

Determination of Lead, Cadmium and, Mercury in Some Medicinal Plants and their User's Urine Samples

Hatem Abdel Moniem Ahmed, Al Saad Mohammed Ali, Muhammad Naeem Janjua,
Majed Ahmed Hassan Hazazi

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Abstract: Herbal medicines constitute an important part of healthcare throughout the world. Although many benefits can be derived from the use of herbs, potential areas of concern include possible product contamination and/or adulterations and potential toxicity. This study evaluates the prevalence of toxic heavy metals, (Pb, Cd, and Hg), in medicinal herbs and their level in urine samples of users of these herbs. 5 different types of medicinal plants were collected from the herb market in Riyadh. A total of 60 urine samples, consisting of 30 users and 30 control, was collected and processed for the determination of toxic metals. The herbs were digested using (HNO₃+HF+H₂O₂), while urine samples were digested with (HNO₃+H₂O₂). The heavy metals content in herbs and urine samples were determined by AAS. The results showed that Cd and Pb concentration in medicinal herbs did not exceed the maximum permissible levels of WHO, while Hg exceeded the maximum permissible levels. On the other hand, the average concentration of Cd and Pb in urine samples was less than the maximum permissible levels of WHO, while the concentration of the Hg exceeded the maximum permissible levels of WHO indicating associated toxicity and risk of using these herbs as therapeutic agents. This study have proved that exposure to these metals through consumption of medicinal plants unsafe.

Keywords: Heavy metals (Pb,Cd,Hg); Medicinal plants; urine; AAS.

INTRODUCTION

With the development and progress of modern medicine, there has been a significant improvement in the quality of human life all over the world. Modern medicines consist of active ingredients, which are extracted and purified from plants and animals, and are synthesized by qualified scientists in specialized laboratories. In order to ensure their safety in patients, they are put to rigorous clinical trials before their approved for human use. However, despite their tremendous success in treating many serious diseases and increasing life expectancy, their prolonged use is associated with certain known and unknown adverse reactions and serious side effects (R) which have been found harmful for human health [1]. This is one of the factors that provided the base for the development of alternative or traditional medicines among the general public.

According to a report published in JAMA, 20.7% of medicinal herbs contain one or more of these toxic heavy metals with concentrations higher than the daily allowed limits. One of the main reasons is the prior contamination of the soil, water, and air with toxic metals, which are then incorporated into the herbs during their growth phase. These herbs are harvested and stored without having the knowledge of all the toxins, which are already present in the harvested plants [2, 3]. These toxic heavy metals enter the

Hatem Abdel Moniem Ahmed, Department of Forensic Chemistry, College of Forensic Sciences, Naif Arab University for Security Sciences, Riyadh, Saudi Arabia. E-mail: Hatemahmed29@yahoo.com; Hatemahmed29@nauss.edu.sa

Al Saad Mohammed Ali, Department of Forensic Chemistry, College of Forensic Sciences, Naif Arab University for Security Sciences, Riyadh, Saudi Arabia. E-mail: dr.alsaad@nauss.edu.sa

Muhammad Naeem Janjua, Department of Forensic Chemistry, College of Forensic Sciences, Naif Arab University for Security Sciences, Riyadh, Saudi Arabia. E-mail: dr.mhaji@nauss.edu.sa

Majed Ahmed Hassan Hazazi, Department of Forensic Chemistry, College of Forensic Sciences, Naif Arab University for Security Sciences, Riyadh, Saudi Arabia. E-mail: mahazazi@sfd.gov.sa

