Comparative analysis of the requirements of foreign pharmacopoeias to the quality of medicinal vegetable raw materials for the content of heavy metals

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SUMMARY

As a result of environmental pollution, various ecotoxicants accumulate in medicinal plants, among which heavy metals are one of the most dangerous. As it was established earlier, the content of heavy metals in medicinal plant raw materials can reach high concentrations and exceed their content in food products. However, in the domestic pharmacopoeia, the content of heavy metals in medicinal plant raw materials is not standardized. The article presents analytical materials on the levels of heavy metals in medicinal plant raw materials supplied to the world pharmaceutical market from different countries in 1978-2008, and an analysis of the quality requirements of a number of foreign pharmacopoeias (European, UK, Japan, Belarus, USA). medicinal plant materials for the content of heavy metals,

Key words: heavy metals, medicinal plant raw materials, quality requirements.

Modern environmental conditions lead to the accumulation of various ecotoxicants in medicinal plants, among which one of the most dangerous are heavy metals (HM) [8]. They can enter medicinal plants as a result of anthropogenic pollution of the environment (industrial emissions, discharges and waste, transport, the use of mineral and organic fertilizers, ameliorants, plant protection products), as well as various natural processes (weathering of rocks and minerals, soil erosion, volcanic activity, tectonic shifts, forest and steppe fires) [1, 6, 7, 10]. Environmental studies of medicinal plants began in the 60s of the last century in Germany. It was in them that it was found that the content of HM in medicinal plant raw materials (MPR) can reach higher concentrations than in food products,

Currently, HMs are found in almost all elements of the biosphere, and their entry into the human body can harm health. However, in the State Pharmacopoeia of the Russian Federation of the XI edition, the indicator regulating the content of heavy metals in medicinal plant raw materials (MP) is still absent. The purpose of this work was to study the experience of foreign pharmacopoeias in the field of determining HM impurities, standardizing their content in medicinal plant raw materials and assessing the levels of their content in medicinal plant raw materials on the world pharmaceutical market.

To achieve this goal, an information and analytical study was carried out to study the levels of heavy metals in raw materials and the requirements of the pharmacopoeias of different countries - the European, British Pharmacopoeia, the Pharmacopoeia of Japan, the State Pharmacopoeia of the Republic of Belarus, the US Pharmacopoeia, the State Pharmacopoeia of the USSR XI edition to the quality of medicinal plant raw materials in terms of content heavy metals.

A large amount of toxic metals enters the environment due to the combustion of coal and oil, the use of fertilizers, and wastewater. Heavy metals enter plants from soil and atmosphere as a result of dust pollution [1, 7, 9]. Cd, Cu, Zn come from the soil and accumulate in plant tissues; Pb predominantly settles on the surface of leaves, flowers, fruits, and to a lesser extent on stems. Heavy metals can enter soils with wastewater (Zn, Cr, Pb, Hg and, to a lesser extent, Cd) [10, 12]. Heavy metals have unequal ability to accumulate in plants, for example, Cd is easily absorbed; Zn, Cu are absorbed to a lesser extent; Mn, Ni are absorbed weakly; Fe and other elements are inaccessible to plants. Therefore, the problem of the content of heavy metals in medicinal plant raw materials attracts the attention of researchers all over the world. At the first stage of the study, an analysis of literature data on the nomenclature and levels of HM content in raw materials from different countries was carried out. It was found that researchers in most countries pay close attention to the content of the most toxic metals Pb, Cd and Hg in medicinal plant raw materials (Table 1).

In second place in terms of the frequency of determination are Zn, Ni, Fe, Cu, which belong to essential metals, but in concentrations exceeding those necessary for living organisms, they can exhibit toxicity. Less often, some of the essential, conditionally toxic and toxic metals (Sr, Cr, Al, Mo, Ca and others) are determined in medicinal plant raw materials, which is primarily due to the environmental conditions of different regions of medicinal plant procurement [13, 15, 16, 17].

A number of organizations, including the World Health Organization, Food Drug Administration, as well as departments of the world's leading universities and laboratories of a number of countries (India, China, Thailand, Malaysia, Austria, Poland, Jordan, Nigeria, Turkey and others).

