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DAILY EXPOSURE ASSESSMENT OF As, Ni, Hg, Al AND Mn IN ANTI DIABETIC HERBAL PREPARATIONS (ADHPs)

Rausan Zamir[1,*], Nazmul Islam[2], M. Anisur Rahman[3], and M. Safiur Rahman[4]

[1]Department of Chemistry, University of Rajshahi, Rajshahi- 6205, Bangladesh

[2]Department of General Educational Development, Daffodil International University, Dhaka-1207, Bangladesh

[3]Department of Chemistry Biochemistry, Uppsala University, Sweden

[4]Atmospheric and Environmental Chemistry Laboratory, Chemistry Division, Atomic Energy Center, 4-Kazi Nazrul Islam Avenue, Dhaka-1000, Bangladesh

Email address: *rsnzamir@yahoo.com

Abstract

With the prevalence of heterogeneous disorder diabetes, mass sought for the ailment of the disease was expected and forced people to move for comparative low cost, available and safe cure. And it makes herbal preparations predominant in comparison with its allopathic counterparts in a country where a significant amount of people lives below poverty line. From the very beginning, the safety of herbal preparations was not studied and thus left uninvestigated and putting public life under threat. Therefore, present study was to investigate the metal toxicity in eighteen anti diabetic herbal preparations (ADHPs) available in Bangladesh in terms of their toxicity as presence of toxic element pose a great threat to human health and thus put the drug safety in danger zone. In our investigation, trend of metal concentration was identified in the order of Hg < Ni, As < Mn < Al. No heavy metal under investigation (As and Hg) crossed the permissible safety limit in all regulatory body permissible standards. Additionally, heavy metals (As and Hg) were found safe under US FDA standard of permitted daily exposure (PDE) and Canada's National Health Product and California Proposition. Chronic accumulation of elemental impurities is likely due to prolonged intake or overdose of these ADHPs, which poses severe hazardous effects upon human health.

Keywords: *Elemental impurities, heavy metals, PDE and ADHPs*

Introduction

Phytotherapy is the study of botany and use of plants directed to medical purposes, which deals with medicinal herbs and their preparations. Medicinal herbs and their preparations are widely used by human beings all over the world [1]. Looking into history, the use of medicinal plants and their preparations in Asia has been found long since. At present use of medicinal plants is becoming increasingly popular worldwide. So, this indicates a massive consumption of medicinal plants and their preparations. It is evident that 80% populations of the developing world rely on herbal medicines as their primary healthcare [2,3].

The number of diabetic patients have been increasing rapidly. As a non- communicable heterogeneous group of disorder, diabetes affects an approximation of 200 million populations globally. Certainly, this is a threat to health care and social welfare [4]. The number of people suffering from complications related to diabetes will surge to 552 million by 2030 wherein 90% will be related to type-2 diabetes [5]. This number of people will constitute 7% of the population in the world by then. Another research represents that by 2035, 10% population of the world will be suffering from diabetes, which amounts 592 million people [6]. There is an increasing trend of people suffering from diabetes worldwide. The pace of this surging is faster in developing countries in comparison with other parts of the world [7].

However, there is a series of medications available in the management of diabetes. Insulin sensitizers, insulin secretagogues, DPP4 inhibitors and alpha glucosidase inhibitors are common medications provided by doctors. However, using modern allopathic drugs possesses certain side effect. Severe hypoglycemia, idiosyncratic liver cell deficit, digestive discomfort, lactic acidocis, permanent neurological deficits are some of them with people being treated with modern therapeutics in diabetes management. Moreover, there is more grieving report, which shows adverse effect of modern drugs is attributed to death in some cases also [8]. Allopathic drugs due to their high price and unavailability restricts their ease of access [9]. Having been of natural origin, the herbal medicines are considered to us as harmless, free from adverse effect and their consumption is not dangerous. Therefore, including ease of access, therapeutic efficacy, relative low cost in comparison with other medications and low side effects associated with their administration have been making anti diabetic herbal preparations (ADHPs) [10,11] popular as ailment of diabetes type-2. With this surge, the vast majority of the ADHPs made their way to the end user without licensing.