consumer's body through different routes, including sniffing, absorption through the skin, and/or oral consumption, causing acute illness when exposed to it frequently for short intervals or accidental exposure to high doses. Chronic effects of heavy metal toxicity may result after prolonged exposure to low doses. If the rate of entry into the body is fast then they will accumulate to the point of danger, and hidden symptoms of heavy metal poisoning appear to be difficult to interpret because of similarity to other organic diseases [4]. Heavy metals are known contaminants and adulterant of numerous traditional medicines or herbal remedies. The Asian and Indian traditional medicines have been reported to contain large amounts of As, Pb, Hg and high limit of lead [6; 5]. Therefore, resorting to laboratory analysis, where a correlation between the secretions of body fluids (Blood, urine, and stool) and the concentration of these heavy metals toxic to the organs and tissues of the body, so as a reflective of heavy metals inside the body accumulated caused different symptoms of toxic metals according to the type of these metals, and also acute and chronic exposure mechanisms [7]. In view of the aforementioned dangers posed by uncontrolled practice and use of medicinal herbs, most of the countries have taken preventive measures to reduce the risks and to increase therapeutic benefits of medicinal herbs in the future. In some countries, strict laws have been made to issue the medical license to qualified herbalists who practice and sell these herbs. From laboratory tests to clinical studies, monitoring bodies comprising qualified medical scientists and toxicologists have been set up to ensure the safe use of medicinal herbs [8, 9]. The main objective of this study is to determine the concentrations of toxic metals (Pb, Cd, and Hg) in 5 medicinal herbs (Cassia Angustifolia, peganumharmala, Vitex agnus-castus, Teucrium and Horsetail) which are commonly used in various parts of the kingdom of Saudi Arabia. In addition, levels of these heavy metals (Pb, Cd, and Hg) in urine samples of the users of these herbs were also determined. It is hoped that the results of this study will add to the existing state of knowledge about the heavy metal toxicity of commonly used medicinal plants in the Kingdom of Saudi Arabia.

MATERIALS AND METHODS

Reagents and Solutions

Standard Stock solutions of Pb, Cd, and Hg with concentrations of 1000 mg/L were purchased from Chem Service (Panreac Quimica SA). All chemicals were of analytical grade purity. For the preparation of working standard solutions of lead, cadmium and mercury ultra-pure water (18.2 M-ohm) from a MilliQ-Element A10 system (Millipore, Milford, USA) was used. Nitric acid (69.0 %, CL CHEM-LAB, Belgium), hydrofluoric acid (48 %, Panreac Quimica S.A.U., Spain) and hydrogen peroxide (35%, Riedel-de Haen, Germany) were used.

Samples

A total of 5 medicinal plants were selected and purchased from the local herbal stores, Riyadh, Saudi Arabia. These medicinal herbs are commonly used for slimming, treating constipation, softening the bowel and colon. The herbs samples were prepared for analysis of selected heavy metals constituents (Table 1). Our study was focused on the herb (Cassia Angustifolia), because of high concentrations of Pb, Cd and Hg metals were reported by most of the research workers. 30 urine samples from treated (10 male and 20 female) and 30 from healthy subjects (control) (15 male and 15 female), the age between (19-50) year. The treated and control individuals were confirmed that they were not exposed to environmental pollution. A questionnaire was served among volunteers, both treated and healthy controls, to obtain information on the type of food, water, and beverages they were using. It was also made sure that the food and liquids they were consuming were almost free or had a very low concentration of the elements under study and they do not have systemic risk factors. The urine samples were collected from volunteers, who had been using (Cassia Angustifolia) herb from one month to more than one year. The herb "Cassia Angustifolia" was used by all individuals after boiling it in water for 15 to 45 minutes at mild flame or temperature. The boiled extract was used by the age group of 19-50 year. The urine specimens were collected in the sterilized and acid-washed plastic container. At the time of sample collection, 50 µl of concentrated nitric acid was added to each sample to avoid any fungal and bacterial growth. The collected samples were stored in the icebox at the 4 °C and transferred to the laboratory as soon as possible for analysis. In the laboratory, the urine specimens were filtered by a Millipore membrane filter (0.45 µm). The filtered urine sample was frozen at -20 °C until further analysis.