Table 1

Metals, the content of which is controlled in medicinal plant raw materials from different countries

Страна	Металлы
Индия	Fe Cu Mn Zn Cr Ni Pb Cd Hg
Иордания	Fe Cu Zn Ni Pb Cd
Австрия	Fe Cu Mn Zn Pb Cd
Польша	Zn Ni Pb Cd Mo
Турция	Pb Cd Hg
Таиланд	Fe Cu Mn Zn Cr Co Ni Sr Pb Cd Hg Al Ca Se V Mg
Малайзия	Pb Hg
Нигерия	Fe Cu Mn Zn Cr Ni Sr Ca Se
Китай	Cd Hg
Италия	Pb Cd
США	Pb Hg

The information and analytical studies carried out have shown that the data on the content of Pb and Cd are of the greatest interest, from the point of view of the ecological purity of raw materials. It was found that at the end of the 70s. XX century the content of these metals in raw materials coming from European countries was almost 5 times higher than in raw materials from Asian countries. Concentrations of metals in raw materials sold through the pharmacy chain at the end of the 80s. XX century were (in μg / g): 0.01–3.91 for Pb; for Cd 0.005–1.28. The maximum concentrations were found: Pb - in chamomile flowers, St. John's wort, buckthorn bark, birch buds; Cd - in the grass of a string, grass of violets, leaves of mother-and-mother, and kelp thallus (Table 2).

table 2

The types of raw materials most contaminated with toxic metals

Период исследований	Металлы	
	Pb	Cd
1975–1980 гг.	Цветки ромашки	Трава череды
	Трава зверобоя	Трава фиалки
	Кора крушины	Листья мать-и-мачехи
	Почки березы	Слоевища ламинарии
2000–2008 гг.	Листья розмарина	Листья розмарина
	Корни одуванчика	Трава зверобоя
		Листья мяты перечной

Analysis of the ecological purity of medicinal plant raw materials at the beginning of the XXI century revealed a tendency towards an increase in the content of heavy metals in raw materials from regions with developed industry. If at the end of the 20th century (according to research data from 1975–1980), the content of toxic metals in raw materials on the world pharmaceutical market was (in μg / g): Pb - 0.01–4.18; Cd - 0.01-0.6; then at the beginning of the XXI century they increased by 7.9–26.5 times and amounted to 0.02–106.89 for Pb; for Cd - 0.001–4.77. The concentration of Pb in medicinal plant raw materials reached 30.00 μg / g, Cd - 5.72 μg / g [8]. The raw materials are especially polluted with Pb, harvested relatively close to highways (up to 82.28 μg / g) on the territory of Poland and certain types of raw materials from China (safflower flowers), more than 20 times higher than the permissible

levels for food. The Pb concentration in medicinal plant raw materials from Jordan reached 86.5 μg / g; from India - 106.89 μg / g, from Austria - 4.30 μg / g, Thailand - 64.40 μg / g [13, 15, 16, 18].

The analysis showed that the content of heavy metals in medicinal products in the world pharmaceutical market can reach high concentrations (Table 3). The maximum Pb content was noted in medicinal plants in Germany (258.90 ppm), India (106.89 ppm), Jordan (86.50 ppm), Poland (82.28 ppm). The maximum concentrations of Cd were observed in medicinal plants in Germany (2.00 ppm), Jordan (3.50 ppm), Poland (1.70 ppm), and herbal teas in Thailand (4.77 ppm). The minimum concentrations of Pb were found in medicinal plants from Austria (0.02 ppm), Ayurvedic harvest from India (0.38 ppm), and vegetables from Turkey (0.008 ppm). The minimum concentrations of Cd were observed in medicinal plants from Austria (0.01 ppm), herbal preparations from China (0.018 ppm), Ayurvedic collections in India (0.025 ppm) and vegetables in Turkey (0.001 ppm).

Table 3

The content of heavy metals in raw materials supplied to the global pharmaceutical market from different countries in 2000-2008.

Страны	Диапазоны содержания (в мкг/г)	
	Pb	Cd
Индия	2,19–106,89	0,037–1,55
Китай	0,125–4,79	0,091–0,422
Иордания	6,70–86,50	0,30–3,50
Австрия	0,02–4,30	0,01–0,98
Польша	4,72–82,28	0,36–1,70
Тайланд	0,06–64,40	0,001–4,77

The highest Pb concentrations were found in safflower flowers, dandelion herb, rosemary leaves; Cd - in willow bark, rosemary leaves, peppermint herb.

There was a tendency to an increase in the content of heavy metals in medicinal plants in comparison with previous studies (1975–1989), while the concentration of Pb increased on average 18.3 times, Cd - 2.13 times. The concentration of heavy metals in medicinal plants significantly exceeded the limit levels established for food (SanPin), for Pb, on average, more than 20 times, for Cd - more than 19 times.

This necessitates standardizing the content of heavy metals as a requirement for the quality of raw materials. In this regard, an analysis was carried out of the requirements of the pharmacopoeias of leading foreign countries for the quality of medicinal plant raw materials in terms of the content of heavy metals.

