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Metallic Mineral Elements and Heavy Metals in Medicinal Plants

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ABSTRACT

A large proportion of the world's population relies on medicines from the herbal sources. In this review, data about the mineral element content of medicinal and aromatic plants, including major elements, trace elements and toxic heavy metals, will be discussed and compared. Plants and drugs with remarkable elemental compositions will be pointed out. The main focus will be given on plants used in and originating from Europe and the Mediterranean region. The main metallic mineral macronutrients accumulate usually in the order K > Ca > Mg. The contents of beneficial trace elements decrease commonly from Fe > Mn > Zn > Cu > Ni > Mo. Higher concentrations occur in the leaves compared to other plant parts. Amongst the toxic heavy metals Cd, Pb and Hg are the best investigated. Due to its high mobility in the soil and good availability to plants, monitoring Cd merits special attention. A range of plants shows the tendency to accumulate higher concentrations of this element. For these plants, which may display problematic Cd levels, production measures should be taken to minimize the Cd accumulation, taking into consideration the growing site, planting material and fertilization regime. Interactions in the uptake between various elements have been described. The most prominent one occurs between Cd and Zn. Furthermore, it will be discussed that during the preparation of herbal tea using boiling water, only a proportion of the minerals is extracted. Finally regulations to set limits for toxic heavy metals at the national or international level are considered.

Keywords: aromatic plants, cadmium, heavy metals, herbal drugs, lead, macronutrients, medicinal plants, micronutrients, spices

CONTENTS

INTRODUCTION

Medicinal plants, herbs and spices are grown in various regions under quite different ecological conditions with a range of agricultural practices. The plants may also be collected in the wild conditions. Owing to the great number of species and different plant organs used, a high variability in plant compounds is observed. In the quality assessment of medicinal plants and plant derived drugs, the main focus lies, generally, on active compounds or, when they are not clearly defined, on lead compounds.

Metallic ions play an important role in the metabolism of all the living organisms and are, therefore, integral components of plants (Marschner 1995; Lüttge *et al*. 2010). Mineral and trace elements of root, leaf, stem, fruit vegetables and legumes have been widely studied and compiled (Souci *et al*. 2000; Heseker and Heseker 2007). Until now there is no systematic collection of the data obtained about metallic elements in medicinal and spice plants. The data and reports available come from the studies that were performed with different purposes. These include the data regarding surveys of the elemental content of plants grown in a given region or country or drugs on the market in the region, specific experiments to investigate the metal uptake by the plants, plants grown on sites heavily contaminated with metals, and the studies to test and develop analytical methods for trace metals in plant material.

In this review mainly plants used in and originating from Europe and the Mediterranean region will be considered.

MINERAL MACRONUTRIENTS

K, Ca and Mg are referred as mineral macronutrients in higher plants because of the high requirements of these elements for plant growth. The uptake, accumulation and repartition of these elements are usually studied to determine the fertilization needs of plants to obtain optimized yields. To grow medicinal and aromatic plants, various recommendations, according to the specific plant species have been developed. Although these instructions contain concrete details about fertilization rates, exact data about mineral element contents of these plants are rather scarce. Examples of macronutrients in medicinal plants are listed in **Table 1**.

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Invited Review

Table 1 Major mineral element contents in various medicinal and aromatic plants (g/kg).

		Ca	Mg	K	Reference*
Achillea millefolium	Herb	9.81	2.16	3.13	Ra08
Arbutus andrachnae	Fruits	7.20	0.87	9.85	Se10
Arbutus unedo	Fruits	5.48	1.93	13.66	Se10
Artemisia absinthium	Herb	8.66	2.65	10.64	Ra08
Artemisia dracunculus	Leaves	8.16	0.52	1.89	Öz08
Betula pubescens	Leaves	11.0	3.94	10.3	Re01
Cassia angustifolia	Leaves	26.1	3.32	-	Ba06
Coriandrum sativum	Fruits	6.42	0.13	19.9	Öz08
Crataegus orientalis	Leaves	19.7	2.17	10.8	Öz08
Cynara scolymus	Leaves	11.8	3.86	9.03	Ra08
Echinaceae sp.	Herb	20.0	8.9	54.5	Ga06
Empetrum nigrum	Leaves	6.12	1.63	5.08	Re01
Eucalyptus globulus	Leaves	18.6	1.62	7.02	Qu05
Filipendula vulgaris	Herb	0.9 – 1.4	0.1 – 0.2	14.5	Im10
Foeniculum vulgare	Fruits	10,8	2.77	-	Ba06
Foeniculum vulgare	Fruits	5.12	2.43	17.5	Öz08
Helichrysum italicum	Herb	7.0	1.9	13.5	Bi09
Inula helenium	Roots	2.62	1.85	2.62	Ra08
Lavandula angustifolia	Flowers	10.6	3.4	24.5	Ra05
Marrubium vulgare	Herb	11.0	2.3	62.4	Ra05
Matricaria recutita	Flowers	12.7	1.64	-	Ba06
Matricaria recutita	Flowers	7.11	3.23	6.48	Ra08
Matricaria recutita	Flowers	8.19	2.16	27.5	Öz08
Matricaria recutita	Flowers	9.28	2.64	23.5	Qu05
Melissa officinalis	Leaves	13.2	6.7	18.8	Ra05
Melissa officinalis	Leaves	10.2	3.18	20.7	Öz08
Mentha x piperita	Herb	11.7 – 20.2	4.98 – 8.48	-	Fi03
Mentha x piperita	Leaves	21.1	5.48	24.8	Qu05
Mentha x piperita	Leaves	19.6	7.9	40.2	Ga06
Mentha x piperita	Leaves	4.20	2.32	18.5	Öz08
Mentha x piperita	Leaves	14.3	5.3	18.0	Ra05
Ocimum basilicum	Herb	13.3	10.9	34.8	Ra05
Ocimum basilicum	Herb	0.57	0.51	11.2	Öz08
Origanum vulgare	Herb	9.0	1.7	23.8	Ra05
Papaver somniferum	Seeds	10.9 – 15.3	3.2 – 3.7	6.1 – 8.2	Ch07
Pimpinella anisum	Fruits	2.48	0.95	4.41	Öz08
Plantago lanceolata	Leaves	48.0	6.41	19.2	Qu05
Rosa canina	Fruits	17.6	1.91	-	Ba06
Rosa canina	Fruits	3.48	1.02	5.32	Öz08
Rosmarinus officinalis	Leaves	9.5	2.3	21.1	Ra05
Rosmarinus officinalis	Leaves	0.22	0.23	11.2	Öz08
Rubus idaeus	Leaves	21.6	8.5	33.2	Ga06
Salix sp.	Leaves	11.0	3.01	16.5	Re01
Salvia fruticosa	Leaves	7.16	2.39	11.0	Öz08
Salvia officinalis	leaves	23.6	2.14	-	Ba06
Salvia officinalis	Leaves	9.0	2.8	21.6	Ra05
Sideritis spp.	Herb	4.51	0.76	7.12	Öz08
Taraxacum officinale	Leaves	29,2	4.46	29.7	Qu05
Taraxacum officinale	Leaves	22.9	6.0	82.2	Ga06
Thymbra spicata	Herb	1.93	0.50	1.20	Öz08
Tilia cordata	Flowers	3.00	0.15	21.4	Öz08
Tilia vulgaris	Flowers	22.7	1.98	-	Ba06
Trifolium pratense	Leaves	28.7	7.0	30.9	Ga06
Urtica dioica	Herb	30.5	3.78	-	Ba06
Urtica dioica	Herb	45.4 – 59.0	5.21 – 8.65	-	Fi03
Urtica dioica	Herb	8.65	1.32	8.08	Öz08
Vaccinium myrtillus	Leaves	18.8	12.6	9.9	Ga06
Vaccinium myrtillus	Leaves	7.89	2.28	8.73	Re01
Vaccinium vitis-idaea	Leaves	5.60	1.41	4.99	Re01

* See **Table 10** for references and annotations

K: Potassium (K) is the mineral element found usually in the highest concentrations in plant tissues. It is involved in a large number of metabolic functions including enzyme activation, protein synthesis, photosynthesis, phloem transport, osmoregulation, etc. K is easily mobile in the phloem and may be redistributed within the plant. For optimal growth, a K concentration of 2-5% of plant dry weight is required (Marschner 1995; Lüttge *et al*. 2010). Many of the plant drugs have K levels within this range, but there is also a range of products with lower K contents. The differences may arise from the great variability of the plant species belonging to different origins and the K availability in the respective soils.

Ca: In the plant cell, Ca is present mainly in the cell wall and in the vacuole, where it is involved in cell wall stabilization and secretory processes. A further function of Ca is its role as second messenger in signal transduction. Ca is rather immobile in the phloem, therefore it accumulates in older plant parts and the fruits are generally lower in Ca than leaves (Marschner 1995). Depending on the growth conditions, the Ca contents in plants can vary greatly, ranging from 0.1 to more than 5% Ca in the plant dry matter. Sometimes, Ca concentration in old leaves can reach more than 10% Ca in the dry matter without showing serious symptoms of growth inhibition (Marschner 1995). This range also applies for medicinal and aromatic plants. Some herbs may be rich in Ca as *Urtica dioica*. Another plant with high Ca contents is poppy (*Papaver somniferum*), where not only in the leaves but also in the seeds the Ca concentration is higher than the K concentration (Chizzola and Dobos 2007).

