Heavy Metal-Mediated Changes in Growth and Phytochemicals of Edible and Medicinal Plants

Shohreh Fahimirad and Mehrnaz Hatami

Abstract One of the most important kinds of environmental contaminates is heavy metals pollution. Plants which are exposing to high metal concentrations illustrate down regulated growth and development. Various alterations in the medical plants production of bioactive compounds have been documented. On the other hand, many researches have illustrated the high toxic residuals of heavy metals in several parts of medical plants which are potent to cause hazard to human health. Interestingly, phytoremediation is most effective and promising methods among several strategies already used to clean up the environment from heavy metals. Medical plants with high potential in heavy metal accumulation can be good candidates for soil heavy metal remediation. The cultivation or deliberate usage of medical plants in soil polluted by heavy metals must be managed carefully to diminish the final heavy metal residuals in marketing products. This chapter explains the mechanisms of plants heavy metal tolerance, the studies on transgenic plants tolerant to heavy metals, heavy metal impacts on medical plant growth and metabolites, phytoremediation ability of medical plants and standard heavy metal residuals concentration in medical plants.

Keywords Heavy metals · Medicinal plants · Phytoremediation · Secondary metabolites · Heavy metal residuals concentration

Introduction

Heavy metals are major environmental pollutants, and large amount of them are toxic ultimately at absolutely low concentrations. Fossil fuels burning, mining, municipal wastes, fertilizers and pesticides are primary sources of heavy metals

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Table 1 Types of heavy metals and their effect on human health with their permissible limits (Singh et al. 2011)

Pollutants	Major sources	Effect on human health	Permissible levels (mg/L)
As	Pesticides, fungicides, metal smelters	Bronchitis, dermatitis, poisoning	0.02
Cd	Welding, electroplating, pesticides, fertilizer	Renal dysfunction, lung disease, lung cancer, bone defects, kidney damage, bone marrow	0.06
Pb	Paint, pesticides, smoking, automobile emission, mining, burning of coal	Mental retardation in children, development delay, fatal infant encephalopathy, chronic damage to nervous system, liver, kidney damage	0.1
Mn	Welding, fuel addition, ferromanganese production	Inhalation or contact damage to central nervous system	0.26
Hg	Pesticides, batteries, paper industry	Tremors, gingivitis, protoplasm poisoning, damage to nervous system, spontaneous abortion	0.01
Zn	Refineries, brass manufacture, metal plating	Damage to nervous system, dermatitis	15
Cr	Mine, mineral sources	Damage to nervous system, irritability	0.05
Cu	Mining, pesticide production, chemical industry	Anemia, liver and kidney damage, stomach irritation	0.1

pollutions (Dhir et al. 2008; Wei and Zhou 2008). Any non-biologically degradable metal causes an environmental problem considered to be a "heavy metal". Fifty three elements with an atomic density greater than 6 g cm^{-3} now fall into the category of heavy metal. Common toxic metals are mercury (Hg), lead (Pb), cadmium (Cd), copper (Cu), 35 chromium (Cr), manganese (Mn), zinc (Zn), and aluminum (Al) (Herrera-Estrella and Guevara-Garcia 2009).The Types of heavy metals and their effect on human health with their permissible limits are enumerated in Table 1.

Effect of Heavy Metal Polluted Soil on Plant Growth

Although plants require certain heavy metals for their growth and uptake, excessive amounts of these metals can become toxic to plants. The ability of plants to accumulate essential metals equally enables them to acquire other nonessential metals. Some of the direct toxic effects caused by high metal concentration include inhibition of cytoplasmic enzymes and damage to cell structures due to oxidative stress. The Toxicity of heavy metals to life forms are shown in Table 2 (Chibuike and Obiora 2014). Due to the high prevalence of heavy metals in the environment, their residues also reach and are assimilated into medicinal plants (Sarma et al. 2012). Contamination during cultivation, inadvertent cross-contamination during processing and the purposeful introduction of heavy metals for alleged medicinal purposes are three key mechanisms that have been proposed to explain heavy metal contamination of medical plant-based products (Denholm 2010).

Plant Survival Strategies to Increasing Metal Concentrations

Plants have devoted three various behaviors against heavy metals. First group named as metal excluders avoid heavy metals to enter their aerial parts. Second group, known as metal indicators, accumulate metals in their above-ground tissues and the metal levels in the tissues of these plants generally reflect metal levels in the soil.

The third and most important group of plants includes around 500 plant species is hyper accumulators which concentrate metals in their above-ground tissues to levels far exceeding those present in the soil. Localization of metal ions in roots and shoots in nontoxic forms, binding of toxic metals in cell walls of roots and leaves and sequester metals into the vacuoles or compartments of the cytosol are three major procedure for heavy metal accumulation and keep them away from active metabolic sites in plant cells in tolerant plants (Cosio et al. 2004) (Fig. 1).

Novel approaches such as transcriptomics, proteomics, and metabolomics clear the function of the plants cells in heavy metal area. Heavy metal accumulators are increasing steadily and some are presented in Table 3 (Memon and Schroder 2009).

In the last few decades many scientists in different parts of the worlds has worked out the metals bioaccumulation potential of various species and some are presented in Table 4.