But unfortunately worldwide numerous studies have been shown that both in developed and developing countries have high levels of potentially toxic heavy metals in herbal products available to the public [12- 17] Subsequently, another report showed that Asian herbal remedies, collected from United States, China and Vietnam contained significant levels of heavy metals, having approximately 74% holding amounts greater than that of current recommended public health guidelines [14]. Several complex factors might be involved for the high level of heavy metals in raw herbal products. For instance, metal uptake variation of different herb species, cultivation ways, harvesting time, topography, geographical origin, storage etc. [18]. On the other hand, when the plants are grown in polluted areas, such as near roadways or industrial areas (i.e., textile, brick field, smelting operations, metal mining [19], toxic elements transfer from the contaminated soil into plants [20], thereafter into herbal formulations [21], and eventually those heavy metals enter into human body. In addition to the environmental sources, high levels of toxic metals can be found due to use of some agricultural expedients including some pesticides, which contain organic mercury or lead, cadmium containing fertilizers, and even though contaminated irrigation water [22, 23].

There is an evidence to use of heavy metals, which can have synergistic effects on the potency of the drugs [24]. Therefore, heavy metals have also been added in herbal formulations in many countries, and high level of toxic metals can occur in herbal formulations as well as they used as active ingredients, as in the case of Pb and Hg are used in some Chinese, Mexican and Indian herbal medicines [25, 26]. But unfortunately, heavy metals may be causing serious health hazards such as symptoms of

chronic toxicity, renal failure, and liver damage [27, 28]. Several heavy metals including Pb, Cd, Cr, As, Hg etc. must absolutely be controlled in herbal medicines for reassuring their efficacy and safety [29]. However, WHO/FDA has given the permissible limits of arsenic, mercury, lead, and cadmium in herbal drugs, i.e., 10, 1, 10, and 0.3 ppm, respectively. But unfortunately; quality, safety and efficacy data on indigenous medicines is lacking worldwide [30]. Therefore,

It is an important field of study to monitor the herbal formulations for evaluating their quality, safety and efficacy following International regulatory bodies.

Like several countries the herbal preparations are approved dosage system without guidelines and regulations in Bangladesh. Now there is a raising question on whether pharmacological procedures are in place. So, without authenticated and categorized scientific procedure ensuring safety of these preparations is a challenge. Therefore, we undertook the following objectives: Evaluation of selected elemental impurities in terms of heavy metals and trace elements in eighteen frequently used ADHPS and Toxicological investigation of the elemental impurities under regulatory body standards.

Methods

Sample preparation

All samples of herbal formulations were taken out from the medicine strips, which were collected from the local market, Dhaka, Bangladesh. Thereafter, all herbal formulations were place into individual porcelain dishes distinctly and each dish with the particular sample was placed in an oven at around 70°C until a constant weight was attained. The dried mass of each sample was pulverized to fine powder using a mortar and pestle, and preserved in a plastic vial with the identification mark inside a desiccator. Herbal medicines are composed of organic materials. Therefore, 1 g of homogeneous powder for herbal medicine was taken in a Teflon vessel and initially 10 mL HNO_3 acid was used to decompose and abolish the organic materials. Thereafter, an acid mixture of 6 mL conc. HNO_3 (Merck, Germany), 3 mL conc. $HClO_4$ (Merck, Germany) and 10 mL HF (Wako, Japan) was used for digestion the samples. The solution was evaporated to dryness on a ceramic hot plate (As One, Japan) at 180 °C temperature inside a fume hood on a hot plate. Then the solid sample was dissolved in 5 mL of HF and 1 mL of $HClO_4$ acid and heated to near dryness. This procedure was repeated three times to complete dissolution. Thereafter, and HF was removed from the solution by addition of HNO_3 acid and heated until white fumes were observed [31]. Eventually the residue was diluted to 0.1 N HNO_3 and volume made up to 25 mL in a PFA volumetric flask. The same procedures were followed for the blank and standard reference materials (SRM 1753 a Tomato leaves), received from received from National Institute of Standards and Technology (NIST, Gaithersburg, Maryland, USA).

Sample analysis by AAS

An atomic absorption spectrophotometer (AAS 3110 Perkin-Elmer, Waltham, Massachusetts, USA) along with single element hollow cathode lamps (AAS AA-7000, Shimadzu Corporation Japan) and a 10-cm air acetylene burner was used for the analysis of heavy metal ions. For arsenic and mercury analysis two separate hydride vapor generator (HGA-600 atomizer) equipped with AAS were used. The spectral band pass, the wavelengths and other instrumental conditions were applied as prescribed by the manufacturer. The calibration curves for each element were prepared by diluting of stock standard solution of 1000 mg/L (Wako Chemicals, Japan). This study was conducted in Bangladesh Scientific and Industrial Research (BCSIR, Dhaka, Bangladesh).