Mg: Magnesium (Mg) is a constituent of chlorophyll. It is involved in the activation of many ATP dependent enzymes and carbohydrate partitioning. The usual range of Mg content in the green tissues is 0.15 to 0.35% in the dry matter (Marschner 1995). The similar range is also found in medicinal plants. Some medicinal plants (e.g. *Urtica dioica*, *Mentha x piperita*), however, may have higher Mg contents in their leaves.

ESSENTIAL, BENEFICIAL AND OTHER METALLIC TRACE ELEMENTS

A range of metallic elements, referred as micronutrients, are essential for the plant metabolism in small amounts. These elements are iron, manganese, copper, zinc, nickel and molybdenum (Lüttge *et al*. 2010; Kabata-Pendias 2011). Deficiency symptoms may develop in plants when they are not present in adequate concentrations. In high concentrations these metals are toxic. Mineral elements, which stimulate growth and are essential only for certain species, are defined as beneficial elements. These elements are sodium, silicon and cobalt (Marschner 1995). Examples of Fe, Mn, Cu and Zn in medicinal and spice plants are presented in **Table 2**. The main features of these elements can be summarised as follows:

Fe: The relative easiness of Fe to change its oxidation state between Fe^{++} and Fe^{+++} is essential for the physiological role of this element. Iron is present in the redox systems of heme proteins and iron-sulfur proteins and it is involved in chloroplast development and photosynthesis (Lüttge *et al*. 2010). Due to the association of Fe with photosynthesis, the leaves display higher iron contents than other plant parts. In leaves, 50-100 mg Fe/kg appears to be the critical level below that deficiency symptoms develop in the plants. On the other hand, leaves may reach up to about 2000 mg Fe/kg. Because of the low toxicity of iron, these high levels are not of concern for human health. In fact, within a species, the iron content may vary greatly.

Mn: Manganese occurs at different oxidation states. Mn (II) is the prevalent form in plants. Mn plays an important role in redox processes, acts as an activator for numerous enzymes, and the O_2 evolution in photosynthesis is Mn-dependent (Marschner 1995; Lüttge *et al*. 2010). Generally, Mn levels in leaves range from 20 to 300 mg/kg (Kabata-Pendias 2011). This broad range is also valid for medicinal plants. Some fruits may also display much lower levels. On the other hand some species have Mn-rich leaves. Amongst them are the tea plant (Mehra and Baker 2007), some plants of the Ericaceae family such as *Vaccinium mytillus* (**Table 2**), and *Cistus ladanifer*, a plant growing in Mediterranean macchie formations (Alvarenga *et al*. 2004). In this case, toxicity may be avoided by sequestering Mn in non-metabolic compartments, such as the cell wall.

Cu: Copper in plants is present in copper-proteins that include some enzymes also and is essential for photosynthesis and other important processes, such as lignification, pollen formation and fertilization (Marschner 1995). The sufficient or normal range of Cu in plants is 5 to 20 mg/kg that is required for growth. The Cu toxicity symptoms develop when the concentrations exceeds 30 mg/kg (Kabata-Pendias 2011). As per **Table 2**, the Cu contents of medicinal plants are within this range. Some plant samples, however, may display comparatively low Cu contents. Various medicinal plants from Turkey, contain less than 6 mg/kg Cu (Zengin *et al.* 2008), whereas anis seeds, coriander, chamomile and fennel from Egypt are reported to have 13–21 mg/kg Cu (Dogheim *et al.* 2004). Some preparations used in plant protection during plant production contain Cu, so that the problem of Cu-containing residues may arise.

Zn: Zinc is a constituent or activator of a large number of enzymes. It is essential for the structural integrity of the ribosomes and is required for the membrane integrity (Marschner 1995). The zinc concentrations, found ordinary in leaves, are between 25 and 150 mg/kg. The Zn toxicity symptoms may develop when it exceeds 400 mg Zn/kg (Kabata-Pendias 2011), except in the case of tolerant plants (Walker and Bernal 2004). In view of the examples of medicinal and aromatic plants displayed in **Table 2**, the following values of Zn content have been documented: 4-162 mg/kg in fruit drugs, 3.5-205 mg/kg in herbs and leaves and 8-221 mg/kg in flower drugs. Comparable levels of the above mentioned trace elements were also found in plant-derived medicinal products. The median elemental concentrations of Cu, Fe, Mn and Zn were considered to be 9.1, 22.8, 39.8 and 46.6 mg/kg in pollen samples and 9.0, 62.5, 21.2 and 37.3 mg/kg in propolis capsules, respectively (Falcó *et al.* 2005).

Ni: Nickel may be involved in the nitrogen metabolism. It is present in the enzyme urease. The normal Ni concentrations in leaves are 0.1 to 5 mg/kg (Kabata-Pendias 2011). Ni may accumulate in the seeds of some Fabaceae members such as lupins (Marschner 1995). According to the examples of medicinal plants listed in **Table 3**, up to 11 mg/kg Ni are reported, generally. The higher Ni levels, recorded in some plants (*Crataegus*, *Salix*), might be the characteristic of these species, but it must be confirmed by further detailed studies. The reported level of 9.0 mg/kg Ni in willow is the average from 23 analysed samples from Northern Europe (Reimann *et al.* 2001).

Mo: Molybdenum has been recognised as an essential element for plants. It is involved in nitrogen metabolism as it is a constituent of the enzymes nitrate reductase and nitrogenase (Marschner 1995). However, information about Mo in medicinal herbs and spices is lacking. Wild collected plants in the boreal zone of Finland including *Vaccinium* species, birch and willow had Mo contents in the order of 0.046 mg/kg (Reimann *et al.* 2001).

Na: Sodium is ubiquitous in soils and the levels recorded in the soils may vary greatly. Na is highly mobile and readily available for plants. Szentmihalyi *et al.* (1998) measured the Na content in 22 different medicinal plants and found a range from 37–5584 mg Na/kg. High Na contents in various *Helichrysum italicum* samples from Corsica have also been reported by Bianchini (2009). Plants from the northernmost inland parts of Europe may be low in Na (Reimann *et al.* 2001). However, plants grown in saline soils may accumulate even higher Na concentrations. Plants adapted to saline soils are called halophytes. The scientists have interest, especially in arid regions, to develop medicinal plant varieties tolerant to salinity stress.

Some of the other metallic elements, analysed in various medicinal plants, are given below, illustrating the concentration range in which they occur in plant systems.

Al: Al is widely present in soils as it is a constituent of silicate minerals. Al is toxic to plant growth and may become a problem in acidic soils, where Al ions become available to plants. Seven different herbal drugs, widely consumed in Turkey, ranged from 87 to 596 mg Al/kg, the highest amount being found in *Urtica dioica* (Başgel and Erdemoğlu 2006). In 8 different Lamiaceae species, the Al content of plants from Serbia ranged from 49 to 378 mg/kg (Ražsić *et al.*

Table 2 Micronutrient contents in selected medicinal plants (mg/kg).