Molecular Basis of Metal Uptake

ESTs expressed sequence tags analysis and Comparing EST sequences of the target species with the appropriate reference model species or additional public databases is one of important performance to survey gene expression pattern and determining major gene involved in heavy metal tolerance for species whose complete genome sequence information is not available (Roosens et al. 2008). Analysis of quantitative trait loci (QTLs) involved in metal tolerance is a perfect method for identifying

Table 2 Toxicity of heavy metals to different plant species (Chibuike and Obiora 2014)

Heavy metal	Plant species	Effects	References
As	Rice (*Oryza sativa*)	Reduction in seed germination; decrease in seedling height; reduced leaf area and dry matter production	Abedin et al. (2002)
	Tomato (*Lycopersicon esculentum*)	Reduced fruit yield; decrease in leaf fresh weight	Barrachina et al. (1995)
	Canola (*Brassica napus*)	Stunted growth; chlorosis; wilting	Cox et al. (1996)
Cd	Wheat (*Triticum* sp.)	Reduction in seed germination; decrease in plant nutrient content; reduced shoot and root length	Yourtchi and Bayat (2013)
	Garlic (*Allium sativum*)	Reduced shoot growth; Cd accumulation	Jiang et al. (2001)
	Maize (*Zea mays*)	Reduced shoot growth; inhibition of root growth	Wang et al. (2007)
Co	Tomato (*Lycopersicon esculentum*)	Reduction in plant nutrient content	Jayakumar et al. (2013)
	Mung bean (*Vigna radiata*)	Reduction in antioxidant enzyme activities; decrease in plant sugar, starch, amino acids, and protein content	Jayakumar et al. (2008)
	Radish (*Raphanus sativus*)	Reduction in shoot length, root length, and total leaf area; decrease in chlorophyll content; reduction in plant nutrient content and antioxidant enzyme activity; decrease in plant sugar, amino acid, and protein content	Jayakumar et al. (2007)
Cr	Wheat (*Triticum* sp.)	Reduced shoot and root growth	Sharma and Sharma (2003)
	Tomato (*Lycopersicon esculentum*)	Decrease in plant nutrient acquisition	Moral et al. (1995)
	Onion (*Allium cepa*)	Inhibition of germination process; reduction of plant biomass	Nematshahi et al. (2012)
Cu	Bean (*Phaseolus vulgaris*)	Accumulation of Cu in plant roots; root malformation and reduction	Cook et al. (1997)
	Black bindweed (*Polygonum convolvulus*)	Plant mortality; reduced biomass and seed production	Kjær and Elmegaard (1996)
	Rhodes grass (*Chloris gayana*)	Root growth reduction	Sheldon and Menzies (2005)

(continued)

Table 2 (continued)

Heavy metal	Plant species	Effects	References
Hg	Rice (*Oryza sativa*)	Decrease in plant height; reduced tiller and panicle formation; yield reduction; bioaccumulation in shoot and root of seedlings	Du et al. (2005)
	Tomato (*Lycopersicon esculentum*)	Reduction in germination percentage; reduced plant height; reduction in flowering and fruit weight; chlorosis	Shekar et al. (2011)
Mn	Broad bean (*Vicia faba*)	Mn accumulation shoot and root; reduction in shoot and root length; chlorosis	Arya and Roy (2011)
	Spearmint (*Mentha spicata*)	Decrease in chlorophyll a and carotenoid content; accumulation of Mn in plant roots	Asrar et al. (2005)
	Pea (*Pisum sativum*)	Reduction in chlorophylls a and b content; reduction in relative growth rate; reduced photosynthetic O_2 evolution activity and photosystem II activity	Doncheva et al. (2005)
	Tomato (*Lycopersicon esculentum*)	Slower plant growth; decrease in chlorophyll concentration	Shenker et al. (2004)
Ni	Pigeon pea (*Cajanus cajan*)	Decrease in chlorophyll content and stomatal conductance; decreased enzyme activity which affected Calvin cycle and CO_2 fixation	Sheoran et al. (1990)
	Rye grass (*Lolium perenne*)	Reduction in plant nutrient acquisition; decrease in shoot yield; chlorosis	Khalid and Tinsley (1980)
	Wheat (*Triticum* sp.)	Reduction in plant nutrient acquisition	Pandolfini et al. (1992)
	Rice (*Oryza sativa*)	Inhibition of root growth	Lin and Kao (2005)
Pb	Maize (*Zea mays*)	Reduction in germination percentage; suppressed growth; reduced plant biomass; decrease in plant protein content	Hussain et al. (2013)
	Portia tree (*Thespesia populnea*)	Reduction in number of leaves and leaf area; reduced plant height; decrease in plant biomass	Kabir et al. (2009)
	Oat (*Avena sativa*)	Inhibition of enzyme activity which affected CO_2 fixation	Moustakas et al. (1994)

(continued)

Table 2 (continued)