In foreign pharmacopoeias for analysis for heavy metals, semi-quantitative (sulfide method) or quantitative analysis (AAS) (Table 4). Quantitative analysis by atomic absorption spectrometry is used to determine heavy metals in medicinal plant materials in the European Pharmacopoeia, British Pharmacopoeia, State Pharmacopoeia of the Republic of Belarus. According to the study, the European and British Pharmacopoeias have a monograph "Heavy metals in herbal drugs and fatty oils", which prescribes the determination of the content of heavy metals Cd, Cu, Fe, Pb, Ni, Zn Hg in herbal medicines by atomic absorption spectrometry. The monograph describes the composition of the device, the method of sample preparation (mineralization), the operating parameters of the method and the metals to be determined. Determination of heavy metals is carried out by atomic absorption spectrometry with atomization in a graphite cell (for the determination of Cd, Cu, Fe, Pb, Ni and Zn) and by the hydride method (for the determination of Hg). Samples are prepared for analysis in polytetrafluoroethylene autoclaves using nitric and hydrochloric acids. Mineralization is carried out in a microwave oven [17].

Table 4

Pharmacopoeial methods for determining the content of heavy metals

Фармакопея	Название ОФС	Определяемые металлы	Фармакопейный метод
European Pharmacopoeia	«Heavy metals in herbal drugs and fatty oils»	Cd, Cu, Fe, Pb, Ni, Zn Hg и элемента As	Атомно-абсорбционная спектрометрия
British Pharmacopoeia	«Heavy metals in herbal drugs and fatty oils»	Cd, Cu, Fe, Pb, Ni, Zn Hg и элемента As	Атомно-абсорбционная спектрометрия
United State Pharmacopoeia	«Heavy metals»	*	Сульфидный метод
Pharmacopoeia Japonica	«Heavy metals limit test»	*	Сульфидный метод
ГФ XI	Испытание на соли тяжелых металлов	*	Сульфидный метод
Государственная Фармакопея республики Беларусь	«Определение содержания токсических веществ методом атомно-абсорбционной спектроскопии»	*	Атомно-абсорбционная спектрометрия

Примечание: *металлы в статье не указаны.

The British Pharmacopoeia monograph "Heavy metals in herbal medicines and fatty oils" is harmonized with the corresponding monograph of the European Pharmacopoeia, has the same sections and uses atomic absorption spectrometry as a method for the determination of heavy metals [14].

The general pharmacopoeial article "Determination of the content of toxic substances by atomic absorption spectroscopy" is included in the State Pharmacopoeia of the Republic of Belarus [2]. It consists of 3 sections: the technique of sample preparation, the method of dry and wet mineralization. Dry mineralization of samples is carried out using a nitric acid solution. It is based on the complete decomposition of organic substances by burning a sample of raw materials weighing 3–5 g (accurately weighed) in quartz crucibles in an electric furnace under a controlled temperature regime, followed by dissolving the ash in diluted nitric acid.

The method of wet mineralization is based on the complete destruction of organic substances of the sample when heated with sulfuric and concentrated nitric acids with the addition of perchloric acid or hydrogen peroxide, or when heated only with hydrogen peroxide in Kjeldahl flasks or flat-bottomed flasks. Determination of toxic elements is carried out by atomic absorption spectroscopy. The description of the AAS method coincides with that in the monograph of the European Pharmacopoeia. Semi-quantitative analysis of heavy metals - by the sulfide method, is used to determine heavy metals in the Japanese Pharmacopoeia, the US Pharmacopoeia, the Russian Federation State Pharmacopoeia XI edition [3, 4, 19, 20].

The Japanese Pharmacopoeia does not provide for the determination of heavy metals in medicinal plant raw materials, however, it regulates their determination in the substances of dosage forms by the semi-quantitative sulfide method in the monograph "Heavy metals limit test", which includes the methods for preparing the test and control solutions (I-IV). The main sections of the monograph include 4 methods for the preparation of the test and control solutions. The methods differ in the method of sample preparation: wet mineralization with the addition of dilute acetic acid (method 1) and various methods of dry mineralization in quartz, porcelain or platinum crucibles at 500–600 ° C (methods 2–4). Determination of the amount of impurities of heavy metals in drugs is carried out after the reaction with sodium sulfide in comparison with the control solution of Pb [19].

The Japanese Pharmacopoeia includes the method of atomic absorption spectroscopy, but it is not used to determine the content of heavy metals in medicinal plant materials.

