Detection of Heavy Metals in the Herbal Medicines from Unlicensed Apothecary Using EDX-RF

Priyabrata Mohapatra¹, Md Alim²

^{1,2}Department of Forensic Science, Kalinga University, Raipur (C.G)

Abstract

The evidence of heavy metals in herbal medicines from unregulated apothecaries impacts forensic science regarding matters of public health, product adulteration, or criminal negligence. This paper employs Energy-Dispersive X-Ray Fluorescence (EDX-RF) to identify contamination (lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg)) in unregulated herbal products. The resultant forensic tool can be used to track the incidence of toxic exposure. Given the non-destructive nature of EDX-RF, the original sample remains intact, enabling repeatable testing for legal decisions. Additionally, because EDX-RF only requires minimal sample preparation, such as weighing, it aligns with forensic standards for chain-of-custody and turnaround time. EDX-RF can detect multiple elements at very low levels (sensitivity range: 4.2-5.1 µg/L), making it useful for labeling products and checking for contamination, as it helps link toxic substances to people being investigated for poisoning. Being non-destructive allows forensic analysts to retain the original sample for confirmation via another test (such as AAS or ICP-MS), an invaluable feature when put against evidence for litigation. Another aspect in favour of EDXRF includes being inexpensive and portable, able to assess field screening when rules are followed during raids or inspecting probable illegal manufacturers, which affords the investigators the opportunity for investigative action on the products EDXRF screening can provide. Additionally, EDXRF can measure contamination levels that exceed the acceptable limits set by WHO for Pb, Hg, etc., thereby strengthening the important relationship between forensic science, analytical chemistry, and forensic toxicology by providing legally admissible data; it can also incriminate illicit vendors. As such, EDXRF will be a functionally significant forensic tool, marrying scientific rigor with real-world functionality to unpack the areas of public health, environmental crime, and consumer fraud.

Keywords: Heavy metals, Herbal medicine, Unlicensed apothecaries, Forensic toxicology, ICP-MS, AAS, XRF, EDX, Traditional medicine, Public health, Heavy metal contamination, WHO

Acknowledgement: We extend our heartfelt gratitude to scientist of State FSL, Raipur Dr. T. L. Chandra, Dr. H.S. Bhawara, Dr. Kulvir Singh and Dr. Dinesh Kumar Sahu for their unwavering

support, expert guidance, and generous contributions throughout the course of study.

Introduction

Herbal medicine, also referred to as botanical medicine or phytomedicine, is the use of plants or parts of plants—including seeds, berries, roots, leaves, bark, or flowers—to treat disease or encourage health and well-being. Herbal medicine is widely recognized as a major part of traditional medical systems around the world and is based on the belief that natural compounds found in plants may help restore balance to the body and promote healing. Considered in many cultures to be therapeutic, herbal medicine remedies can be prepared at different concentrations of the herbs, including as herbal teas, extracts, capsules, topical administration, or other preparations. Herbal medicines are thought to be natural and safe because they aren't "drugs," but they can have serious effects and interact with other medicines, especially if there is no regulation or oversight in their preparation or use. Attention to safety, effectiveness, and quality of herbal medicine is important to incorporating them into practice in healthcare (Benzie & Wachtel-Galor, 2011).

Traditional medicine systems such as Ayurveda (India), Siddha (South India), TCM, Unani (Middle East/South Asia), and African Indigenous Medicine have historically positioned herbal medicines as their very foundation. Most of such formulations originate from plants, but they may equally feature animal parts and minerals, including certain toxic heavy metals, as essential ingredients (Pandey et al., 2013).

Use of Heavy Metals in Medicine

Heavy metals, despite their notorious toxicity, have had a complex and intriguing role in the history of medicine. For centuries, their powerful biological effects made them attractive as treatment options, often long before anyone really understood how they worked—or the dangers they posed. Many of these therapeutic benefits were stumbled upon through trial and error, without a clear scientific explanation of their molecular actions (Duffus, 2002; Guzzi & La Porta, 2008). Some of the most famous historical applications of heavy metals in medicine include mercury, arsenic, bismuth, and gold. Mercury was a go-to treatment for syphilis from the 16th to the 19th centuries, thanks to its antibacterial properties and its ability to interfere with the enzymes crucial to the Treponema pallidum bacterium. Unfortunately, prolonged exposure to this approach often resulted in severe mercury poisoning for patients (Clarkson & Magos, 2006).