Table 1: Basic information about medicinal herbs used in this study

	Medicinal Herb	Brand (Manufacturer)	Country of Packing
1	Cassia angustifolia	Ben Munchash	Saudi Arabia
2	Peganum harmala	Ben Munchash	Saudi Arabia
3	Vitex agnus-castus	Ben Munchash	Saudi Arabia
4	Teucrium	Ben Munchash	Saudi Arabia
5	Horsetail	Ben Munchash	Saudi Arabia

Herbal and Urine Sample Preparation

The medicinal herb specimens were washed with deionized water 2-4 times and allowed to be dry in dampness extraction furnace for 48 hours at 65 °C. The specimens were then ground with a Wiley grinder for 2-3 minutes and sieved through a 0.5 mm diameter sieve. The ground herbs were stored in acid washed polythene bags at room temperature (25°C) in the dry atmosphere. High-performance microwave digestion system (ETHOS ONE, Italy) was used for the digestion process as described by Sandra [10]. Briefly, 0.5 gram of the powdered plant specimens were digested with 5 ml of 69 % nitric acid, 1 ml of 48 % HF and 2 ml of 35% H₂O₂. After the digestion process was completed, the digested clear solution was transferred into acid-washed 50 ml volumetric flask and the total volume was made up to 50 ml with deionized distilled water. Ready-to-use digested samples were refrigerated until elemental analysis was performed.

For urine samples, microwave digestion, 5 ml of each urine sample was transferred, along with 5 ml of 69 % nitric acid and 2 ml of 35% hydrogen peroxide, to a 125 ml pressure-resistant PTFE vessel for digestion [11]. The clear, digested solution of urine samples was transferred to acid washed 50 ml volumetric flask and the total volume was made up to 50 ml with deionized water. The digested, ready-to-use herb and urine samples were subjected to atomic absorption spectrometry using 240 FS atomic absorption spectrophotometer (Agilent Technologies) fitted with Graphite Furnace GTA 120 and programmable sample dispenser. Argon was used as a carrier gas.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows. Correlations between all metal fractions and total metal content were explored.

RESULTS AND DISCUSSION

The present study was conducted to estimate the concentration of Cd, Pb, and Hg in the extracts of 5 medicinal plants which are commonly used as herbal remedies in various parts of the Kingdom of Saudi Arabia. At the same time, Cd, Pb, and Hg were also estimated in urine samples of persons who were taking these herbs as a treatment for various types of illnesses.

Table 2 shows the limit of detection (LOD) and the limit of quantitation (LOQ), where all values lie in the acceptable range. The mean concentration of heavy metals in our studied medicinal plants is shown in figure 1. The mean concentration of heavy metals in our studied medicinal plants is shown in figure 1. Cassia Angustifolia contained the highest level of Cd (0.69±0.005 mg/kg), Pb (9.7±0.005 mg/kg) and Hg (3.8±0.001 mg/kg), followed by Teucrium (Cd: 0.60±0.005; Pb: 6.2±0.006 and Hg: 3.1±0.002, mg/kg) and Peganum harmala (Cd: 0.60±0.005; Pb: 4.2±0.001 and Hg: 1.9±0.0002, mg/kg). Mercury (Hg and Pb) were detected in all of the 5 herbs whereas Cd was found only in 4 plants, figure 1. The main concentration of Hg was higher in Cassia Angustifolia (3.8 mg/kg) than all plants. Figure 2, Table 3 shows the mean±SD concentration of Cd, Pb of 30 urine samples collected from subjects who were using these medicinal plants. The Cd levels range from 0.001±0.001 to 0.005±0.002 mg/kg, whereas Pb levels range from 0.01±0.006 to 0.06±0.002 mg/kg. The level of Hg ranges from 0.9±0.0002 to 3.5±0.0008 mg/kg (Fig 2.)