The US Pharmacopoeia regulates the determination of heavy metals in substances of dosage forms and medicinal plant raw materials by the semi-quantitative sulfide method in the monograph "Heavy Metals", which includes the methods for preparing the test, standard and control solutions depending on the properties of the starting substances (methods I-III). This test is designed to show that the content of impurities of metals, colored in the presence of sulfide ion, does not exceed the limit of their content in the analyte in comparison with a standard solution of Pb nitrate, which is determined visually. The content of heavy metals is determined by method I, unless otherwise indicated in a separate monograph. Method I is used for substances that, under certain conditions of analysis, form transparent, colorless preparations. Method II is used for substances not forming transparent, colorless preparations under the conditions of analysis of method I, or for substances that, due to their complexity of their nature, interfere with the precipitation of heavy metals by the sulfide anion, or for non-volatile and volatile oils. And method III, the wet mineralization method, is applied only in cases where neither the first nor the second method can be used.

Method I uses an acetate buffer solution (pH 3.5) and makes a number of dilutions [20].

Method II does not detect Hg. Sample preparation is carried out by dry mineralization using sulfuric and nitric acids. For the analysis, acetate buffer solution with pH 3.5 and thioacetamide-glycerol base are added to each of the tubes containing the standard preparation and the test sample. The color is observed from top to bottom on a white background: the color of the solution of the test drug should not be darker than the color of the standard drug.

Method III describes the method of wet mineralization in a Kjeldahl flask with nitric, sulfuric acids and 30% hydrogen peroxide solution. When determining, the solution is brought to pH 3-4 with the help of ammonium hydroxide. If thioacetamide cannot be used, add 10 ml of freshly prepared hydrogen sulfide solution to each tube, mix, leave for 5 minutes, and observe from top to bottom on a white surface.

The State Pharmacopoeia of the Russian Federation XI edition regulates the semi-quantitative sulfide method for the determination of heavy metals in tinctures and extracts from medicinal plant materials. The GF RF XI edition includes a sulfide method for the determination of heavy metals only in medicines. The test is based on the formation of a black precipitate or brown color of the solution during the interaction of Pb salts, depending on the concentration, with solutions of sodium sulfide or hydrogen sulfide [3, 4].

For the XII edition of the State Pharmacopoeia of the Russian Federation, a draft general pharmacopoeia article "Determination of the content of heavy metals in medicinal plant raw materials" has been developed, which prescribes the determination of the most toxic heavy metals Pb, Cd, Hg. Atomic absorption spectrometry was proposed as a determination method [5].

In accordance with the study, it was found that there are no uniform norms in the pharmacopoeias (Table 5) governing the maximum content of heavy metals in medicinal plant raw materials (with the exception of certain types), and standards for food products are used as indicative criteria in all countries [eleven].

Table 5

Permissible levels of heavy metals in medicinal plant raw materials in different countries

Страна	Показатель	Допустимые уровни, мг/кг					
		Pb	Cd	Hg	Cu	Zn	Ni
Россия[1]	Овощи, фрукты, соки	0,5	0,03	0,02	–	–	–
	Чаи	6,0	1,0	0,1	–	–	–
	БАД на основе концентратов (экстракты растений и др.)	5,0	1,0	1,0	–	–	–
Швейцария[2]	Fucus	5,0	4,0	0,1	–	–	–
Германия	German Pharmaceutical Manufactures Association (BAH) 2002						
	Ориентировочные значения для свежих листовых овощей и растений	10	1,0	0,1	40	–	10
Германия	ZEBS ориентировочные значения вредных веществ для продуктов питания	2,0	0,1	–	–	–	–
Китай	Предельные уровни тяжелых металлов для растительных лекарств традиционной медицины Singapore Medicines Order 1995	20,0	-	0.5	150	–	–

Примечание: данные представлены в соответствии с нормативными документами:
[1] – Сан Пин 2.3.2.1078-01; [2] – European Pharmacopoeia.

conclusions

1. Studies have shown that the content of heavy metals in medicinal herbal raw materials on the world pharmaceutical market can reach concentrations significantly exceeding the standards for food products. The most polluted species include dye safflower, medicinal dandelion, medicinal rosemary, and peppermint. Medicinal plant raw materials of these types come mainly from Poland, Germany and Asian countries. Relatively environmentally friendly plant species include coriander and common fennel.

2. Pharmacopoeias of different countries regulate the determination of heavy metals in medicinal vegetable raw materials by atomic absorption spectrometry or sulfide method.

3. As a guideline criterion in all countries it is customary to use the norms for food products. The most strictly regulated content of heavy metals in food in Russia.

4. Conducted information and analytical studies show the need for rationing the content of heavy metals in medicinal plant raw materials and confirm the timeliness of the development in Russia for the State Fund of the XII edition of the general pharmacopoeial article "Determination of the content of heavy metals in medicinal plant raw materials."

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