Arsenic trioxide (As₂O₃), which was once used for various health issues, has made a comeback in modern medicine as a treatment for acute promyelocytic leukemia. Under careful medical supervision, it triggers programmed cell death (apoptosis) in cancer cells (Shen et al., 1997). Over-the-counter remedies like Pepto-Bismol for gastrointestinal problems still contain bismuth compounds, especially bismuth subsalicylate. Bismuth is relatively non-toxic and can effectively bind to bacteria that cause ulcers, making it a safe choice for treatment (Sun et al., 2001). Gold salts have also been used, particularly for rheumatoid arthritis. These compounds were prized for their anti-inflammatory effects and were utilized before the advent of modern biologic therapies. While they have mostly been phased out today, they were among the earliest examples of using metals for immunomodulatory treatment (Furst, 1997). As shown in Table 1.1

Metal Use		Reason		
Mercury	Treating syphilis (16th–19th	Antibacterial; disrupts pathogen		
(Hg)	centuries)	enzymes		
Arsenic	Leukemia treatment (modern			
trioxide	use)	Induces apoptosis in cancer cells		
Bismuth	Gastrointestinal treatments	Din la ta vila en acuain a ha atania		
(Bi ³⁺)	Gastrointestinai treatments	Binds to ulcer-causing bacteria		
	Rheumatoid arthritis	Anti-inflammatory properties		
Gold salts	treatment			

Table1.1 Heavy metal uses in Medicare

While these applications may not have been entirely clear in their mechanisms back then, they certainly set the stage for the development of metal-based therapies. Sadly, the harmful side effects—like mercury poisoning seen in syphilis patients—weren't fully understood until much later. This incident really underscores the delicate balance between the potential benefits of medicine and the toxic risks associated with heavy metals.

Scientific Revolution

The 19th and 20th centuries marked a significant milestone in comprehending the harmful impacts of heavy metals. As clinical medicine, pathology, and analytical chemistry progressed, scientists began to uncover the biological and health impacts of both long-term and short-term exposure to heavy metals. This period laid the foundation for modern toxicology and environmental health sciences (Grandjean, 2010). Lead was one of the first metals recognized as a serious health risk. Medical studies linked it to brain damage, anemia, kidney problems, and developmental delays, especially in children. The sensitivity of the developing brain to even small amounts of lead raised increasing concern among pediatricians and public health experts (Needleman, 2004). Mercury became widely known in the mid-20th century with the outbreak of Minamata disease in Japan. Industrial pollution caused methylmercury to build up in seafood, leading to severe neurological damage in coastal communities. This incident marked a decisive moment in raising global awareness about environmental toxicology (Harada, 1995).

Researchers found that arsenic, a strong carcinogen, harms multiple body systems, causing skin cancer, blood vessel problems, and nerve damage. The arsenic poisoning crisis in Bangladesh, caused by contaminated groundwater, exposed millions to chronic arsenic toxicity and is considered one of the largest mass poisoning events ever (Smith et al., 2000). Cadmium toxicity was brought to light through the Itai-Itai disease in Japan during the 1940s and 50s. Industrial cadmium pollution contaminated rice fields, and long-term consumption led to bone softening and kidney damage, mostly affecting postmenopausal women (Nogawa & Kido, 1993). These important discoveries and public health crises sparked the development of environmental toxicology, regulatory toxicology, and occupational health sciences. They made it a priority to prevent exposure, assess risks, and create international safety standards. Recent scientific studies employing methods like X-ray diffraction (XRD), scanning electron microscopy (SEM), and inductively coupled plasma mass spectrometry (ICP-MS) have shown that many ancient herbal medicines contain metallic nanoparticles, oxides, and salts (Kulkarni et al., 2010). However, the safety and effectiveness of these formulations are largely influenced by factors such as particle size, oxidation state, and purity. Unfortunately, these characteristics can vary, which raises concerns about the potential toxicity of some preparations (Thatte & Rege, 2004).