		Cu	Fe	Mn	Zn	Reference*
Achillea millefolium	Herb	9.1	80.0	63.5	22.9	Ra08
Achillea millefolium	Herb	2.1	36.2	20.3	12.8	Di09
Achillea millefolium	Herb	6.8	66.9	66.0	28.5	Ch03
Angelica litoralis	Flowers	14.5 – 23.5	33.7 – 56.4	44.4 – 78.2	97.7 – 127	Wi96
Angelica litoralis	Fruits	12.1 – 44.8	41.8 – 136	43.4 - 107	76.6 – 162	Wi96
Angelica litoralis	Leaves	9.0 – 21.3	13.4 – 210	48.5 – 111	36.4 – 79.3	Wi96
Angelica litoralis	Roots	6.0 – 33.9	35.2 – 259	72.8 – 189	51.9 – 142	Wi96
Arbutus andrachnae	Fruits	17.9	61.5	27.7	33.8	Se10
Arbutus unedo	Fruits	6.5	24.2	11.7	12.4	Se10
Artemisia absinthium	Herb	10.1	80.0	59.0	41.9	Ra08
Artemisia dracunculus	Leaves	1.76	26.5	126	4.0	Öz08
Artemisia herba-alba	Leaves	12.5	17.7	22.4	9.6	Kh09
Betula sp.	Leaves	2.2	108	-	165	Ka07
Betula pubescens	Leaves	5.7	82	1470	205	Re01
Capsella bursa-pastoris	Herb	8.2	30.5	33.5	35.1	Di09
Carum carvi	Fruits	11.2	54.6	29.9	35.5	Ch03
Cassia angustifoli	Leaves	3.9	323	23.0	23.3	Ba06
Centella asiatica	Leaves	7.5 – 13.0	101 – 761		104 – 246	On11
Centella asiatica	Roots	10.2 – 17.8	136 – 1205	-	134 – 273	On11
Coriandrum sativum	Fruits	0.38	6.6	0.4	14.1	Öz08
Crataegus orientalis	Leaves	3.66	214	16.9	17.9	Öz08
Crataegus sp.	Flowers	7.9	79.4	-	221	Ka07
Cynara scolymus	Leaves	8.0	124	63.2	26.5	Ra08
Echinaceae sp.	Herb	17.0	460	65.5	31.5	Ga06
Empetrum nigrum	Leaves	5.2	60	510	13	Re01
Eucalyptus globulus	Leaves	10	89	2134	23	Qu05
Filipendula vulgaris	Herb	12.3 – 16.8	21 – 37	3.5 – 4.0	10.4 – 11.8	Im10
Foeniculum vulgare	Fruits	16.2	225	27.8	37.0	Ba06
Foeniculum vulgare	Fruits	11.8	60.7	32.6	37.4	Ch03
Foeniculum vulgare	Fruits	3.74	66.0	13.6	10.9	Öz08
Glycyrrhiza glabra	Roots	2.1	12.0	5.1	6.1	Kh09
Glycyrrhiza glabra	Roots	6	175	15	8	Se08
Helichrysum italicum	Herb	11.8	196	267	58.0	Bi09
Hypericum perforatum	Herb	10	91	12	23	Se08
Hypericum perforatum	Herb	6.8	35.4	124	78.8	Di09
Hypericum perforatum	Herb	7.7	163	76.5	36.5	Ch03
Inula helenium	roots	9.9	325	53.0	20.5	Ra08
Laurus nobilis	Leaves	5	83	29	14	Se08
Lavandula angustifolia	Flowers	9.1	152	25	25.7	Ra05
Levisticum officinale	Leaves	7.0	248	78.9	24.4	Ch03
Linum usitatissimum	Seeds	12	-	26	55	Jo93
Marrubium vulgare	Herb	8.4	390	52	24.4	Ra05
Matricaria recutita	Flowers	8.3	503	60.2	30.6	Ba06
Matricaria recutita	Flowers	37.4	291	158	107	Di09
Matricaria recutita	Flowers	9.6	228	53.0	38.6	Ra08
Matricaria recutita	Flowers	20	701	76	49	Qu05
Matricaria recutita	Flowers	7.40	245	24.3	26.0	Öz08
Matricaria recutita	Flowers	7	382	26	21	Se08
Matricaria recutita	Flowers	10		32,2	36	Gj11
Matricaria recutita	Leaves	8		75,9	31	Gj11
Melissa officinalis	Herb	8.4	544	45.8	32.2	Ch03
Melissa officinalis	Leaves	10.4	285	38	21.4	Ra05
Melissa officinalis	Leaves	7.88	1296	36.3	21.7	Öz08
Mentha x piperita	Leaves	19	376	116	45	Qu05
Mentha x piperita	Leaves	33.0	734	139	51.5	Ga06
Mentha x piperita	Leaves	6.47	451	43.5	10.8	Öz08
Mentha sp.	Herb	56.9	333	148	74.6	Di09
Mentha spicata	Leaves	9	195	52	22	Se08
Mentha x piperita	Herb	10.2 – 13.8	95.0 – 244	110 – 237	34.3 – 54.3	Fi03
Mentha x piperita	Herb	15.4	305	54.0	28.7	Ch03
Mentha x piperita	Leaves	10.9	405	111	25.7	Ra05
Ocimum basilicum	Herb	9.1	-	-	20.0	Kr07
Ocimum basilicum	Herb	14.8	438	68	24.5	Ra05
Ocimum basilicum	Herb	0.64	44.7	4.8	23.3	Öz08
Ocimum basilicum	Leaves	11	390	46	16	Se08
Origanum vulgare	Herb	7.3	74	32	35.7	Ra05
Papaver somniferum	Blue seeds	10	-	120	71	Jo93
Papaver somniferum	Seeds	15.8 – 20.0	35.8 – 49.9	49.3 – 73.4	52.2 – 59.3	Ch07
Papaver somniferum	Seeds	16.9	66.3	57.8	56.9	Ch03
Papaver somniferum	Whit seeds	14	-	67	49	Jo93
Pimpinella anisum	Fruits	3.27	320	20.6	9.56	Öz08
Pimpinella anisum	Leaves	2.6	10.1	3.8	4.5	Kh09

Table 2 (Cont.)

		Cu	Fe	Mn	Zn	Reference*
Plantago lanceolata	Herb	17,0	219	29.6	30.6	Di09
Plantago lanceolata	Leaves	13	373	46	56	Qu05
Primula veris	Flowers	8,0	92.5	13.0	31.2	Di09
Rosa canina	Fruits	4.9	267	244	21.9	Ba06
Rosa canina	Fruits	0.71	8.9	13.9	4.0	Öz08
Rosa canina	Fruits	24	84	10	15	Se08
Rosmarinus officinalis	Leaves	5.9	546	29	15.0	Ra05
Rosmarinus officinalis	Leaves	0.04	20.5	1.7	7.4	Öz08
Rosmarinus officinalis	Leaves	5	173	17	9	Se08
Rubus idaeus	Leaves	18.5	1944	172	54.0	Ga06
Salix sp.	Leaves	7.7	79	310	125	Re01
Salvia fruticosa	Leaves	2.83	352	22.5	12.4	Öz08
Salvia officinalis	Leaves	35.8	297	32.6	48.4	Ba06
Salvia officinalis	Leaves	6.5	331	35	43.0	Ra05
Salvia officinalis	Leaves	10.0	635	52.8	33.0	Ch03
Satureja hortensis	Herb	7.4	-	-	30.8	Kr07
Sideritis congesta	Herb	6	44	7	10	Se08
Sideritis spp.	Herb	1.63	55.7	7.5	12.2	Öz08
Taraxacum officinale	Leaves	9.5	522	-	19.1	Ka07
Taraxacum officinale	Leaves	27	853	101	68	Qu05
Taraxacum officinale	Leaves	64.5	6376	307	109	Ga06
Taraxacum officinale	Leaves	10.7	37.9	15.3	127	Di09
Taraxacum officinale	Leaves	8	-	28	10	Gj11
Taraxacum officinale	Roots	16.7	-	50	38.7	Gj11
Teucrium polium	Flowers	8	147	20	21	Se08
Thymbra spicata	Herb	0.72	79.2	5.7	3.5	Öz08
Thymbra spicata	Herb	8	520	27	50	Se08
Thymus pannonicus	Herb	5.26 – 14.1	25.9 – 1454	89.3 – 278	1.8 – 10.6	Ar11
Thymus serpyllum	Herb	12.9	51.6	43.4	245	Di09
Tila argentea	Flowers	4	53	5	3	Se08
Tilia cordata	Flowers	0.31	39.2	4.9	8.3	Öz08
Tilia vulgaris	Flowers	9.6	228	71.2	35.6	Ba06
Trifolium pratense	Leaves	31.0	1196	144	61.0	Ga06
Urtica dioica	Herb	7.3 – 13.0	56.2 – 266	50.1 – 204	24.4 – 58.9	Fi03
Urtica dioica	Herb	10.0	40.6	21.3	63.8	Di09
Urtica dioica	Herb	5.6	810	79.8	47.2	Ba06
Urtica dioica	Herb	1.53	107	10.6	3.3	Öz08
Urtica dioica	Herb	4	85	14	8	Se08
Urtica dioica	Leaves	8	-	35	12	Gj11
Vaccinium myrtillus	Leaves	17.0	6726	1305	51.0	Ga06
Vaccinium myrtillus	Leaves	6.5	45	1900	14	Re01
Vaccinium vitis-idaea	Leaves	4.1	37	1210	26	Re01

* See **Table 10** for references and annotations

2005b). A former report from the same working group mentioned 28 to 416 mg/kg Al in various herbs (Ražić *et al.* 2005a). The medicinal plants, namely *Vaccinium myrtillus*, *V. vitis-idea* and *Empetrum nigrum* collected as wild plants in the North-eastern Europe were reported to have 59–113 mg/kg Al (Reimann *et al.* 2001). López *et al.* (2000) found various commercially available herbs and spices in Spain in the range of 6.2 to 35.3 mg/kg Al. In the tested samples of 26 herbal drugs, the Al content varied from 26 to 422 mg/kg (Ražić *et al.* 2005a). Black tea leaves may contain up to 1000 mg/kg Al, whereas various vegetables and herbs reach 100–200 mg Al/kg (Schafer and Seifert 2006). Various tea (*Camellia sinensis*) samples were found to contain 485–1307 mg/kg Al (Mehra and Baker 2007). Occasionally, very high Al values were also found in some plants, reaching an Al level up to 1722 mg/kg in sage and 1446 mg/kg in coriander (Zegin *et al.* 2008).

Ba: In *Taraxacum officinalis*, *Betula* species and *Crataegus* species, Ba levels of 25.0, 72.6 and 55.0 mg/kg, respectively, have been reported (Kalny *et al.* 2007). Ba content varied from 5.4 to 74 mg/kg in various herbal drugs from Turkey (Basgel and Erdemoglu 2006). Eight medicinal plants of family Lamiaceae, originating from Serbia, had Ba concentrations between 15.5 and 69.8 mg/kg (Ražić *et al.* 2005b).

Co: The values, reported in the **Table 3**, show Co contents from 0.05 to 1.76 mg/kg, but most of the samples were below 0.5 mg/kg. In another Turkish investigation, the Co levels were found to be below 1.1 mg/kg (Zengin *et al.* 2008).