Table 2: LOD, and LOQ for calibration curve in plant and urine samples

	Cd mg/kg	Pb mg/kg	Hg mg/kg	Cd mg/l	Pb mg/l	Hg mg/l
	Plants			Urine		
LOD	0.11	1	0.3	0.0012	0.002	0.22
LOQ	0.34	3	1.0	0.0037	0.006	0.66

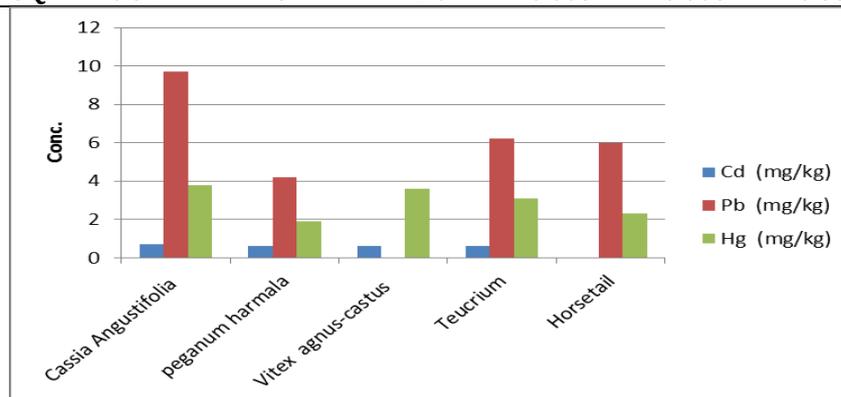


Figure 1: The mean concentration of heavy metals in different medicinal herbs

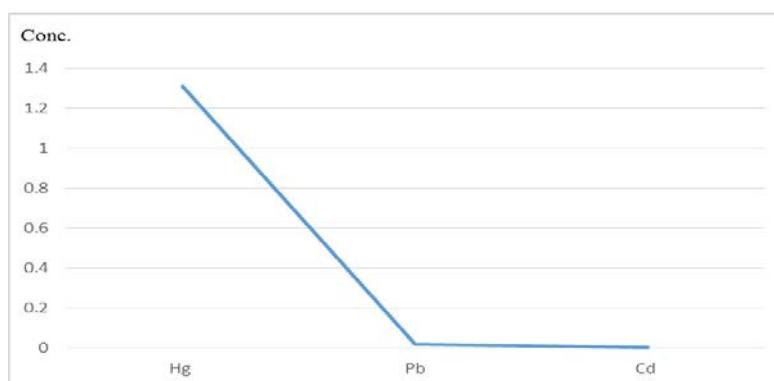


Figure 2: The mean concentration of heavy metals in the urine samples of volunteers using Cassia Angustifolia herb

Table 3: The mean \pm SD concentration of heavy metals in urine samples of volunteers using Cassia angustifolia herb