Heavy metal	Plant species	Effects	References
Zn	Cluster bean (*Cyamopsiste tragonoloba*)	Reduction in germination percentage; reduced plant height and biomass; decrease in chlorophyll, carotenoid, sugar, starch, and amino acid content	Manivasagaperumal et al. (2011)
	Pea (*Pisum sativum*)	Reduction in chlorophyll content; alteration in structure of chloroplast; reduction in photosystem II activity; reduced plant growth	Doncheva et al. (2001)
	Rye grass (*Lolium perenne*)	Accumulation of Zn in plant leaves; growth reduction; decrease in plant nutrient content; reduced efficiency of photosynthetic energy conversion	Bonnet et al. (2000)

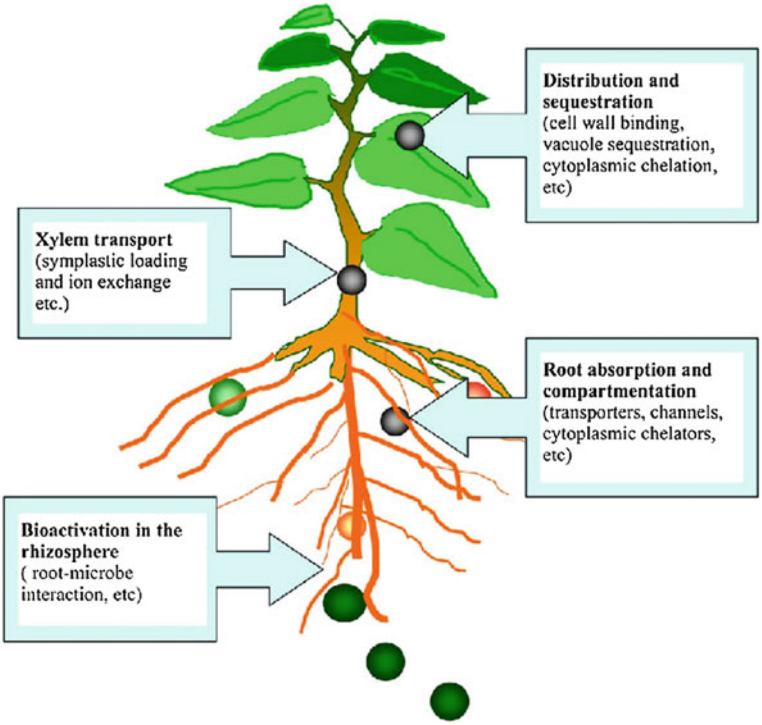

Fig. 1 Major processes proposed to be involved in heavy metal hyperaccumulation by plants (Yang et al. 2005)

Table 3 Examples of some plants and metals they can remediate (Sarma 2011)

Plant species	Metal	Reference
Alyssuim wulfenianum	Ni	Reeves and Brooks (1983)
Azolla pinnata, Lemna minor	Cu, Cr	Jain et al. (1990)
Brassica Juncea	Cu, Ni	Ebbs and Kochian (1997)
Arobiadopais hallerii	Cd	Kupper and Kochian (2010)
Pteris vittata	Cu, Ni, Zn	Ma et al. (2001)
Psychotria douarrei	Ni	Davis et al. (2001)
Pelargonium sp.	Cd	Dan et al. (2002)
Thlaspi caerulescens	Cd and Ni	Assuncao and Schat (2003)
Arabidapsis hallerii	Cd	Bert et al. (2003)
Amanita muscaria	Hg	Falandysz et al. (2003)
Arobis gemmifera	Cd and Zn	Kubota and Takenaka (2003)
Pistca stratiotes	Ag, Cd, Cr, Cu, Ni, Pb	Odjegba and Fasidi (2004)
Piptathertan miliacetall	Pb	Garcia et al. (2004)
Astragulus bisukatus, Brassica Juncea	Selenium	Ellis et al. (2004)
Sedum alfredli	Pb	Xiong et al. (2004)
Sesbania drummondi	Pb	Sharma et al. (2004)
Lemn agibba	As	Mkandavire and Dude (2005)
Pteris vittata	As	Dong (2005)
Thlaspi caerulescens	Zn, Pb, Zn, and Cd	Sun et al. (2005)
Sedum alfredii	Pb	Banasova and Horak (2008)
Chengiopanax sciadopkvltoides	Mn	Mizuno et al. (2008)
Tamarix smyrnensis	Cd	Manousaki et al. (2008)
Brassica napus	Cd	Selvam and Wong (2008)
Arabidopsis thaliana	Cd/Zn	Saraswat and Rai (2009)
Crotalaria juncea	Ni and Cr	Saraswat and Rai (2009)
Rorippaglobosa	Cd	Sun et al. (2010)

major genes in plants which their genome maps are trolley identified (Deniau and Pieper 2006). Many researchers have tried to introduce new hyperaccumulating transgenic plants after finding the major genes involved in heavy metal tolerance. The responses of transgenic plants and its biosynthetic pathway genes against heavy metal stress are listed in Table 5 (Yang et al. 2005). A summary of the most effective transgenes and the effects of their expression on tolerance, accumulation, and volatilization of metals in plants is given in Tables 5 and 6.