Cr: Table 3 shows the Cr contents that varied from less than 0.1 to 11.2 mg/kg. There was no obvious relation between a species and the Cr content. A Turkish study showed that liquorice and sage (*Salvia triloba*) had 21.0 and 12.2 mg/kg Cr, respectively. The other analysed sample had the Cr values below 6.0 mg/kg (Zengin *et al.* 2008). High content of Cr were found in several medicinal plants collected in Nigeria along a roadside with heavy traffic. The contents recorded ranged from 66 to 162 mg/kg (Ayoola *et al.* 2010).

Li: In an investigation of various Turkish herbs and spices, Li contents were found ranging from 0.1 to 3.0 mg/kg (Özcan 2004). In another study from the same country, most of the samples were below 2 mg/kg Li, while a mint sample contained 23.5 mg Li/kg (Zengin et al. 2008). Spanish table olives had a mean Li content of 6.6 mg/kg (López-López *et al.* 2008).

Rb: The values of Rb ranged from 0.7-3.2 mg/kg in Syrian samples of *Pimpinella anisum*, *Glycyrrhiza glabra* and *Artemisia herba-alba* (Khuder *et al.* 2009).

Table 3 Contents of Cr, Co and Ni in selected medicinal plants (mg/kg).

		Cr	Co	Ni	Reference*
Achillea millefolium	Herb	0.64	-	3.27	Ra08
Agrimonia eupatoria	herb	0.10	-	4.0	Sa01
Arbutus andrachnae	Fruits	11.5	-	0.05	Se10
Arbutus unedo	Fruits	5.4	-	0.01	Se10
Artemisia absinthium	Herb	0.40	-	1.84	Ra08
Artemisia dracunculus	Leaves	3.70	0.21	1.39	Öz08
Betula sp.	Leaves	0.39	-	4.52	Ka07
Beutla pubescens	Leaves	< 0.2	0.36	3.9	Re01
Cassia angustifolia	Leaves	0.34	Ndet	0.9	Ba06
Coriandrum sativum	Fruits	5.97	0.24	0.24	Öz08
Crataegus orientalis	Leaves	5.24	0.14	1.89	Öz08
Crataegus sp.	Flowers	0.66	-	11.3	Ka07
Cynara scolymus	Leaves	0.91	-	4.13	Ra08
Empetrum nigrum	Leaves	< 0.2	0.051	2.6	Re01
Equisetum arvense	Herb	0.20	-	1.8	Sa01
Foeniculum vulgare	Fruits	1.04	0.40	5.4	Ba06
Foeniculum vulgare	Fruits	3.03	0.72	3.05	Öz08
Inula helenium	Roots	7.78	-	3.54	Ra08
Linum usitatissimum	Seeds	0.05	0.56	1.9	Jo93
Matricaria recutita	flowers	0.45	-	2.6	Sa01
Matricaria recutita	Flowers	0.48	-	4.4	Sa07
Matricaria recutita	Flowers	1.22	0.32	1.8	Ba06
Matricaria recutita	Flowers	3.51	-	3.14	Ra08
Matricaria recutita	Flowers	11.2	0.24	3.71	Öz08
Melissa officinalis	Leaves	6.46	0.31	2.91	Öz08
Mentha x piperita	Leaves	6.28	0.20	3.52	Öz08
Ocimum basilicum	Herb	0.06	0.12	0.08	Öz08
Papaver somniferum	Blue seeds	0.06	0.15	1.3	Jo93
Papaver somniferum	White seeds	0.55	0.30	1.2	Jo93
Pimpinella anisum	Fruits	3.39	0.12	2.53	Öz08
Rosa canina	Fruits	0.92	0.40	2.9	Ba06
Rosa canina	Fruits	1.33	0.32	0.67	Öz08
Rosmarinus officinalis	Leaves	0.31	0.37	0.36	Öz08
Salix sp.	Leaves	< 0.2	1.76	9.0	Re01
Salvia fruticosa	Leaves	2.77	0.28	1.63	Öz08
Salvia officinalis	leaves	2.12	0.34	2.9	Ba06
Sambucus nigra	Flowers	0.44	-	2.8	Sa01
Sideritis spp.	Herb	7.79	0.34	0.71	Öz08
Taraxacum officinale	Leaves	0.91	-	3.86	Ka07
Taraxacum officinale	Roots	0.85	-	0.55	Sa01
Thymbra spicata	Herb	0.60	0.05	1.34	Öz08
Tilia cordata	Flowers	5.08	0.22	0.30	Öz08
Tilia vulgaris	Flowers	0.34	0.14	2.46	Ba06
Urtica dioica	Herb	1.20	0.48	3.6	Ba06
Urtica dioica	Herb	0.66	0.19	0.72	Öz08
Urtica dioica	Leaves	0.08	-	0.10	Sa01
Vaccinium myrtillus	Leaves	< 0.2	0.044	1.0	Re01
Vaccinium vitis-idaea	Leaves	< 0.2	0.041	0.7	Re01
Viscum album	herb	0.28	-	0.54	Sa01

* See **Table 10** for references and annotations

Se: In Turkish spices and herbs, up to 5 mg/kg Se were recorded. The highest value was found in a mustard sample (Özcan 2004). Indian mint (*Mentha spicata*) displayed a mean Se content of 0.18 mg/kg (Choudhury *et al.* 2006).

Sn: Various medicinal plants and spices from Egypt displayed up to 0.1 mg/kg Sn (Abou-Arab and Abou-Donia, 2000). Spanish table olives had a mean Sn content of 18.4 mg/kg (López-López *et al.* 2008).

Sr: Herbal drugs, widely consumed in Turkey, showed Sr concentrations from 17 to 174 mg/kg (Basgel and Erdemoglu 2006). In another study from the same country, 10 to 153 mg/kg Sr were found in various medicinal plants (Özcan 2004). Syrian plants displayed 2.2 to 23.1 mg/kg Sr (Khuder *et al.* 2009).

Ti: Chemical analyses were carried out for titanium in the case of some medicinal plants by Queralt *et al.* (2005). The Ti levels recorded were between 15 and 83 mg/kg.

V: Vanadium levels in various Turkish herbs and spices were between 0.25 and 20.0 mg/kg (Özcan 2004). Fruits of Turkish *Arbutus andrachnae* and *A. unedo* had 12.4 and 16.2 mg/kg V, respectively (Şeker and Toplu 2010).

The idea regarding the great variability in the accumulation of mineral elements in plants is also related to physiological peculiarities of the considered taxons. It has been put forward nearly half a century ago and tested by analysing a great number of wild plants growing ordinary in different ecological situations (Kinzel 1982) and in nutrient solution experiments (Kinzel and Lechner 1992). Very recently, it has been attempted to differentiate medicinal plants from other plants using statistical methods according to their specific mineral element content (Arceusz *et al.* 2010). The authors observed significant differences in contents of Zn between the families Apiaceae and Fabaceae, of Fe and Na between the families Asteraceae and Rosaceae, of Fe between the families Apiaceae and Rosaceae, and of Ca between the families Asteraceae and Fabaceae, Rosaceae and Lamiaceae and Asteraceae and Lamiaceae.

TOXIC HEAVY METALS

The presence of toxic metals in drug plants and spices can be attributed to many reasons including environmental pollution, soil composition and use of fertilizers. The contamination of the herbal raw material leads to contamination of the products during the manufacturing process. A substantial input of heavy metals is due to human activities such as metallurgic processing of ores, running of cement plants, emissions from refineries and uncontrolled discharge of sewage sludge (Han 2002). Pesticides, containing arsenic and mercury, were widely used until a few years ago and, unfortunately, they are still being used in some countries (WHO 2007). Although great efforts have been achieved in reducing metal emissions, the toxic heavy metals are still present in the environment. There are still point sources of contamination with heavy metals such as metal smelters in Europe (Giorgieva *et al*. 2010; Stafilov *et al*. 2010; Gjorgieva *et al*. 2011).

Another reason to monitor toxic metals in medicinal plants was the observation regarding some exotic herbal drugs, mainly those of Asian origin, which contained critical levels of heavy metals and arsenic (Chan 2003; Guédon *et al.* 2007; Han *et al.* 2008). Very recently known, the high load of toxic metals in Chinese plant-drugs available in The Netherlands, could be a matter of concern (Martena *et al.* 2010). A further survey of 334 samples representing 126 species used in Chinese herbal medicines collected throughout China found that 20.4% of the samples exceeded 0.3 mg/kg cadmium and 19.2% of the samples 2 mg/kg chromium. Mercury was only in 0.9% higher than 0.2 mg/kg and arsenic in 0.6% higher than 5 mg/kg whereas lead was below 10 mg/kg in all samples (Harris *et al*. 2011).

During the last decade, the data have been collected to evaluate the status of such critical levels of metals in various medicinal and spice plants. The studies comprise surveys of plant drugs traded by large companies (Kabelitz 1998), plant drugs of a certain regional provenance (Chizzola *et al.* 2003; Salamon *et al.* 2007a), plants growing on contaminated sites (Zheljazkov *et al.* 1999; Alvarenga *et al.* 2004; Angelova *et al.* 2005), plants growing on fields amended with sewage sludge (Weightman 2006) and plants growing on experimentally contaminated substrates (Grejtovský and Pirć 2000; Chizzola 2005; Grejtovský *et al.* 2006; Pavlović *et al.* 2006).