Sample	Cd mg/l	Pb mg/l	Hg mg/l
1	0.001 \pm 0.002	0.01 \pm 0.005	1.2 \pm 0.0003
2	0.001 \pm 0.001	0.01 \pm 0.002	1.0 \pm 0.0006
3	0.003 \pm 0.007	0.03 \pm 0.006	1.5 \pm 0.0004
4	0.001 \pm 0.007	0.01 \pm 0.002	1.1 \pm 0.0003
5	0.001 \pm 0.004	0.02 \pm 0.001	1.1 \pm 0.0003
6	0.001 \pm 0.008	0.02 \pm 0.005	1.2 \pm 0.0008
7	0.001 \pm 0.001	0.01 \pm 0.001	1.2 \pm 0.0006
8	0.001 \pm 0.001	0.02 \pm 0.001	1.5 \pm 0.0005
9	0.001 \pm 0.003	0.02 \pm 0.001	1.2 \pm 0.0003
10	0.001 \pm 0.008	0.01 \pm 0.002	1.1 \pm 0.0002
11	0.002 \pm 0.004	0.02 \pm 0.002	1.2 \pm 0.0002
12	0.001 \pm 0.002	0.01 \pm 0.002	3.5 \pm 0.0008*
13	0.001 \pm 0.006	0.018 \pm 0.001	1.4 \pm 0.0004*
14	0.001 \pm 0.008	0.01 \pm 0.001	1.1 \pm 0.0004
15	0.001 \pm 0.001	0.01 \pm 0.001	1.3 \pm 0.0005
16	0.001 \pm 0.006	0.02 \pm 0.000	1.3 \pm 0.0006
17	0.001 \pm 0.004	0.02 \pm 0.002	0.9 \pm 0.0002
18	0.002 \pm 0.017	0.02 \pm 0.002	1.0 \pm 0.0004
19	0.001 \pm 0.014	0.02 \pm 0.003	1.0 \pm 0.0002
20	0.004 \pm 0.001	0.01 \pm 0.000	1.1 \pm 0.0001
21	0.003 \pm 0.005	0.02 \pm 0.002	1.3 \pm 0.0003
22	0.001 \pm 0.005	0.01 \pm 0.001	1.2 \pm 0.0002
23	0.001 \pm 0.004	0.01 \pm 0.001	1.2 \pm 0.0008
24	0.005 \pm 0.002*	*0.06 \pm 0.002	1.0 \pm 0.0002
25	0.003 \pm 0.01*	*0.05 \pm 0.004	1.8 \pm 0.0004
26	0.003 \pm 0.005	0.03 \pm 0.004	1.4 \pm 0.0002
27	0.001 \pm 0.016	0.02 \pm 0.001	1.3 \pm 0.0005
28	0.002 \pm 0.005	0.03 \pm 0.004	1.5 \pm 0.0003
29	0.001 \pm 0.01	0.01 \pm 0.003	1.3 \pm 0.0003
30	0.002 \pm 0.011	0.02 \pm 0.001	1.3 \pm 0.0000
Mean	0.0016 \pm 0.007	0.019 \pm 0.002	1.31 \pm 0.0004

Table 3 showed that The high concentration of Hg in Cassia Angustifolia, may due to the method of using Cassia Angustifolia is to drink its drenched leaves, where plant paper is better than their roots or seeds and the ability of 97% gave results indicating high concentrations of toxic substances because of the process of absorption by the digestive system.

Concentration of Heavy Metals in Herbs

The presence of heavy metals in herbal medicines is well documented [12, 13]. The concentration of heavy metals and their expected presence in the medicinal plants was a varying but there was a difficult to set the world record rates for some of them [7]. The outcomes of this study demonstrated that the concentrations of heavy metals (Pb and Cd) in the medicinal herbs were found to be under the World Health Organization (WHO) [14] permitted levels, while the concentration of Hg was higher than the

quality requirement for traditional medicines in Malaysia, which is enough to cause adverse health effect when taken daily [15]. The maximum concentration of Cd, Pb, and Hg are (0.69 ± 0.005 , 9.7 ± 0.005 and 3.8 ± 0.001 mg/kg), was found in the *Cassia Angustifolia* herb respectively, where the concentration of Cd and Pb are considered to be in an acceptable range of (WHO) (5-30 and 10 mg/day), respectively, while the concentration of Hg exceeds the quality requirement of traditional medicines in Malaysia (0.5 mg/kg) [15]. A similarity was found by Ang [16], who examined medicinal herbs in a dense environment such as Islamabad to measure the effect of environmental pollution in general and air pollution especially in the presence of heavy metals in medicinal herbs, and other rural environments as Rawalpindi to measure the impact of the agricultural environment and agricultural fertilizers. Maghrabi examined some types of medicinal herbs in local markets in the western region of Saudi Arabia, the results showed that the ratio of Cd and Pb were lower than (WHO) [14], while the level of Hg agrees with the study done by Ang, who analyzed the mercury content of 100 pharmaceutical dosage forms of luzonensis that were purchased in the Malaysian market [16].