Researches on gene expression pattern during heavy metal stress have demonstrated that genes coding membrane transporters responsible for the uptake, efflux, translocation, and sequestration of mineral nutrients overexpressed under adaptive situations. Plants ability in take up and translocate of metals to avoid their direct

Table 4 Examples of some metal hyperaccumulator (Sarma 2011)

Plant species	Metal	Bioaccumulation	References
Sebertia acuminate	Ni	25% by wt, dried sp	Jaffre et al. (1976)
Ipomea alpine	Cu	12,300 mg kg^{-1}	Baker and Walker (1989)
Eichornia crassipes	Ni	6000 mg kg^{-1}	Lytle et al. (1998)
Alternanthera sessilis	Cv	1017 mg kg^{-1}	Sinha et al. (2002)
Zea mays L. Cv Ganga 5	Cr	2538 mg kg^{-1}	Sharma and Sharma (2003)
Pteris vittata	As	2300 mg kg^{-1}	Dong (2005)
Sesbania drummondi	Cd	1687 mg kg^{-1}	Israr et al. (2006)
Thlaspi caerlescens	Zn	19,410 mg kg^{-1}	Banasova and Horak (2008)
Thlaspi caerlescens	Cd	80 mg kg^{-1}	Banasova and Horak (2008)
Myriophyllurn heterophyllum	Cd	21.46 μg g^{-1}	Sivaci et al. (2008)
Potamogetan crispus	Cd	49.09 μg g^{-1}	Sivaci et al. (2008)
Sorghum sudanense	Cu	5330 mg kg^{-1}	Wei et al. (2008)
Phragrnites australis	Cr	4825 mg kg^{-1}	Calheiros et al. (2008)
Arabis paniculata	Cd	1127 mg kg^{-1}	Zeng et al. (2009)
Atriplex halimus	Cd	60,651 μg g^{-1} DW	Nedjimi and Daoud (2009)
Sedum alfredii	Cd	2183 mg kg^{-1}	Jin and Liu (2009)
Sedum alfredii	Zn	13,799 mg kg^{-1} DW	Jin and Liu (2009)
Brassica juncea	Ni	3916 mg kg^{-1} DW	Pollard et al. (2009)
Potentilla griffithii	Zn	19,600 mg kg^{-1} DW	Saraswat and Rai (2009)
Rorippa globosa	Cd	218.9 μg g^{-1} DW	Hu et al. (2009)
Thlospi praecox Wulfen	Cd	>1000 μg g^{-1} DW	Sun et al. (2010)

toxicity for cells are consequence of powerful heavy metal transportation systems. Transport proteins and intracellular high-affinity binding sites mediate the uptake of metals across the plasma membrane. The overview of the metal transporters and their tissue-specific expression in plants is summarized in Table 7 (Memon and Schroder 2009).

Phytoremidation

Remediation is the main strategy to protect the environment from heavy metal toxic effects. Phytoremediation is one of most promising technologies that is used for remediation of vast quantities of heavy metals. The potential of heavy metal phytoremediation depends on the capability of a plant to accumulate excessive concentrations of metals (Ullah et al. 2015).

Table 5 Genes introduced into plants and the effects of their expression on heavy metal tolerance, accumulation, or volatilization (Yang et al. 2005)

Gene	Target	Product	Source	Maximum observed effect
merA	Hg(II) reductase	Gram-negative bacteria	*Liriodendron tulipifera*	50 mmol l1 $HgCl_2$; 500 mg $HgCl_2$ kg^{-1}
merA	Hg(II) reductase	Gram-negative bacteria	*Nicotiana tabacum*	V: Hg-volatilization rate increase 10-fold
			Arabidopsis thaliana	T: 10 mmol l1 CH_3HgCl (440-fold)
merB	Organomercurial lyase	Gram-negative bacteria	*A. thaliana*	V: Up to 59 pg Hg(0) mg^{-1} fresh biomass min^{-1}
APS1	ATP sulfurylase	*A. thaliana*	*B. juncea*	A: Two-fold increase in Se concentration
MT-I	MT	Mouse	*N. tabacum*	T: 200 $mmol^{-1}$ $CdCl_2$ (20-fold)
CUP1	MT	*Saccharomyces cerevisiae*	*B. oleracea*	T: 400 $mmol^{-1}$ $CdCl_2$ (approximately 16-fold)
gsh2	GSH synthase	*E. coli*	*B. juncea*	A: Cd concentrations 125%
gsh1	g-Glu-Cys synthase	*E. coli*	*B. juncea*	A: Cd concentrations 190%
NtCBP4	Cation	Channel	*N. tabacum*	A: Pb concentrations 200%
				T: 250 $mmol^{-1}$ $NiCl_2$ (2.5-fold), Pb-sensitive
ZAT1	Zn	Transporter	*A. thaliana*	T: Slight increase
TaPCS1	PC	Wheat	*Nicotian aglauca* R. Graham	A: Pb concentrations 200%

Relative values refer to control plants not expressing the transgene. References are given in the text. *A* accumulation in the shoot; *GSH* glutathione, *MT* metallothionein; *T* tolerance; *V* volatilization

Phytoremediation involves accumulation of heavy metals in the roots and shoots of plants. Plants used for phytoextraction usually possess the following characteristics: rapid growth rate, high biomass, extensive root system, and ability to tolerate high amounts of heavy metals (Chibuike and Obiora 2014). Phytoremediation of contaminated soils is generally believed to be effective through one or more of the following mechanisms or processes: phytoextraction, phytostabilization, phytodegradation, phytovolatilization, and rhizodegradation are phytoremediation mechanisms of contaminated soils. These mechanisms are described briefly in Table 8 (Oh et al. 2013). Numerous kindes of medical plants have been explored for phytoremediation (Padmavathiamma and Li 2007; Sarma 2011) however investigation to prevent elevated concentrations of heavy metals in medicinal plants should be done before marketing (Sharma et al. 2009; Steenkamp et al. 2000).