Cd and **Pb**: The focus of most studies about toxic heavy metals in medicinal plants was on cadmium and lead. In view of a reasonable assessment of heavy metal contents in plants, it is important to know as to which levels occur usually in such uncontaminated samples, and the levels that are unavoidable. To establish such a basis, a large compilation of Cd and Pb levels in medicinal plant drugs, traded in Germany, has been carried out (Kabelitz 1998). Recently a

Table 4 The 90% percentile values of Cd and Pb contents in plant drugs according to two large surveys (mg/kg).

		Kabelitz (1998)			Gasser *et al.* (2009)		
		n	Cd	Pb	n	Cd	Pb
Achillea millefolium	Herb	109	0.49	1.09	52	0.55	0.85
Alchemilla vulgaris	Herb	56	0.54	3.64	26	0.17	0.66
Althaea officinalis	Leaves	58	0.26	2.83	-	-	-
Angelica archangelica	Roots	49	0.58	1.01	21	0.76	
Anthyllis vulneraria	Flowers	44	0.18	1.06	-	-	-
Arctostaphylos uva-ursi	Leaves	63	0.05	1.27	-	-	-
Artemisia absinthium	Herb	49	0.42	0.97	56	0.85	0.63
Betula pubescens	Leaves	245	0.67	3.38	88	0.66	1.87
Calendula officinalis	Flowers	89	0.18	2.57	122	0.44	0.92
Carum carvi	Fruits	82	0.15	0.25	45	0.1	< 0.4
Cassia sennae	Leaves	126	0.04	0.41	20	< 0.07	0.44
Centaurium erythraea	Herb	44	0.15	0.82	-	-	-
Crataegus monogyna	Fruits	74	0.08	0.67	56	< 0.07	< 0.4
Cynara scolymus	Leaves	146	0.36	3.49	210	0.43	2.2
Elymus repens	Rhizome	51	0.20	1.46	-	-	-
Equisetum arvense	Herb	129	0.21	1.27	70	0.26	0.92
Foeniculum vulgare	Fruits	172	0.12	0.70	114	0.09	< 0.4
Frangula alnus	Bark	80	0.10	7.04	27	0.08	2.02
Humulus lupulus	Flowers	59	0.06	1.35	85	< 0.07	0.51
Hypericum perforatum	Herb	496	1.30	2.00	188	0.95	1.63
Linum usitatissimum	Seeds	45	0.54	0.15	29	0.5	< 0.4
Matricaria recutita	Flowers	338	0.42	1.55	109	0.5	1.2
Melissa officinalis	Leaves	236	0.06	1.96	84	< 0.07	1,53
Mentha x piperita	Leaves	420	0.16	3.00	109	0.08	1.21
Petroselinum crispum	Leaves	165	0.21	1.18	-	-	-
Pimpinella anisum	Fruits	78	0.15	0.45	57	0.11	< 0.4
Plantago lanceolata	Herb	82	0.28	1.85	-	-	-
Quercus robur	Bark	50	0.24	3.19	-	-	-
Rosa canina	Fruits	63	0.08	0.38	26	< 0.07	< 0.4
Rosmarinus officinalis	Leaves	65	0.03	1.65	32	< 0.07	1.91
Rubus fruticosus	Leaves	63	0.19	3.05	-	-	-
Salix sp.	Bark	120	1.80	2.37	61	1.7	0.75
Salvia officinalis	Leaves	160	0.08	2.48	94	< 0.07	2.39
Sambucus nigra	Fruits	69	0.13	1.22	-	-	-
Solidago gigantea	Herb	54	0.21	1.36	73	0.84	0.75
Taraxacum officinale	Herb	161	0.69	2.16	46	0.55	2.57
Thymus vulgaris	Herb	157	0.48	2.66	92	0.55	1.81
Tilia sp.	Flowers	151	0.14	1.86	38	0.11	3.24
Tussilago farfara	Leaves	50	0.40	2.43	20	0.31	1.44
Urtica dioica	Leaves	173	0.16	3.73	123	< 0.07	1.5
Valeriana officinalis	Roots	292	0.30	3.26	132	0.27	2.4
Viscum album	Herb	210	0.48	1.95	176	0.64	1.33

n: number of samples analysed for the respective drug

Table 5 Some more cases of Cd and Pb contents in selected medicinal plants (mg/kg).

		Cd	Pb	Reference*
Achillea millefolium	Herb	0.24	11.6	Ra08
Achillea millefolium	Herb	0.21	1.0	Ch03
Agrimonia eupatoria	Herb	0.08	0.28	Sa01
Allium sativum	Bulbs	0.13 – 0.25	0.9 – 14.8	Ba10
Artemisia absinthium	Herb	0.5	2.25	Ra08
Atropa belladonna	Leaves	0.34	-	Un96
Betula sp.	Leaves	0.68	0.9	Ka07
Capsicum annuum	Fruits	0.05	0.31	Kr07
Capsicum frutescens	Fruits	0.05	0.39	Kr07
Capsicum frutescens	Fruits	0.07	-	Un96
Carum carvi	Fruits	0.05	0.2	Ch03
Centella asiatica	Leaves	0.32 – 1.62	13.3 – 50.2	On11
Centella asiatica	Roots	0.42 – 2.44	18.6 – 63.0	On11
Centella asiatica	Stems	0.09 – 0.91	7.6 – 41.2	On11
Crataegus sp.	Flowers	0.16	1.51	Ka07
Cynara scolymus	Leaves	0.77	4.59	Ra08
Datura stramonium	Leaves	0.20 – 1.92	-	Un96
Equisetum arvense	Herb	0.02	0.07	Sa01
Foeniculum vulgare	Fruits	0.004	0.48	Ba06
Foeniculum vulgare	Fruits	0.03	0.4	Ch03
Foeniculum vulgare	Fruits	Not detectable	0.93 – 2.65	Ga10
Hyoscyamus niger	Leaves	0.14	-	Un96
Hypericum perforatum	Herb	0.59	0.4	Ch03
Inula helenium	Roots	0.12	3.65	Ra08
Levisticum officinale	Leaves	0.6	0.6	Ch03
Linum usitatissimum	Seeds	0.42	0.016	Jo93
Matricaria recutita	Flowers	0.44	0.72	Ba06
Matricaria recutita	Flowers	0.19	0.55	Sa01
Matricaria recutita	Flowers	0.22	0.75	Sa07
Matricaria recutita	Flowers	0.35	3.48	Ra08
Melissa officinalis	Herb	0.02	0.8	Ch03
Mentha x piperita	Herb	0.06 – 0.09	0.33 – 2.48	Fi03
Mentha x piperita	Herb	0.05	0.8	Ch03
Ocimum basilicum	Herb	0.07	0.55	Kr07
Papaver somniferum	Blue seeds	0.84	0.08	Jo93
Papaver somniferum	Seeds	0.25	0.1	Ch03
Papaver somniferum	White seeds	0.04	0.14	Jo93
Rosa canina	Fruits	0.07	0.34	Ba06
Ruta chalepensis	Leaves	0.58 – 0.71	0.2 – 1.4	Ba10
Salvia officinalis	Leaves	0.01	0.8	Ch03
Sambucus nigra	Flowers	0.01	0.24	Sa01
Satureja hortensis	Herb	0.07	0.79	Kr07
Taraxacum officinale	Leaves	0.33	0.73	Ka07
Taraxacum officinale	Roots	0.07	0.37	Sa01
Thymus serrulatus	Leaves	0.46 – 0.58	1.1 – 98.2	Ba10
Urtica dioica	Herb	0.06 – 0.10	1.10 – 1.75	Fi03
Urtica dioica	Herb	0.06	4.8	Ba06
Urtica dioica	Leaves	0.6	0.09	Sa01
Viscum album	Herb	0.16	0.32	Sa01
Zingiber officinale	Rhizomes	0.17 – 0.25	0.3 – 0.4	Ba10

* See **Table 10** for references and annotations

new report has been published based on the data collected between 2002 and 2007 (Gasser *et al*. 2009). The data regarding the drugs, having a sufficiently higher number of analyzed samples (usually > 50) are recorded in **Table 4**. The 90th percentile level, i.e. the level below 90% of the values, occurred for a given drug plant listed in this table. In the case of such an analysis, an unnatural contamination of the sample becomes very likely.

Examples of Cd and Pb contents in the medicinal plants are presented in **Table 5**. Most specimens analysed had less than 0.2-0.3 mg/kg Cd. Nineteen of the species obtained in local shops in southern Turkey had Cd contents below 0.13 mg/kg, and the highest content was found in chamomile flowers (Sekeroglu *et al.* 2008). In another study from the same country, various medicinal plants were found to contain 0.3 to 0.6 mg/kg Cd and 0.7 to 1.7 mg/kg Pb (Zengin *et al.* 2008). Cd and Pb, found in Bulgarian herbal teabags, varied from 0.02 to 0.26 and 0.2 to 8.6 mg/kg, respectively, the highest Pb values being observed in thyme (*Thymus serpyllum*) (Arpadjan *et al.* 2008). Samples from Egypt, including those of chamomile, had less than 0.05 mg/kg Cd and 0.3 to 1.8 mg/kg Pb (Dogheim *et al.* 2004). A higher value for Pb could be found in Iceland moss (*Cetraria islandica*) and safflower (*Carthamus tinctorius*) flowers, where the 90th percentile value obtained from 31 samples, was 53.1 mg/kg (Gasser *et al.* 2009).