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Concentration of Heavy Metals in Urine

The study of the heavy metals content such as Cd, Pb, and Hg in medicinal herbs and their reflection on the urine of its users is very important. This in line with the recommendations of the study by Teresa [11]. Many studies proved that the tests on the plant paper are better than their roots or seeds due to plants are predominately taken orally and the ability of 97% gave results indicating high concentrations of toxic substances because of the process of absorption by the digestive system. As we have already pointed out that the method of using *Cassia Angustifolia* is to drink its drenched leaves. The results showed that the average level of Cd in the experimental and control urine samples for *Cassia Angustifolia* (0.002 ± 0.007 and 0.001 ± 0.007 mg/l), respectively, within the allowable limits from international organizations (14, 17), Low levels of Cd don't give absolute safety to people because of the big half of lifetime of Cd (over 10 years), which may lead to mild or moderate chronic injury over time. Jarup demonstrated in his study that there were no symptoms during the first year of exposure to Cd, and the urine samples can't give a clear picture of the nature and conditions of the kidneys which consider the main target for cadmium [1]. In the United States, the level of Cd in the urine of a healthy non-smoker (0.08 mg/l) was increased to (26 mg/l) with age according to the National Health and Nutrition Examination Survey (NHANES), the risk is increased when the person smoke or contact with Cd where an irritating localized effect on the skin when the concentration exceeds (10 mg/l) [18]. The previous study agrees with the present study where some samples have a high concentration of Cd, as samples 24 and 25 (0.005 ± 0.002 and 0.003 ± 0.01 mg/l) respectively (Table 3), This is due either to the fact that the two samples are related to smokers or eating vegetables grown in the soil with phosphate fertilizers, where the level of Cd reach to (100 mg/l) based on the study of Susan on the effect of agricultural fertilizers on soil and plants [13]. The results revealed that the average concentration of Pb was (0.019 ± 0.002 and 0.011 ± 0.003 mg/l), in the tested and control urine samples for *Cassia Angustifolia* respectively, within the allowable limits of Pb from international organizations (< 10 mg/l) [14, 17], listed in (Table 3).

Most Pb concentrations that are found in the environment are a result of human activities. It may be ingested by eating or drinking contaminated food and by swallowing large particles (diameter greater

than 5 mm) [19]. Lead in air may be transferred to plants directly through fallout or indirectly through uptake from the soil. Plants on land tend to absorb Pb from the soil and retain most of this in their roots according to recommendations of United Nations Environment Program, World Health Organization, and International Labor Organization. According to the World Health Organization (WHO) regulations with Food and Agriculture Organization (FAO) [17], they set a weekly level Pb by 25 mg/kg bw., so the concentration Pb in the current study was classified as relatively safe even with two high concentrations of Pb in samples (24 and 25) (0.06 ± 0.002 mg/l and 0.05 ± 0.004 mg/l) respectively, (Table 3), However according to the Center of Disease Control and Prevention (CDC) at low level of Pb concentrations in the body, it may lead to chronic brain, muscles, bones fetal malformations and mental retardation in children to cancer, this confirmed by the International Agency for Research on Cancer (IARC) [20].

Respecting to Hg, the average concentration in the tested and control urine samples (1.31 ± 0.0004 mg/l and 0.9 ± 0.0003 mg/l), respectively, exceeding the allowable limits from international organizations (2 mg/l) [14, 17], (Table 3). The present results are consistent with a previous study by Cheng who measure the high concentration of Hg in medicinal herbs and their reflection on biological body fluids. High concentration of Hg can be attributed to various reasons as insecticides, some traditional medicines such as Makarov (mercury sulfide) (Makarov is prepared by mixing gold, mercury, and sulfur in an accurate proportion) [21]. It also corresponds to a study carried out in South Africa about the determination of Cd and Pb in herbs and their reflection on biological body fluids, where it was lower than the international allowable rates compared to Hg that exceeded the international allowable levels at very high concentrations [8].

The high-level of Hg in the urine may be interpreted as a chronic exposure, where various studies proved that 58% of it is taken out by urine at a chronic exposure of >10 mg/l). As Yoshida pointed out in his study that half-life time of Hg is 70-day, this explains that the level of Hg in urine samples has been halved compared with the average level of Hg in the herb but remains high and this is not safe for the person's health [22].