Table 6 Transgenic plants and heavy metal stress (Singh et al. 2016)

Antioxidant and/or its Source biosynthetic pathway gene (s)	Source	Target transgenic	Response of transgenic plants and/or organisms	References
CAT3	*Brassica juncea*	*Nicatiana tabacum*	Cd stress tolerance, better seedling growth, and longer roots	Gichner et al. (2004)
CAT	*Brassica juncea*	*Nicatiana tabacum*	Zn and Cd stress tolerance, 2.0-fold higher CAT activity than wild type, lower H_2O_2 level, and cell death	Guan et al. (2009)
CAT1 and CAT2	*Brassica oleracea*	*Arabidopsis*	Low level of H_2O_2 and enhanced stress tolerance	Chiang et al. (2013)
Cu/Zn SOD and/or CAT	*Zea mays*	*Brassica compestris*	Less reduction in photosynthetic activity than wild type under SO_2 stress SOD activity was 1.5–2.5-fold greater than wild type and enhanced Al tolerance	Tseng et al. (2007)
Mn SOD	*Trificumaestivum*	*Brassica napus*	SOD activity was 1.5–2.5-fold greater than wild type and enhanced Al tolerance	Basu et al. (2001)
cylGR/cpGR	*Bacterial*	*Brassica juncea*	cpGR transgenic showed lower Cd accumulation and 50 times higher GR activity than wild type plants	Pilon-Smits et al. (1999)
GR	*Brassica rapa*	*Eschenthia coli*	Increased tolerance against H_2O_2 induced by Cd, 2n, and Al due to an enhanced OR activity	Kim et al. (2009)
DHAR/GR/GST	*Escherichia coil*	*Nicatiana tobacum*	Overexpression enhanced metal tolerance due to maintained red-tax couples such as ascorbate and glutathione	Le Martret et al. (2011)
DHAR	*Oryza sativa*	*Eschenthia coli*	DHAR-overexpressing E. colt strain was more tolerant to oxidant and metal-mediated stress conditions than the control E coil strain	Shin et al. (2008)
MDHAR/DHAR	*Arabidopsis*	*Nicatiana tobacum*	DHAR but not MDHAR enhanced Al tolerance by maintaining ascorbate level	Yin et al. (2010)

(continued)

Table 6 (continued)

Antioxidant and/or its Source biosynthetic pathway gene (s)	Source	Target transgenic	Response of transgenic plants and/or organisms	References
GST	*Tericoderm aviens*	*Nicatiana tobacum*	Enhanced Cd tolerance simultaneously no Cd accumulation, increased activity of SOD, CAT, GST, APX, and GPX than wild type	Dixit et al. (2011)
Sulfite oxidase (SO)	*Zea mays*	*Nicatiana tobacum*	Increased tolerance against S due to enhanced OAT-mediated H_2O_2 scavenging	Xia et al. (2012)
TcPCS1	*Thlaspi caerulescens*	*saccharcrnycescerevisiae and Nicotianatabacurn*	Increased tolerance to Cd due to the decreased lipid peroxiclation and enhanced activities of SOD, POD, and CAT	Liu at at. (2011)
Serin acetyl transferase	*Thlaspi goesingense*	*Escherichia coil*	Imparts Ni and Co tolerance due to involvement of glutathione	Freeman et al. (2005)

Table 7 Some of the identified metal transporters and their expression patterns in plants

Plant species	Protein families	Gene name	Metals	Tissue expression	References
A. thaliana, *A. halleri,* *L. esculentum*	P-Type ATPase	AtHMA1-8, AhHMA3-4, TcHMA4, GmHMA8, OsHMA9	Cu, Zn, Cd, Co, Pb	Shoots and roots	Bernard et al. (2004), Xing et al. (2008), Talke et al. (2006)
A. thaliana, *A. halleri,* *T. caerulescens,* *G. max,* *O. sativa*	Nramp	AtNRAMP1-6, LeNRAMP1-3, AhNRAMP3	Fe, Cd	Shoots and roots	Bereczky et al. (2003), Lanquar et al. (2005)
A. thaliana, *O. sativa*	ZIP	AtZIP1-12, OsZIP4	Zn	Shoots and roots	Filatov et al. (2006), Ishimaru et al. (2005), Roosens et al. (2008)
A. thaliana, *T. caerulescens,* *L. esculentum,* *O. sativa,* *N. tabacum*	IRT	AtIRT1, OsIRT1-2, LeIRT1-2, TcIRT1-2, NtIRT1	Cd, Zn	Shoots and roots	Kerkeb et al. (2008), Plaza et al. (2007)
A. thaliana, *A. halleri,* *T. goesingense,* *N. tabacum,* *P. trichocarpa,* *P. deltoids*	CDF	AtMTP1, TgMTP1, AhMTP1, PtdMTP1, NtMTP1	Zn	Roots	Kawachi et al. (2008), Shingu et al. (2005), Willems et al. (2007)