Daily Exposure

For the assessment of drug safety in terms of elemental impurities value of health based exposure limits or daily exposure (DE) of herbal preparations is determined using the formula given and compared with permitted daily exposure (PDE) limits set by WHO, US FDA, Chinese Pharmacopoeia and HAS Singapore. Here, in this current work we have developed a formula for calculating daily exposure as:

Daily Exposure (DE) = $\frac{Conc.of\ element\ in\ mg\ in\ drug * weight\ of\ drug\ in\ mg * no\ of\ exposure\ per\ day}{1000\ mg}$

Where the value of number of drug exposure per day has been taken from herbal drug consumption instruction manual supplied with the drug under investigation. One tablet/ capsule has been weighted and concentration of element in the drug has been obtained from our current analysis Table-1 of concentration of elemental impurities in ADHPs.

Results

This study revealed that the concentration of arsenic in 18 different ADHPs were ranged from 0.014 to 0.453 mg/kg with a mean value of 0.121 mg/kg. The highest and lowest As concentration were found in the samples of ADHP-5 and ADHP-16 respectively. However, ANOVA test (α = 0.05) (Table-2) revealed that the concentration variation in 18 different ADHPs were not statistically significant at a 95% confidence level (Table 1). Nickel (Ni) concentration were found to be varied from 0.07 to 8.7 mg/L with a mean value of 2.91± 2.7 mg/kg. A big standard

Deviation value was observed due to higher values for the samples of ADHP-3, ADHP-8 and ADHP-11 respectively. However, Ni concentration in most of the samples were not significantly varied at a 95% confidence level ($F_{cal.}$ = 1.306 <F_{crit}= 1.775; α = 0.05; p = 0.216). On the other hand, mercury (Hg) concentration in most the samples were found to be below the detection limit (BDL for Hg is 0.005 ppm) However, the average Hg concentration in rest of the ADHP samples were found to be 0.024±0.018 mg/kg. The average aluminum concentration for this study was found to be 648.45 mg/kg. Subsequently, average Mn concentration in this study was found to be 79.4 mg/kg. However, F test revealed that revealed that the value for F ratio ($F_{calcuâlated}$ = 1.306) for this experimental data was very close to the tabulated value ($F_{4,\ 69,0.05}$ = 1.775), which indicated that there might have variation in Mn concentration in different brands of antidiabetic herbal preparation but variation was not statistically significant as well probability value for this test is greater than 0.05 (Table 1). The concentration of the studied metal in antidiabetic herbal preparation samples were not found in the existing literature. Therefore, it's not possible compare to our finding with reported results in the literature.

The relationships between the studied anti diabetic herbal preparations (ADHPs) samples were analyzed by the Pearson's correlation matrix (Table - 3). The correlation values higher than 0.50 were only conveyed in bold considering as significant relationship. It was observed that Ni was significantly correlated with Hg (r = 0.720, α = 0.01), Al (r = 0.611, α = 0.01) and Mn (r = 0.675, α = 0.01) respectively at 99% confidence level. Reversely, As had only correlation with Al (0.437, α = 0.01) at 95% confidence level. The correlation among the other elements could be found in the same table (Table - 3). From this study, it has been suggested that the source of the elements was same is the studied 18 ADHPs samples as well as they are significantly correlated each other.

Discussion

Most frequently used eighteen ADHPs were subjected to AAS analysis for the determination of elemental impurities (As, Hg, Ni, Al and Mn). The findings from this study were compared with standard regulatory bodies (WHO, Chinese Pharmacopoeia, US FDA and HAS Singapore) for screening them whether the ADHPs are safe to consume in terms of elemental impurities as often there might have possibility of potential risk of accumulation of metals, which leads to toxicity (Table 3). However, the level of each metals and their daily exposure (DE) were individually discussed below.