The data about the accumulation of heavy metals in dependence with plant development are scarce. The Cd content in *Datura stramonium* plants was found to increase during the vegetation period, reaching 0.33 mg/kg in May and 0.72 mg/kg in September in the leaves (Unterhalt and Fritsch 1996). In the field grown peppermint (*Mentha x piperita*), material from a later cutting had significantly higher Cd contents than that observed in the case of earlier cuttings (Plescher *et al.* 1995). Seasonal differences in Cd contents could also be observed in the wildly growing pasture plants in Northern Europe with tendency of reaching higher Cd levels during spring (Brekken and Steinnes 2004). No conclusive results have yet been obtained whether organic farming may lead to reduce the levels of Cd and other potentially harmful metals in the plant products (Jorhem and Slanina 2000).

An observation that some species may contain higher concentrations of a given heavy metal than most of the plants has already been made three decades ago. For instance, kernels samples of sunflower (*Helianthus annuus*) from North America and Europe contained 0.32–54 mg/kg Cd and 2.5–5.3 mg/kg Ni (Andersen and Hansen 1984). As sunflower is an important crop, efforts have been undertaken to select genotypes and varieties low in Cd (Li *et al.* 1995). The analysis of 54 seed samples of poppy (*Papaver somniferum*) gave a mean Cd content of 0.74 mg/kg (Hoffmann and Blasenbrei 1986).

Plant species with the tendency to take up higher concentration of Cd are denominated as Cd accumulator species. The comprehensive survey of Kabelitz (1998) and Gasser *et al.* (2009) has pointed out a wide range of medicinal plants falling in this category (**Table 9**). Amongst them are yarrow (*Achillea millefolium*), St. John's wort (*Hypericum perforatum*), willow (*Salix* sp.), chamomile (*Matricaria recutita*), linseed (*Linum usitatissimum*) and some species of the Solanaceae family including tobacco (*Nicotiana* sp.) (Dorosewska and Berbeć 2004). The mean Cd content in tobacco leaves from different regions in the world varied from 0.3 to 2.2 mg/kg Cd (Lugon-Moulin *et al.* 2006). Therefore, smokers may have a higher Cd burden than non-smokers. Misletoe (*Viscum album*) is another plant in which higher Cd levels have been found. This plant is a hemiparasite growing on trees and the plant Cd content is strongly dependent on the host tree. Misletoes grown on apple, hawthorn, lime tree and oak are low in Cd, whereas that grown on fir, pine, poplar and willow are high in Cd (Gasser *et al.* 2009). Seaweed also appeared to be particularly high in Cd (Gasser *et al.* 2009).

Cadmium is regarded an easily mobile element in the soil: the availability of Cd for plants is governed by several soil factors which influence the binding of this metal to soil components. Soil pH is a major factor determining the transfer of Cd from soil to the plant (Radanovic *et al.* 2002). *Hypericum* specimens, collected from various regions of Eastern Austria having acidic soils, had higher Cd contents than those collected from calcareous soils (Chizzola and Lukas 2005). Another important soil factor is the humus or organic carbon content. However, good correlations between organic carbon in the soil and Cd in the plant were not always obtained. The relationship seems to be complex, because the experiments conducted on sorghum grown in nutrient solutions reveal that the presence of organic matter might partially retain Cd in the solution but at the same time could promote Cd transfer from the root to the shoot (Pinto *et al.* 2004). The Cd accumulation in chamomile flowerheads seems to depend on some other climatic factors also as found in the studies conducted in Eastern Slovakia (Salamon *et al.* 2007a).

The variability in Cd accumulation in some accumulator species has been studied extensively. A high Cd variability was shown in St. John's wort (*Hypericum perforatum)*, in which the Cd content in 56 accessions varied from 0.04 to 7.8 mg/kg (Schneider and Marquard 1996; Schneider *et al.* 2002). Similar observations have been made on linseed (*Linum usitatissimum*) and poppy (*Papaver somniferum*) (Schneider and Marquard 1996). However, different poppy varieties that showed great differences in the Cd content of the seeds when grown on a contaminated soil had low Cd contents when grown on uncontaminated soils (Chizzola 2001). Therefore, it seems that the selection of accessions low in Cd may be a way to limit the presence of this toxic metal in plant products. The careful choice of the growing site and the management of soil conditions in order to avoid enhanced Cd input into the food chain are recommended at the time of growing these plant species.

The Cd uptake capacity of some of the Cd accumulator species was tested in experiments with artificially contaminated substrates (Grejtovský and Pirč 2000; Chizzola 2005; Grejtovský *et al.* 2006; Salamon *et al.* 2007b). Depending on the soils and the contamination situation, growth reductions have and have not been observed in various studies. Usually, critical metal concentrations could be found in plants before the significant growth reductions might occur. The accumulation of the metals affects the plant organs differently. In clary sage (*Salvia sclarea*) heavy metals in different parts have been found in decreasing order, for instance, in the case of Cd and Pb: leaves > roots > inflorescences > stems, in the case of Cu and Mn: roots > leaves > inflorescences > stems, and in the case of Zn: leaves > inflorescences > root > stems (Zheljazkov and Nielsen 1996).

In the case of moderately contaminated soil, even high Cd contents could be obtained in the plants. However, adding Cd to the soil in a soluble form ($CdSO_4$ or $CdCl_2$) at the beginning of the experiment can afford higher Cd contents in the plants as there was not enough time to fix the metal to soil particles (Pluquet *et al.* 1990).

Zn and **Cu**: An exogenous supply of Zn (up to 300 mg/kg) to the soil lead to an accumulation of Zn up to 271 mg/kg in chamomile shoots, while the plants did not show any sign of excessive Zn (Grejtovský *et al.* 2006). The application of a high Cu-compost, resulting in about 760 mg/kg Cu in the substrate, had no significant adverse effect on growth of mint (*Mentha x piperita*) and dill (*Anethum graveolens*), and both the species accumulated only about 12 mg/kg Cu in their tissues (Zheljazkov and Warman 2004). Seed yield of *Silybum marianum*, grown on highly contaminated soils, was reduced, because the plants contained critical concentrations of heavy metals; however, the content of fat and silymarin was not affected. These final products were not contaminated with heavy metals (Zheljazkov and Nikolov 1996). Plants of clary sage, grown on contaminated sites, contained high levels of Cd, Pb and Zn, but the resulting essential oil was not contaminated (Zheljazkov and Nielsen 1996). Similarly, the essential oil obtained from highly contaminated mint (*Mentha x piperita* and *M. arvensis*) was not contaminated. As these plants removed moderate amounts of heavy metals from the soil, they might be suitable for a long term remediation of contaminated soils (Zheljazkov *et al.* 1999). Higher metal accumulation was also found in some *Chenopodium* accessions from different species, they might also facilitate phytoremediation of soils contaminated with heavy metals (Barghava *et al.* 2008). Some willow clones showed promising results in extracting Cd and Zn from moderately contaminated soils (Tlustoš *et al.* 2007).

Some species may also be suitable for biomonitoring purpose. The elemental content of *Taraxacum officinale* leaves collected at different location in the urban area of Zittau, Germany, has been recorded to assess the contamination situation in this town with an ancient lignite mining (Winter *et al.* 1999). Specific plants that can accumulate and tolerate very high concentrations of heavy metals are referred as hyperaccumulators. For instance, the *Thlaspi caerulescens* can accumulate more than 10000 mg/kg Zn in the shoot dry matter (Walker and Bernal 2004). Also, for this species a great variability in hyperaccumulation of Cd, Zn and Ni has been demonstrated (Roosens *et al.* 2003).

As: The arsenic contents in *Mentha x piperita* were 0.05–0.13 mg/kg and in *Urtica dioica* 0.09–0.24 mg/kg (Fijałek *et al.* 2003). Various *Salix* clones grown on a Chernozem with 18 mg/kg As had in their leaves and twigs between 0.2 and 1.2 mg/kg As (Tlustoš *et al.* 2007). Mint from India (*Mentha spicata*) contained on the average 0.2 mg/kg As (Choudhury *et al.* 2006). Fennel fruit samples from India had 0.51–0.59 mg/kg As (Garg *et al.* 2010). Various tea bags of widely consumed herbs in Bulgaria were reported to have 0.02–0.25 mg/kg As (Arpadjan *et al.* 2008). Higher levels of As can be found in some macro-algae and seaweed, in which values of 20–100 mg/kg As could reached (Guédon *et al.* 2007).

Hg: Mercury is a toxic heavy metal of environmental concern. However, as shown by plant uptake studies, this metal

Table 6 Recovery of major mineral elements in infusions (% of total plant material).