Table 8 Phytoremediation mechanisms for treatment of contaminated soils (Oh et al. 2013)

Mechanisms	Description
Phytoextraction	Plants absorb contaminants and store in above-ground shoots and the harvestable parts of roots
Phytostabilization	Roots and their exudates immobilize contaminants through adsorption, accumulation, precipitation within the root zone, and thus prevent the spreading of contaminants
Phytodegradation	Plant enzymatic breakdown of organic contaminants, both internally and through secreted enzymes
Rhizodegradation (phytostimulation)	Plant roots stimulate soil microbial communities in plant root zones to break down contaminants
Phytovolatilization	Contaminants taken up by the roots through the plants to the leaves and are volatized through stomata where gas exchange occurs

Effects of Heavy Metals on Growth and Metabolic Status of Medical Plants

Heavy metal accumulation rate in different parts of medical plants have been reported in Table 9.

Heavy metal stress cause lipid oxidation processes and led oxylipins generation. Oxylipins starts signal transduction process for plant defense mechanism. The induction of biosynthesis and accumulation of secondary metabolites such as phenylpropanoids, terpenoids, and alkaloids are one of the major defense mechanisms of plants (Mithofer et al. 2004).

Table 9 Heavy metal accumulation potency of some medical plants (Nasim and Dhir 2010)

Plant species	Heavy metal	Values	References
Amaranthus dubius	Cd	150 ppm	Chunilall et al. (2005)
Amaranthus hybridus	Hg	336 ppm	Chunilall et al. (2005)
Agave amaniensis	Cd	900 µg g^{-1} dry wt	Kartosentono et al. (2002)
	Pb	1390 µg g^{-1} dry wt	Kartosentono et al. (2002)
Costus speciosus	Cd, Pb	530 µg g^{-1} dry wt	Kartosentono et al. (2002)
Matricaria chamomilla	Zn	271 mg kg^{-1} dry wt	Grejtovsky et al. (2001)
Ocimum tenuiflorum	Cr	419 µg g^{-1} dry wt	Rai et al. (2004)
Matricaria chamomilla	Zn	271 mg kg^{-1} dry wt	Grejtovsky et al. (2001)
Phyllanthus amarus	Cd	82 ppm	Rai et al. (2005)
Hypericum sp.	Cd	0.5 mg kg^{-1} dry wt	Chizzola and Lukas (2006)
Cuminum cyminum	Fe	1.4 mg g^{-1} dry wt	Maiga et al. (2005)
Bombax costatum	Fe	1.5 mg g^{-1} dry wt	Maiga et al. (2005)
Hibiscus sabdariffa	Mn	243 µg g^{-1} dry wt	Maiga et al. (2005)
Spilanthes oleracea	Zn	62.8 µg g^{-1} dry wt	Maiga et al. (2005)
Bombax costatum	Zn	67.1 µg g^{-1}	Maiga et al. (2005)
Aesculus Hippocastanum	Pb	1480 µg g^{-1}	Caldas and Machado (2004)
Tilia sp.	Zn	13.8–32.5 mg kg^{-1}	Celechovska et al. (2004)
Sambucus nigra	Zn	30.8–49.9 mg kg^{-1}	Celechovska et al. (2004)

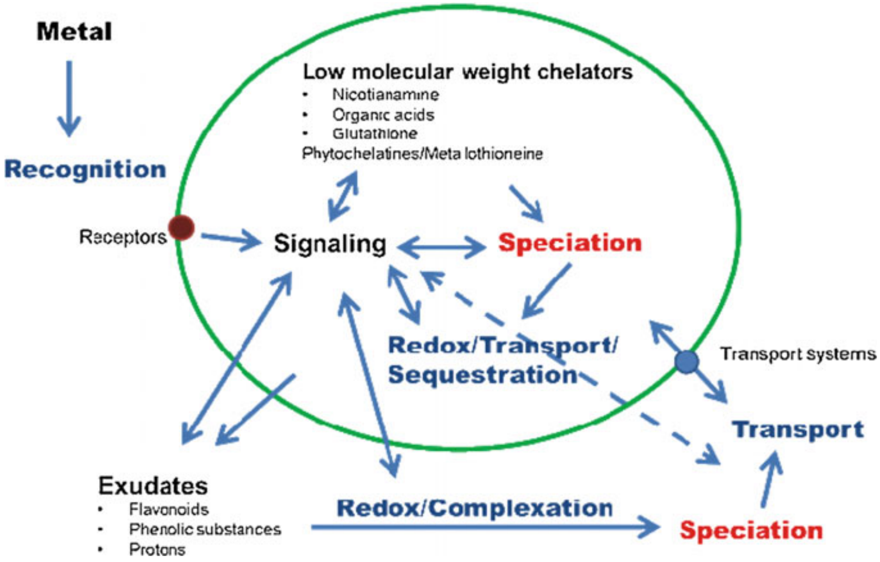

Fig. 2 Short overview about some important aspects of cellular metal interaction (Viehweger 2014)

The general view of heavy metal signal transduction pathway in plants and role of oxylipins and secondary in detoxification process are summarized in Fig. 2.