Arsenic (As)

Arsenic is known carcinogen to cause cancer through respiratory exposure and gastrointestinal exposure [32]. However, this study revealed that the highest concentration (0.45 ppm) of As was found in the sample of ADHP-5 with 0.014 ppm was found to be lowest in the samples of ADHP-11 and ADHP-16 respectively (Table -1). However, arsenic was not found in only one (ADHP-18) sample (as it falls below detection level (BDL= 0.0005 ppm). It should be mentioned that WHO, Chinese Pharmacopoeia, US FDA and HS Singapore are the authorities, who sets the maximum permissible limits for As content as 10, 2, 10 and 5 mg/ Kg

respectively in ADHPs [33]. This study revealed that the highest concentration of As 0.45 ppm in our studies ADHPs sample was below of the standard limits mentioned by different recommended bodies (Zamir et al., 2015). Therefore, it has been suggested that no ADHPs under investigation exceeded the permissible limit in all regulatory body permissible standards. (Table 4). On the other hand, there have also been some national limits for As in finished herbal products set by Canada Malaysia, Singapore and Thailand (WHO, 2007) in their country. The set limits are 5 mg/ Kg, 5 ppm and 4 ppm for Malaysia, Singapore and Thailand respectively (Table-5). Again these limits are found above the highest As concentration in ADHP (0.45 ppm). So, all the 18 ADHPs samples are said to have found at satisfactory level for consuming in Malaysia, Singapore and Thailand.

Daily exposure of As in all ADHPs was found in the range of 0.0001- 0.0034 mg/day (Table-6). PDE value in US FDA 0.015 mg/day, Canada's natural health Product regulation 0.01 mg/day and California Proposition 650.01 mg/day is above highest As DE value 0.0034 mg/day, securing safety (Tables 7-9).

Mercury (Hg)

Only ADHP-3, ADHP-5, ADHP-8 and ADHP-11 were detected with Hg where 0.013 ppm Hg was in ADHP-5, and 0.05 ppm Hg was present in ADHP-11 as lowest and highest amount respectively (Lower detection limit- LDL of Hg is 0.005 ppm for the model of AAS AA-7000, Shimadzu Corporation Japan).

All the four ADHPs (0.05 ppm highest value) were safe under WHO (1mg/kg), Chinese Pharmacopoeia (0.2 mg/kg), US FDA (1 mg/ kg), HS Singapore (0.5 mg/ kg), Malaysia (0.5 mg/kg) and Singapore (5 ppm) (Table 4) (WHO, 2007). 0.000038 mg/day, 0.000013 mg/day and 0.0001 mg/day (Table 6) were daily exposure (DE) value of Hg detected in three ADHPs among 18 ADHPs. These values have been found safe under US FDA (0.03 mg/day) regulation, Canada's natural health product regulations (0.02 mg/day) and national standard by Canada Hg (0.02 mg/day) (Tables 7-9)

Hg, although found in ADHP-3, -5, -8 and -11, has no confirmed vital function in plants (Underwood, 1987). Probably the plant ingredient might have been treated with fungicide containing Hg. Mercury exposure is associated with the development of oscillatory tremors [34]. Mercury-induced cognitive impairments like inattention, excitement and hallucinosis were also reported [35].

Nickel (Ni)

The study revealed that the concentration of Ni ranged from 0.07- 7.82 ppm in all ADHPs (Fig. 1; Table- 1). According to WHO, the permissible limit of Ni was 10 ppm (WHO, 1999). The highest limit of the Ni concentration is below the WHO permissible limit. Therefore, Ni concentrations in all ADHPs is said to be safe considering WHO guidelines.

Using the experimental data, the daily exposure (DE) of Ni in All ADHPs showed a range from 0.0001-0.0565 mg/day(Table-6). To access the potential risk of this range permitted daily exposure (DE) is used. Permitted daily exposure (DE) is the maximum permitted quantity of each element that may be contained in the maximum daily intake of a drug product. Ni has been identified as route-dependent human toxicants as it falls in Class II under US FDA. Subdivision of it as IIA indicates relatively high likelihood of occurrence in the drug product. According to US FDA regulation the permitted DE for Ni is 0.02 mg/day. This standard is over the ceiling of Ni 0.0565 mg/day. Therefore, all the ADHPs were safe in US FDA regulation (Table7). Ni is mostly present in pancreas and required in minute quantity. Thereby has an important role in the production of insulin. Its deficiency results in the disorder of liver [36]. US Environmental Protection Agency (EPA) has recommended that the daily intake of Ni should be less than 1 mg beyond which it is toxic [40]. So, according to EPA the highest concentration of Ni 0.0565 mg/day is not toxic. Toxicity related to Ni is unlikely due to its low absorption by the body [37].