This leads us to the fact that our environment in Saudi Arabia and the Arabian Gulf region countries may have been affected by the negative effects of the Gulf war on marine life. The waters of the Gulf are shallow, and the movement of water is weak. Therefore, seafood is rich in Hg compounds called organic methylmercury, which accumulated in fish and oysters, where its concentration in Arabian Gulf fish is (0.22 mg/kg), as happened in the Minamata city in Japan, where Hg poisoning caused the emergence of hidden symptoms such as the effects on the kidneys and nervous system with numbness, inability to move, loss of vision and hearing and may reach coma or death [23].

Correlation between Metals

Correlations of the metals in the same body biological fluid may be due to an interaction between the different metals in the same compartment so that the concentration of one metal determines the concentrations of the others [24].

Correlation analysis was carried out for trace heavy metals concentration in urinary specimens to understand the significance ($p = 0.05$, $p < 0.05$) of association between the metals in urine. The Pearson correlation coefficient matrix for trace heavy metals (Cd, Pb, and Hg) in urine was presented in (Table 4) and (Fig 3). This study revealed that, the correlation coefficient between the levels of Cd and Pb (0.886) and means a strong positive correlation with a statistical significance at ($0.01 = \alpha$) (Table 4) and (Fig 3), which supported by the study done by Talisman [25]. Hovatta also found that the concentrations of cadmium and lead in seminal plasma were correlated [26].

Table 4: Pearson correlation coefficient for toxic heavy metals with urinary specimens

	Cd	Pb	Hg	Mean	SD
Pearson Correlation	1	0.886**	0.022		
Cd Sig. (2-tailed)		0.000	0.904	1.6026	0.9
N	32	32	32		
Pearson Correlation	0.886**	1	0.023		
Pb Sig. (2-tailed)	0.000		0.901	18.8944	10
N	32	32	32		
Pearson Correlation	0.022	0.023	1		
Hg Sig. (2-tailed)	0.904	0.901		1.3125	0.4
N	32	32	32		

** . Correlation is significant at the 0.01 level (2-tailed).

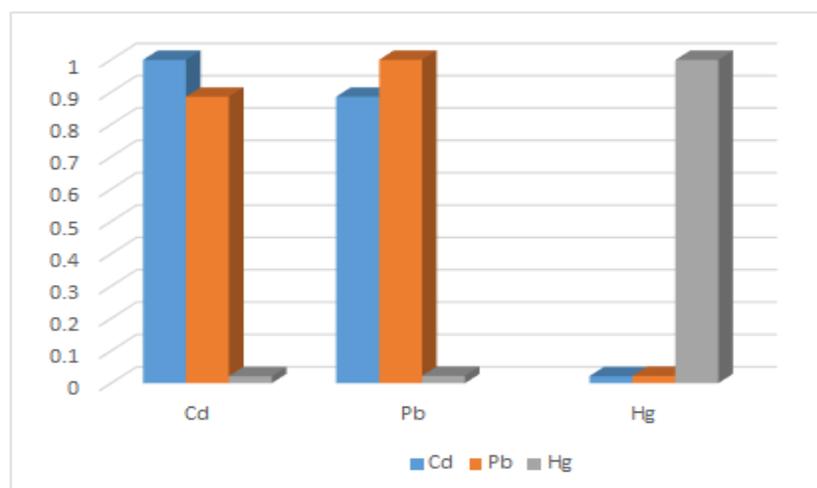


Figure 3: Pearson correlation coefficient for toxic heavy metals with urinary specimens

CONCLUSION

This study demonstrates that the state of research on heavy metals in medicinal plants to date. This study concentrated mainly on the presence and variability of heavy metals in medicinal plants and their users. The researchers have proved that exposure to these metals through consumption of medicinal plants is practically unavoidable. Exposure to toxic metals (e.g., Pb, As, and Cd) is a problem that needs to be addressed because of the huge dangers in human health. Co-introduction to different heavy metals must be precisely considered to synergistic or hostile impacts.

COMPETING INTERESTS

The authors declare that there are no competing interests regarding the publication of this article.

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