Table 10 provides an insight in the complex signaling network induced by various environmental stress conditions and their similarity patterns (Viehweger 2014).

Several researches have showed plants exposed to heavy metal stress show varying degrees of secondary metabolite response (Table 11).

Plants exposed to heavy metal stress show differential responses in synthesis and accumulation of pharmacologically active molecules. Such responses range from negative effects on secondary metabolite production in a few plant species, viz., *Matricaria recutita*, to stimulatory effects that result in enhanced metabolite production in other species. Increases in heavy metal-induced secondary metabolite biosynthesis have been reported to occur in some medicinal plant species (Table 12) (Nasim and Dhir 2010). Utilizing heavy metal as inducers for higher production of secondary metabolites depend on the plant part used as consumer safety needs (Street 2012).

Table 10 Overview of some heavy metal triggered signals in comparison to other environmental stresses

Heavy metal	Signal	Other stress conditions	Cellular responses	References
Cu	Calcium fluxes	Cold, drought, salinity	Phosphoprotein cascades, 2nd signalling molecules	Nielsen et al. (2003)
Cd, Cr	Mitogen activated protein kinase (MAPK) pathways	Osmotic stress, pathogen contact	Activation of transcription factors and stress-responsive genes	Liu et al. (2010)
Fe	pH shifts	Pathogen contact	Induction of secondary metabolism	Viehweger et al. (2006)
Co, Zn	Plant hormones like abscisic acid or ethylene	Cold, drought, salinity	Calcium signaling, guard cell regulation (water balance)	Zengin (2006)
Cd, Cu	Jasmonic acid	Pathogen contact, sugar, drought, salinity	Defence/stress response, development, induction of secondary metabolism	Howe and Schilmiller (2002)
Redox-active metals like Fe, Cu; almost all heavy metals at higher concentrations	Reactive oxygen species	Pathogen contact, cold, drought, salinity, high light intensity	Phosphoprotein cascades, activation of transcription factors and stress-responsive genes, activation of antioxidative defence	Ahmad et al. (2008)

Table 11 Heavy metal stress affecting secondary metabolite production (Street 2012)

Plant species	Main findings relating to secondary metabolites	References
Hypericum perforatum L.	In the presence of Ni, the plant completely lost the ability to produce or accumulate hyperforin and demonstrated a 15–20-fold decrease in the concentration of pseudohypericin and hypericin	Murch et al. (2003)
Ocimum tenuiflorum L.	Cr stress induced the production of eugenol	Rai et al. (2004)
Dioscorea bulbifera L.	The occurrence of Cu stimulated diosgenin production	Narula et al. (2005)
Phyllanthus amarus Schum and Thonn	Phyllanthin and hypophyllanthin was enhanced by Cd stress	Rai et al. (2005)
Bacopa monnieri L.	The level of bacoside-A increased due to increased Fe in the media	Sinha and Saxena (2006)
Trigonella foenum-graecum L.	Cd and Co increased diosgenin levels however Cr and Ni inhibited its production	De and De (2011)

Table 12 List of plants secondary metabolites increment under heavy metal stress (Nasim and Dhir 2010)

Plant species	Heavy metal	Compound	Medicinal properties	References
Catharanthus roseus	Cd 0.05–0.4 mM	Ajmalicine	Anticancer, antidiabetic	Zheng and Wu (2004)
Phyllanthus amarus	Cd (0.1–1 mM)	Hypophyllanthin	Hepatoprotective, diuretic, stomachic	Rai et al. (2005)
Matricaria chamomilla	CuC12 2%, Cd 60–120 µM Zn 50 mg kg^{-1} soil	Herniarin, Umbelliferone essential oil, sesquiterpenes	Anti-inflammatory, spasmolytic effect	Eliasova et al. (2004)
Salvia miltiorrhiza	Ag, Cu, Zn, Fe, Mn15–40 µM	Tanshinon	Broad spectrum bactericide, dilating coronary artery	Zhang et al. (2004), Guo et al. (2005)
Ononis arvensis	Ni, Co, Cr 6.3 µmol	Flavonoid	Anti-inflammatory, antiproliferative, anticancer, antioxidant, cardioprotective	Tumova et al. (2001), Tumova and Blazkova (2002)
Rheum palmatum	Cd 10 µM	Anthracene derivatives	Antioxidant	Kasparova and Siatka (2004)
Thalictrum rugosum	Cu 20–500 µM	Berberine	Antimicrobial in the treatment of dysentery and infectious diarrhea	Kim et al. (1991)
Hibiscus sabdariffa sabdanffa	Co 20 mg kg^{-1} soil Ni 25 mg kg^{-1} soil	Anthocyanins Flavons	Diaphoretic, hepatic and gastric disorders, arteriosclerosis, intestinal infections	Eman et al. (2007)
Ocimum tenuiflorum	Cr 20 µM	Eugenol	Antiseptic, antispasmodic, antibacterial	Rai et al. (2004)
Hypericum perforatum	Cr(VI) 0.1 µM	Hypericin Pseudohypericin	Minor burns, wounds, skin inflammations, nerve pain	Tirillini et al. (2006)
Datura stramonium	Cd 1 mM	Hyoscyamine	Peptic ulcers, diarrhea, and bronchial asthma	Furze et al. (1991)
Mentha arvensis	Zn	Essential oil, menthol	Antibacterial, antifebrile, effective in rhinitis, cough sore throat, colic	Misra (1992)
Costus speciosus	Pb 30 mg L^{-1}	Sitosterol	Purgative, febrifuge, expectorant	Kartosentono et al. (2002)
Pluchea lanceolata	200 µM $ZnSO_4$ or 150 µM $CuSO_4$	Quercetin, Tropane alkaloids	Inflammations, bronchitis, psoriasis, piles, antipyretic, analgesic, laxity, Diuretic, sedative, antispasmodic	Kumar et al. (2004)