		Ca	Mg	K	Na	Reference*
Cassia angustifolia	Leaves	57	50	-	-	Ba06
Echinacea purpurea	Herb	25.7	44.7	80.7	28.5	Ga06
Foeniculum vulgare	Fruits	15.7	55	-	-	Ba06
Matricaria recutita	Flowers	15.7	55.1	-	-	Ba06
Matricaria recutita	Flowers	19.1 – 23.1	46.9 – 48.3	65.2 – 73.4	-	Ch08
Mentha x piperita	Leaves	23.0	48.7	80.6	49.1	Ga06
Mentha x piperita	Leaves	18.9	38.4	-	-	Lo06
Rosa canina	Fruits	5.5	72	-	-	Ba06
Rubus idaeus	Leaves	22.4	53.1	77.9	39.3	Ga06
Salvia officinalis	Leaves	14	29	-	-	Ba06
Taraxacum officinale	Leaves	22.5	40.2	71.8	21.9	Ga06
Tilia vulgaris	Flowers	78	43	-	-	Ba06
Trifolium pratense	Leaves	31.2	52.2	70.9	28.4	Ga06
Urtica dioica	Herb	58	55	-	-	Ba06
Urtica dioica	Leaves	23.7	25.3	-	-	Lo06
Vaccinium myrtillus	Leaves	6.3	19.0	69.7	51.8	Ga06

* See **Table 10** for references and annotations

has a very low availability to plants. So, generally, the content of Hg in medicinal plants is low. For instance, in chamomile flowers, collected from wild plants and from large scale production areas of Slovakia during 1995–2003, a mean of Hg content of 0.004 mg/kg has been recorded (Salamon and Placková 2007). Plant samples of *Vaccinium* species, birch and willow from Finland and Northern European Russia had less than 0.04 mg/kg Hg (Reimann *et al.* 2001). In the recent comprehensive survey of Gasser *et al.* (2009), Hg contents of nearly 120 herbal drugs were below 0.1 mg/kg. However, Hg may be accumulated in algae. Hg concentrations in the genus *Fucus* were higher than in the respective sediments (Cairrao *et al.* 2007).

Tl: Thallium is a highly toxic heavy metal that may disperse in the environment by cement producing plants. In plant drugs this element is not regarded as a matter of concern (Guédon 2007). As per the study reported from the USA, botanical supplements afford less than 0.3 μg/day Tl to the consumer (Raman *et al.* 2004).

Due to low availability to plants, the heavy metals are consumed in small quantities. Hence, the intake of toxic heavy metals through consumption of medicinal plant products can be assumed to be low. For instance, a study from Catalonia, Spain, estimated the contribution of medicinal plants in daily intake of As, Cd and Pb by human beings to be about 0.2%, 1% and 5%, respectively, of the total dietary intake (Falcó *et al.* 2003). Another study calculated the maximum daily intake of As, Cd, Hg and Pb trough plant derived medicinal products from Poland to be less than 4% of the PTWI values (Falcó *et al.* 2005). Nevertheless, a systematic control of the toxic metals in plant drugs and related plant products remains advisable.

INTERACTION BETWEEN SELECTED ELEMENTS

The soil solution, from which the minerals are taken up by plants, is a complex mixture of elements. Therefore, interactions between elements in the plants are common. As there are some chemical similarities between Cd and Zn, interactions between these two elements have been reported in various plants. Cd concentration decreased as Zn concentration increased in the seed of flax (*Linum usitatissimum*), the samples being collected from different plants grown on different soils (Grant and Bailey 1997). In pot experiments, Cd concentration of flax seed could be reduced by addition of Zn to the soil, but a simultaneous supply of Cd and Zn to the soil might lead to an increase of Cd concentration in the seeds as compared to the increase in the seed-Cd content when the Cd was supplied alone (Moraghan 1993). The application of monoammonium phosphate could increase the content of Cd and decrease that of Zn in the flax seeds (Grant and Bailey 1997). More recently, an interaction between Cd and Zn has been demonstrated in chamomile (Chizzola and Mitteregger 2005). The addition of Zn to the experimental soil could decrease substantially the Cd accumulation in the above ground plant parts. However, this reduction in Cd uptake was not sufficient to get plant material with as low Cd contents as could be obtained from uncontaminated sites. In the perennial yarrow (*Achillea millefolium*), the simultaneous supply of Cd and Zn had only little influence on the Cd accumulation (Chizzola 2005).

Interaction, concerning Cd and Mn in *Lactuca*, resulted in significant uptake of Mn and its translocation to the shoots when the Cd concentration in the nutrient solution was increased (Ramos *et al.* 2002). In a nutrient solution experiment, addition of small amounts of Cd enhanced the uptake of Fe in sorghum plants (Pinto *et al.* 2004). In *Picea abies*, an enhanced Ca supply decreased Cd and Zn accumulation in plants, while the supply of Cd or Cu to plants decreased their Ca uptake (Österhas and Greger 2003). Interactions between phosphorous and Zn have been reported at various levels in the plant and in the soils (Marschner 1995).

EXTRACTION OF HEAVY METALS DURING PHYTOPHARMACEUTICAL PREPARATIONS

In many cases, not the plant drug itself, but the extract of the plant is consumed. This is especially the case of herbal teas which are usually prepared as infusion or decoction using hot or boiling water as extraction medium. Therefore the question arises as to what proportion of metal elements, present originally in the plant, is recovered in the specific preparation. Washing the fresh plant material after harvest may prove beneficial to reduce heavy metal contamination in the plants (Schilcher *et al.* 1987; Weightman 2006). The transfer of the metal from the plant to the infusion medium depends on various factors. There is a clear dependency from the element considered, the plant species and the plant part. The particle size, i.e. how fine the plant material is cut or powdered, could also be an important factor. The extraction of various elements may increase or decrease even with infusion time (Özcan 2008). Also, boiling the plant material in the hot water may result in extraction of usually more metal content than that extracted by immersing the plant material in hot water (Abou-Arab and Abou-Donia 2000).

As presented in **Table 6**, usually higher proportions of Mg than Ca are extracted into the infusions, while K attains the highest recoveries. Of the micronutrients, Fe is least soluble, while the recoveries of other elements varied greatly (**Table 7**). Cd is extracted to 6–35%. Infusions using Bulgarian tea bags resulted in extraction of 5–74% Cd and 12–61% As, depending on the kind of herb and its total metal content. From the flowers of hibiscus (*Hibiscus sabdariffa*), containing 1.1 to 3.4 mg/kg Pb, 9–16% of Pb could be recovered in the infusion (Arpadjan *et al.* 2008).

Table 7 Recovery of trace elements in infusions (% of total plant material).

		Cd	Cr	Cu	Fe	Mn	Ni	Zn	Reference*
Betula sp.	Leaves	6.1	n.d	17.9	4.7	-	69.7	57.8	Ka07
Cassia angustifolia	Leaves	-	-	62.5	2.1	-	67	67	Ba06
Crataegus sp.	Flowers	n.d.	n.d.	15.2	10.5	-	60.3	50.5	Ka07
Echinacea purpurea	Herb	-	-	44.4	6.4	17.7	-	44.7	Ga06
Foeniculum vulgaris	Fruits	-	-	50	2.2	-	53.7	19	Ba06
Matricaria recutita	Flowers	-	-	80.9	1.6	-	54.5	41.2	Ba06
Matricaria recutita	Flowers	12 – 21	-	-	-	-	-	23 – 34	Ch08
Mentha x piperita	Leaves	-	-	36.3	6.8	22.7	-	34.4	Ga06
Mentha x piperita	Leaves	8.9	41.9	24.8	-	-	87	12.4	Lo06
Rosa canina	Fruits	-	27	60	14.4	-	66	28	Ba06
Rubus idaeus	Leaves	-	-	26.9	1.2	25.3	-	38.9	Ga06
Salvia officinalis	Leaves	-	-	7.5	36	-	29	29	Ba06
Taraxacum officinale	Leaves	10.5	16.8	59.3	41.7	-	74.0	39.2	Ka07
Taraxacum officinale	Leaves	-	-	33.3	4.9	19.4	-	29.9	Ga06
Tilia vulgaris	Flowers	-	-	40	1.1	-	38.6	27.8	Ba06
Trifolium pratense	Leaves	-	-	32.1	4.3	38.7	-	32.8	Ga06
Urtica dioica	Herb	-	31	60	1.0	-	1.1	29.5	Ba06
Urtica dioica	Herb	35.3	60.8	33.2	-	-	41.2	10.8	Lo06
Vaccinium myrtillus	Leaves	-	-	36.3	0.4	39.3	-	32.6	Ga06

* See **Table 10** for references and annotations, n.d.: not detected

Table 8 Proposed and set limits of Pb, Cd and Hg in scientific publications and regulatory frameworks (mg/kg).

Reference	Pb	Cd	Hg
Schilcher *et al*. (1987, 1990)	10	0.5	-
German Ministry of Health 1991 (Schicher 1994)	5	0.2	0.1
Kabelitz (1998)	10	0.5	-
WHO (1999)	10	0.3	-
WHO (2007)	10	0.3	-
Pharmacopoea Europea Monograph Kelp (2007)	5	4	0.1
EC 1881/2006 and EC 629/2008	3	1.0 (3.0 for seaweed products)	0.1
Herbal drugs monograph 1433 (2008)	5	0.5	0.1

As in the infusions of various herbal teas there was found a mineral concentration of 75-226 mg/100 mL of K, up to 28 mg/100 mL of Ca and 4.7–16.2 mg/100 mL of Mg, these herbal teas can be considered as a good source of minerals (Özcan 2008). Compared to mineral water, a chamomile infusion in simple tap water can afford comparable calcium and magnesium concentrations but the latter results in higher potassium and zinc contents (Misund *et al.* 1999; Chizzola *et al.* 2008). Several working groups draw the conclusion that medicinal herbs and aromatic plants and their infusions are the important source for essential micronutrients (Łozak *et al.* 2002; Zengin *et al.* 2008). This is also true for some herbal medicines that constitute a mixture of several plants (Leśniewicz *et al.* 2006).

