana*, *B. macrostachya*, *B. paniculata* (Pb hyperaccumulator), *B. scordioides*, *E. latrobei*, *S. canina* subsp. *bicolor*, *S. ningpoensis*, *S. scoparia*, *V. bombyciferum*, *V. cheiranthifolium* (Cd, Cu, Pb, and Zn hyperaccumulator), *V. olympicum*, *V. phrygium*, and *V. thapsus* (Cu hyperaccumulator), have demonstrated the ability to grow in mine or HM-polluted soils and accumulate HMs, as well as their use for medicinal purposes.

The ethnomedicinal use of hyperaccumulator plants belonging to the *Buddleja*, *Scrophularia*, and *Verbascum* genera provides a health service to the people who use them, as several of their secondary metabolites, type phenolic compounds (verbascoside, linarin, apigenin, and quercetin), and terpenoids (ajugol, aucubin, and catalpol) have proven outstanding pharmacological effects (e.g., anti-inflammatory effect) that support their use. However, investigations must be conducted on the human health risks of the chronic consumption of medicinal plants that accumulate high concentrations of HMs. Moreover, it is necessary to determine how HM accumulation influences the quality and safety of herbal products derived from plants that accumulate a high amount of HMs in their tissues, with emphasis on the risks to human health and the development of protocols for safety and quality control. PTC represents a safe source of bioactive secondary metabolites, as it allows for the use of a culture medium unpolluted by HMs. In addition,

future research must be carried out to determine the role of secondary metabolism in species under conditions of high HM levels and to assess the genes implicated in the detoxifying mechanisms of HMs in these species.

Abbreviations

2,4-D	2,4-Dichlorophenoxyacetic acid
APX	Ascorbate peroxidase
BA	N ⁶ -benzyladenine
CAD	Cinnamyl alcohol dehydrogenase
CAT	Catalase
CDF	Cation diffusion facilitator
FER	Ferritin Fe (III) binding
GPX	Guaiacol peroxidase
GSH	Glutathione
HM	Heavy metal
HMA _s	Heavy metal ATPases
HMs	Heavy metals
IAA	Indole-3-acetic acid
IBA	Indole-3-butyric acid
IREG	Iron-regulated transporter
Kin	Kinetin
MATE	Multidrug and toxin efflux
MS	Murashige and Skoog culture medium
MT _s	Metallothioneins
NA	Nicotianamine
NAS	Nicotianamine synthase
NRAMP	Natural resistance-associated macrophage protein
PAL	Phenylalanine ammonia-lyase
PC _s	Phytochelatin
POD	Peroxidase
PTC	Plant tissue culture
ROS	Reactive oxygen species
SAM	S-adenosyl-methionine
SAMS	S-adenosyl-methionine synthetase
SKDH	Shikimate 5-dehydrogenase
SOD	Superoxide dismutase
TAL	Tyrosine ammonia lyase
WP	Woody plant culture medium
YSL	Yellow stripe-like transporter
ZRT	ZIP transporter of cations

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Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Studies involving plants must include a statement specifying the local, national, or international guidelines and legislation and the required or appropriate permissions and/or licences for the study

Not applicable.

Competing interest

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