International Standards of Metals Residuals in Medicinal Plants

There are immense discrepancies between countries regarding regulatory requirements to pledge safety and quality of plant-based products (Diederichs et al. 2006). Several regulations have already been established worldwide for medicinal plants such as the US Pharmacopoeia (USP), Italian Pharmacopoeia (FUI), and European Pharmacopoeia (Ph. Eur.). Moreover, there are legal frameworks at national and/or regional levels that are designed to regulate the quality of plant-based products (Sarma et al. 2012). Several countries, including Canada, China, Malaysia, Singapore and Thailand, have developed their own national guidelines to ensure satisfactory levels of heavy metals in medicinal plants and plant-based products (Table 13) (Street 2012).

Conclusions and General Discussion

The presence of heavy metals in medicinal plants may stimulate production of bioactive compounds in many plant species. Although, the exact mechanism by which this happens remains unclear. Oxidative stress induced by heavy metals triggers signaling pathways that affect production of specific plant metabolites. In particular, reactiveoxygen species (ROS), generated during heavy metal stress, may cause lipid peroxidation that stimulates formation of highly active signaling compounds capable of triggering production of bioactive compounds (Nasim and Dhir 2010).

Heavy metal tolerance is a genetically complex process that involves many components of signaling pathways, multigenic in nature (Vinocur and Altman 2005). Therefore, plant-engineering strategies for heavy metal tolerance depend on the expression of gene(s) whose product(s) are involved either in signaling and regulatory pathways or in the synthesis of functional and structural proteins and metabolites that confer heavy metal stress tolerance. Recently, several efforts are being made to improve heavy metal stress tolerance capacity through genetic engineering with several achievements (Singh et al. 2016).

Phytoremediation holds great potential as an environmental cleanup technology and has been investigated substantially since the last two decades. Considerable interest in phytoremediation exists by both government and industry. The biggest advantage of phytoremediation is its low cost. Phytoremediation can be up to 1000-fold cheaper compared with conventional remediation methods such as excavation and reburial. In general, fast-growing, high-biomass, competitive, hardy, and metal-tolerant plant species could either be selected or could be generated by genetic manipulation and be used for remediation of different polluted sites.

The presence of several hundreds of catabolic enzymes and transporter sequences suggest that plants may have rich potential to mobilize and detoxify toxic

Table 13 National limits for heavy metals in herbal medicinal products (Street 2012)

Country		Arsenic (As)	Lead (Pb)	Cadmium (Cd)	Chromium (Cr)	Mercury (Hg)	Copper (Cu)	Lead (Pb)
Canada	Raw herbal materials	5 ppm	10 ppm	0.3 ppm	2 ppm	0.2 ppm		
	Finished herbal products	0.01 mg/day	0.02 mg/day	0.06 mg/day	0.02 mg/day	0.02 mg/day		
China	Herbal materials	2 ppm	10 ppm	1 ppm		0.5 ppm		20 ppm
Malaysia	Finished herbal products	5 mg/kg	10 mg/kg			0.5 mg/kg		
Republic of Korea	Herbal materials							30 ppm
Singapore	Finished herbal products	5 ppm	20 ppm			0.5 ppm	150 ppm	
Thailand	Herbal material, finished herbal products	4 ppm	10 ppm	0.3 ppm				
WHO recommendations			10 mg/kg	0.3 mg/kg				

contaminants including organic and inorganic in their environment within their tissues and organs. Genomic and proteomic information gained from these sequenced plant species will greatly accelerate the phytoremediation process in situ considerable efforts have been taken by the European Science Foundation, and under this context, a COST 859 Action entitled “Phytotechnologies to promote sustainable land use and improve food safety has been launched since 2004. The main objective of this action is to provide a sound understanding of the absorption, translocation, storage, or detoxification mechanisms of essential or toxic mineral elements, as well as organic contaminants, and to prepare the best use of plants for sustainable land use management and improve food safety. Promotion of cooperation and of data exchange between working groups in this action have been encouraged and the present work is a part of such cooperation (Memon and Schroder 2009).

Further knowledge about metal tolerance in plants is mandatory for several purposes: (1) Predictions about health risk which is caused by metal accumulation in crop plants failing visible symptoms of phytotoxicity. (2) Generation of genetically engineered plants having an enhanced accumulation of metals valuable for nutritional purposes (biofortification). (3) Cleanup of metal contaminated soils (phytoremediation) and mining of rare metals which are accumulated in plant tissues (phytomining) (Viehweger 2014).

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