Aluminum (Al)

Concentration of Al in eighteen ADHPs samples were found to be ranged from 20.2- 5400 ppm in (Fig- 1; Table- 1). Nevertheless, as a trace element and not a heavy metal no authority finds it important to document information related to Al on whether it is safe or not. Daily exposure of Al is revealed with a minimum value of 0.162 mg/day in ADHP-18 and maximum value of 12.05 mg/day in

ADHP-5 (Table-6). To assess the potential risk, possess by the elemental impurities US FDA regulation is implemented. But, information related to Al was not available in US FDA probably their no inherit toxicity. Probably for the same reason Canada's natural health Product regulations and Current safe harbor level under California Proposition 65 have not also come out with any data represents the permitted daily exposure value of Al.

Al is the third most prevalent element in the earth where its abundance is highest in earth crust [38]. In nature Al is found in combination with other elements owing to its reactive nature. As a result, trivalent Al ion is found in animal, plant tissues and natural water [39]. This makes Al omnipresent regardless of the source of consumption. However, with normal elimination capacity, a person is not in at risk Al toxicity from natural source with small amount. With a significant aluminum load which exceeds the body's excretory capacity, deposition in various organs like bone, brain, liver, heart, spleen, and muscle is possible which could lead to morbidity and mortality through various mechanisms [38].

Manganese (Mn)

This study revealed that a significant concentration of Mn was found in all studied ADHPs samples. It was observed that Mn concentration was found for a range from 0.13- 211 ppm in all ADHPs with an average value of 79.42 (Fig- 1; Table-1)

Like as aluminum, no authority finds it important to document information on whether it is safe or not. However, daily exposure (DE) of Mn was calculated following Eq. (1), and the highest DE value (0.888 mg/day) was found for the sample of ADHP-11, and the minimum DE value was observed for the sample of ADHP-18 (Table 6).

Conclusion

Under the current screening, eighteen ADHPs were selected for elemental impurities and safety measures in comparison with different international standards. Among five elemental impurities Al was prevalent and found in all ADHPs in high concentration. Mercury was the least found elemental impurity, which was detected in only four ADHPs in ADHP-3, ADHP-5, ADHP-8 and ADHP-11 leaving behind the undetected in rest 14 ADHPs. The rest of the elemental impurities lies in between Hg and Al following the trend: Hg< Ni< As<Mn< Al. No heavy metals among these elemental impurities cross the limits set by International regulation authorities. While these elemental impurities were screen for permitted daily exposure it comes out As, Hg and Ni are safe under US FDA Standard for PDI. Canada's national health product and California proposition 65 also bailed out As and Hg free form health hazard risk. ADHPs within the range of safe limits play a heroic role in public health system. But, considering severe hazardous impact on human health due to prolonged exposure or overdose of HPS containing metals beyond safe limit, precaution should be followed. Safety measures of five elemental impurities were an endeavor to this trend. For this reason, a comprehensive determination and quantification of elements present in ADHPs is accomplished. This will provide a baseline data to conduct studies on other ADHPs.

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Table 1. Descriptive statistics for heavy metals concentration in herbal formulations (mg/kg)

Sl No	Sample Code	As	Ni	Hg	Al	Mn
1	ADHP-1	0.104	2.51	-	1416.0	32.10
2	ADHP-2	0.13	4.71	-	847.0	211.00
3	ADHP-3	0.12	6.41	0.017	1636.0	148.00
4	ADHP-4	0.105	2.86	-	595.0	108.00
5	ADHP-5	0.453	4.97	0.013	5400.0	163.00
6	ADHP-6	0.056	1.33	-	395.0	18.30
7	ADHP-7	0.019	0.16	0.011	52.6	2.16
8	ADHP-8	0.194	8.77	0.014	1278.0	75.00
9	ADHP-9	0.127	2.85	0.013	98.8	15.20
10	ADHP-10	0.047	3.64	-	256.0	23.20
11	ADHP-11	0.014	7.82	0.05	6215.0	458.00
12	ADHP-12	0.098	0.54	0.008	375.0	32.70
13	ADHP-13	0.153	0.63	-	487.0	38.20
14	ADHP-14	0.305	0.63	-	1219.0	79.10
15	ADHP-15	0.019	3.14	0.012	46.6	3.64
16	ADHP-16	0.014	0.07	-	17.9	1.51
17	ADHP-17	0.096	1.2	-	317.0	20.40
18	ADHP-18	-	0.11	-	20.2	0.13
Descriptive statistics						
Mean value		0.121	2.91	0.024	1148.5	79.42
Stdev. value		0.113	2.70	0.018	1776.2	113.20
Std. Error value		0.027	0.64	0.003	418.7	26.68
Min. value		0.014	0.07	0.013	17.9	1.51
Max. value		0.453	8.77	0.050	6215.0	458.00
Geomen value		0.078	1.47	0.020	382.9	24.75