Essential oils obtained from plants grown on contaminated sites may not be contaminated with heavy metals (Zheljazkov and Nielsen 1996; Zheljazkov 1999). However there are also reports of heavy metals in essential oils. For instance in rose oils of various origins the Pb content was between 0.4 and 12 mg/kg whereas Cd was below the detection limit and one sample had 0.15 mg/kg Hg (Knödler *et al*. 2011).

REGULATORY MEASURES

The safe use of medicinal and aromatic plants requires the absence of toxic heavy metals in the products. However, the toxic and heavy metals may be present in the plant products due to environmental contamination during production, harvesting procedure and processing of the plant for manufacturing the plant product. As a total absence of the metal is not achievable in the plant products, it is necessary to set reasonable limits of toxic and heavy metals. First proposals for such limits were discussed more than twenty years ago (Schilcher *et al.* 1987; Schilcher and Peters 1990; Schilcher 1994). As per the Italian pharmacopoeia (Farmacopea Ufficiale della Republica Italiana XII 2008), limits for Pb, Cd and Hg have been set up to 3, 0.5 and 0.3 mg/kg, respectively (Kosalec *et al.* 2009). According to the European Pharmacopoeia (6th edition), the limits for heavy metals in the monograph of Kelp (6.0/1426) (*Fucus* sp. and *Ascophyllum* sp.) are as follows: Hg 0.1 mg/kg, Cd 4 mg/kg, Pb 5 mg/kg and As 90 mg/kg. The relative high limit for arsenic takes into account that the organic As-compounds display only a low toxicity. The Pharmacopoeia Europaea monograph of linseeds (6.0/0095) limits the Cd content to 0.5 mg/kg. The EU limits for heavy metals in foodstuffs and food supplements have also been set (EC 466/2001, EC 1881/2006). In addition to this and to amend these regulations, the following limits have been set: lead 3.0 mg/kg, Cd 1.0 mg/kg and Hg 0.1 mg/kg including a limit of 3.0 mg/kg Cd for seaweed products (EC629/2008). This regulation is effective since 1st July 2009 and is more restrictive for Pb but less exigent for Cd than the limits put forward by the World Health Organisation (WHO 1999, 2007). The Pharmacopoeia Europaea limits 5 mg/kg Pb, 0.5 mg/kg Cd and 0.1 mg/kg Hg (Pharmeuropa 2008). The main proposals and limits regarding toxic and heavy metals are summarized in **Table 8**. In other countries also the comparable limits have been introduced. In various Asian countries the limit for As in herbal products has been set between 2.0 (China) and 5.0 (Malaysia, Singapore) mg/kg (WHO 2007; Kosalec *et al.* 2009).

As in some products higher Cd values are not uncommon for special products, comparatively higher reference values for Cd have been established in Germany. These values include 0.8 mg/kg Cd for poppy seeds, 0.6 mg/kg Cd for sunflower seeds and 0.3 mg/kg Cd for linseed (Anonymous 1997). However, as per the data collected, the list of species prone to Cd accumulation is much longer (Kabelitz 1998; Gasser *et al.* 2009). Based on the 90th percentile values of a larger number of samples analysed regarding the respective species, exemptions for higher limits for lead and cadmium were proposed. These suggestions are presented in **Table 9**.

Table 9 Proposed exemptions for Cd and Pb in herbal drugs (according to Gasser *et al*. 2009).

		Cd	Pb
Achillea millefolium	Herb	0.6	-
Althaea officinalis	Root	0.6	-
Angelica archangelica	Roots	0.8	-
Arnica montana	Flowers	0.8	-
Artemisia absinthium	Herb	0.9	-
Bellis perennis	Flowers	0.6	-
Betula pendula	Leaves	0.7	-
Carthamus tincorius	Flowers	-	10
Drosera rotundifolia	Herb	-	7
Euphrasia officinalis	Herb	1.1	-
Fumaria officinalis	Herb	1.5	-
Helichrysum sp.	Flowers	0.7	-
Hypericum perforatum	Herb	1.0	-
Nasturtium officinale	Herb	1.0	-
Nasturtium officinale	Herb	-	7
Piper methysticum	Rhizome	0.6	-
Potentilla erecta	Rhizome	2.1	-
Pulmonaria officinalis	Herb	0.8	-
Salix sp.	Bark	1.7	-
Solidago sp.	Herb	0.8	-
Spinaca oleracea	Leaves	1.6	-
Taraxacum officinale	Herb	0.6	-
Thymus vulgaris	Herb	0.6	-
Urtica dioica	Roots	-	7
Viola tricolor	Herb	1.0	-
Viscum album	Herb	0.8	-
Cetraria islandica		-	11
Seaweed		5.7	-

FUTURE PERSPECTIVES

Mineral elements are plant nutrients and are therefore essential for plant growth and field production of medicinal plants. The optimisation of culture techniques and fertilization regimes for growing the various species and varieties of medicinal plants in the respective environmental conditions is an evolving field that will be well established in future. A compendium comprising 5 volumes dealing with the cultivation of these special crops is under elaboration (Hoppe et al. 2007ff.). This plant prodution should follow the guidelines of Good Agricultural Practice (GAP) that can be obtained from the European Herb Growers Association (EUROPAM, http://www.europam.net).

Toxic heavy metals may occur in the environment and various regions with a heavy metal contamination history are known, so it is advisable to further monitor the heavy metals in the plant raw material. Plant grown in proximity of industrial areas or heavy traffic highways may reach heavy metal levels exceeding accepted limits for a safe use. The methods for heavy metal analysis are commonly atomic absorption spectrometry (AAS) and inductively coupled plasma-mass spectrometry and should further be validated on the herbal materials (Hofmann 2011). Amongst the toxic heavy metals most data are available on cadmium, lead and mercury, where cadmium is the element of greatest concern. Some species and varieties are prone to enhanced Cd-levels. For the cultivation of such plant species a careful choice of the growing site and variety is necessary to minimize the Cd content in the plant product.

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Table 10 References and annotations for **Tables 1-7**.

Ba 06	Mean of 5 samples, drugs widely consumed, supplied from local herbalists and markets in Turkey.	Başgel and Erdemoğlu 2006
Ar 11	Plants from 12 locations in Serbia.	Arsenijevič *et al*. 2011
Ba 10	Plants from four sites in Ethiopia.	Baye and Hymete 2010
Bi 09	Mean from plants collected at 48 different sites in Corsica.	Bianchini *et al*. 2009
Ch 03	Plants grown in Eastern Austria; mean of 3-15 samples for each species.	Chizzola *et al*. 2003
Ch 07	Four different varieties were cultivated in Eastern Austria during two consecutive years.	Chizzola and Dobos 2007
Ch 08	Data from a pot experiment where the plant grew partly on a Cd and/or Zn enriched soil.	Chizzola *et al*. 2008
Di 09	Plants from Romania, mean of 25-30 samples, collected in four districts. The Cd and Pb concentrations appear to be high. It is not specified whether the samples came from polluted sites.	Diaconu *et al*. 2009
Fi 03	Samples from a Polish herb trader.	Fijałek *et al*. 2003
Ga 06	Herbal teas available in the US.	Gallaher *et al*. 2006
Ga 10	Samples from Utter Pradesh and Gujarat, India.	Garg *et al*. 2010
Gj 11	Samples from uncontaminated sites in the mountains of East Macedonia.	Gjogieva *et al*. 2011
Im 10	Plants sampled at three sites in the mountains of Romania.	Imbrea *et al* 2010
Jo 93	Samples from the Swedish market.	Jorhem and Sundström 1993
Ka 07	Samples from retail pharmacies in Warsaw, Poland. Mean of 5 samples from different manufacturers. Plant parts not specified.	Kalny *et al*. 2007
Kh 09	Plants collected in Syria.	Khuder *et al*. 2009
Kr 07	Products from the Polish market, mean of 4-17 samples.	Krejpcio *et al*. 2007
Lo 06	Tea bags from Polish production.	Lozak *et al*. 2006
On 11	Plants from 13 sites in Malaysia.	Ong *et al*. 2011
Öz 08	Plant provided from local bazaars in Turkey.	Özcan *et al*. 2008
Qu 05	Drugs available on the Spanish market.	Queralt *et al*. 2005
Ra 05	Plants cultivated in Serbia.	Ražič *et al*. 2005b
Ra 08	Plants cultivated in Serbia.	Ražič *et al*. 2008
Re 01	Median values of 23-67 samples of each species origination from 9 regions in Finland and the European part of northern Russia.	Reimann *et al*. 2001
Sa 01	Cultivated medicinal plants in the Zemlin region of Slovakia where soils are polluted with hazardous metals. The metal levels in the plants appear not to be enhanced.	Salamon *et al*. 2001
Sa 07	Mean values. Plants collected in the wild or from large scale production areas in the Slovak Republic during 1995-2003.	Salamon and Placková 2007
Se 08	Plants from local shops in Southern Turkey.	Sekeroglu *et al*. 2008
Se 10	Plants from Canakkale, Turkey.	Şeker and Toplu 2010
Un 96	Plant cultivated in the exprimental garde of University Münster, Germany.	Unterhalt and Fritsch 1996
Wi96	Plants growing along riversides, collected at 9 different sites in Poland.	Wierzchowska-Renke *et al*. 1996