Table 2. Two-way ANOVA test for the different brands of ADHPs samples and different metal concentration

Source of Variation	SS	df	MS	F	P-value	F crit
Between samples	1396203	17	82129.58	1.3058	0.215926	1.775
Between elements	5759289	4	1439822	22.893	5.21E-12	2.506
Error	4276731	68	62893.1			
Total	11432223	89				

Table 3. Pearson's correlation among the studied elements in different ADHPs samples

Name of Element	Elemental concentration (mg/kg) in different ADHPs samples				
	As	Ni	Hg	Al	Mn
As	1				
Ni	0.222	1			
Hg	0.024	0.720**	1		
Al	0.437*	0.611**	0.843**	1	
Mn	0.141	0.675**	0.877**	0.837**	1

* Correlation is significant at the 0.05 level (2-tailed).

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

Table 4. Permissible limit of elemental impurities in ADHPs (mg/Kg)

Heavy or Toxic metal	WHO	Chinese Pharmacopoeia	US FDA	HAS Singapore
Arsenic	10.0	2.0	10.0	5.0
Mercury	1.0	0.2	1.0	0.5

Table 5. National limits for As and Hg in herbal medicines and products

Country	As in finished herbal product	Hg in finished herbal product	Reference
Canada	0.01 mg/day	0.02 mg/day	WHO, 2007
Malaysia	5 mg/Kg	0.5 mg/Kg	WHO, 2007
Singapore	5 ppm	0.5 ppm	WHO, 2007
Thailand	4 ppm	NF	WHO, 2007

Table- 6. Daily exposure (DE) for elemental Impurities through ADHPs samples

Sample ID	Daily Exposure (DE) for elemental Impurities in ADHPs (mg/day)				
	As (mg/Day)	Ni (mg/Day)	Hg (mg/Day)	Al (mg/Day)	Mn (mg/Day)
ADHP-1	0.00046	0.0112	NF	6.34	0.144
ADHP-2	0.00025	0.009	NF	1.626	0.405
ADHP-3	0.00027	0.014	0.000038	3.66	0.3315
ADHP-4	0.0001	0.0028	NF	0.583	0.106
ADHP-5	0.00047	0.005	0.000013	5.508	0.166
ADHP-6	0.00012	0.003	NF	0.87	0.04
ADHP-7	0.00103	0.008	NF	2.84	0.117
ADHP-8	0.0004	0.018	0.0002	2.58	0.15
ADHP-9	0.0015	0.034	NF	1.18	0.18
ADHP-10	0.00014	0.011	NF	0.768	0.0696
ADHP-11	0.00003	0.015	0.0001	12.05	0.888
ADHP-12	0.0002	0.0011	NF	0.75	0.0654
ADHP-13	0.00034	0.0014	NF	1.11	0.087
ADHP-14	0.0006	0.0012	NF	2.49	0.16
ADHP-15	0.0034	0.0565	NF	0.84	0.065
ADHP-16	0.00025	0.00126	NF	0.32	0.027
ADHP-17	0.0002	0.0023	NF	0.627	0.04
ADHP-18	NF	0.001	NF	0.162	0.00104

Table-7. Permitted daily exposure (PDE) for elemental Impurities in US FDA (US FDA, 2000)

Element	Class	Oral PDE (mg/day)
As	I	0.015
Ni	IIA	0.2
Hg	I	0.03

Table- 8. Heavy metal limit for Canada's Natural Health Product (CBER, 2015)

Heavy or Toxic metal	Stated Limit	Calculated daily Limit, Adult 70 Kg in mg/day
Arsenic	0.14 µg "arsenic and its salts and derivatives"/kg bw*	0.01
Mercury	0.29 µg "mercury and its salts and derivatives"/kg bw	0.02

Table 9. Safe harbor level under California proposition 65 (CBER, 2015)

Heavy or Toxic metal	Carcinogen (mg/day) (NSRL)	Reproductive toxicant (MADL) (mg/ day)
Arsenic	0.01	No MADL recorded
Mercury	No NSRL recorded	No MADL recorded

NSRL = No Significant Risk Level,
MADL= Maximum Allowable Detection Level

Fig-1. Box Plot for elemental concentration (mg/kg) in 18 ADHPs samples