It is evident that using herbal medicines from unlicensed apothecaries exposes users to considerable health risks due to potential heavy metal contamination. While metals have been utilized for centuries in the formulations of traditional medicine systems. Toxicological evidence recently has highlighted the very grave dangers of chronic exposure to some of these metals. Despite the exhaustive data documenting Indian medicinal plants, their phytocompounds, and traditional uses by databases such as the Online Structural and Analytics-Based Database for Herbs of India (OSADHI), Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT), and the Medicinal Plant Database of the Botanical Survey of India, there is no documentation of the vendors or apothecaries selling these herbal medicines—particularly the apothecaries

operating without registered licenses. This information is particularly significant when viewed through the forensic lens of traceability, accountability, and evidence-based understanding.

The aim of this study is to examine and identify heavy metals, such as lead, mercury, arsenic, and cadmium, in herbal medicines supplied by unlicensed apothecaries. This study will identify the scope of contamination, risk to public health, and forensic significance. The study aims to evaluate sophisticated and economical analytical techniques for detecting and measuring metals in purported cases of herbal medicine poisoning. This method of tracking contaminated herbal products back to their origins. However, it will assist forensic investigations and regulatory enforcement to investigate and prepare some regulations on the herbal medicine industry and mandatory toxicological screening for herbal medicines. This also helps to assess the levels of heavy metals to existing limits of safety as prescribed by regulatory bodies (e.g., WHO, USFDA, EMA, Indian Pharmacopeia).

Methodology

However, for the detection of heavy metals, I have taken the 9 herbal medicines from the local unlicensed apothecaries' vendors in Chhattisgarh, India. These medicines are not having any license or any specific registered name. Moreover, these herbal medicines are locally known for their use against diseases like rheumatic disease (vata roga), tapeworm, urine infection, anemia, asthma, joint pain, blood pressure, weakness, and gas (flatulence).

The EDX-RF measurements were collected with an EDX-8000 system, which used an SDD_C1 detector, an operating voltage of 50 kV, and an operating current of 30 μ A. We maintained consistent environmental conditions and set an incident angle of 60 degrees and a take-off angle of 45 degrees to optimize the incident and outgoing distances to maximize their chances of exciting and detecting characteristic X-ray emissions. The detector settings were changed in ranges of 0–40 keV and 0–20 keV to increase sensitivity and were adjusted to a temperature of -70 °C to -30 °C to minimize noise while maximizing resolution. We manually adjusted the video capture and independently set the x-ray irradiation coordinates, as well as the collimator diameter, to ensure we were measuring the desired surface of the sample in a consistent manner along with the analytical conditions. In vacuum conditions, the x-ray power supply was set at 15 kV and 10 μ A, which improves detection limits for lighter elements by minimizing air absorption and limits the distance of detection for lower ranges in the periodic table. In the sample chamber, we were able to set the collimator with a diameter of 10 mm and focus the X-ray beam, preventing any scattering outside the focused area of analysis and improving the repeatability of measurement and spatial resolution.

This approach uses the strengths of EDX-RF, including the fact that it can analyze the elements simultaneously and has little preparation, a rapid turnaround or throughput, and a high level of reproducibility. Selective determination of the instrument parameters, along with direct sample presentation, provides quality, accurate, and precise results, making EDX-RF a superior option for a routine elemental analysis method in various pharmaceutical, environmental, and material science applications.

To avoid any error in quantification, we analyze the control sample, like a Mylar sheet, that may be used to place the sample into it for analysis. However, analysis demonstrated the presence of multiple elements, including silicon, aluminum, sulfur, indium, copper, lanthanum, iron, erbium, manganese, chromium, iridium, zinc, and scandium, all at minor or trace levels. In total, plastic accounted for 98.689% of the weight of the sample, and silicon (0.667%) and aluminum (0.383%) were the abundantly detected constituents. Importantly, we did not detect hazardous elements such as cadmium, mercury, lead, and bromine, and we measured chromium to an acceptable hazard level of 27.0 ppm. Overall, the Mylar sheet is comprised of virtually all plastic with only minor elemental additives, contains no hazardous substances above laboratory detection limits, and is therefore considered safe for use as specified.

Results

Anemia sample

Upon conducting an ED-XRF analysis of the anemia sample, it was determined that the sample was comprised of 90.180% plastic, including notable elemental contributions from potassium, calcium, silicon, aluminum, iron, chlorine, and sulfur, at amounts of 3.090%, 2.046%, 1.852%, 0.887%, 0.843%, 0.362%, and 0.351%, respectively and that smaller amounts of other elemental contributions were present (Fig. 2). Although hazardous heavy metals such as cadmium, chromium, mercury, and lead were below reported limit (<4.0 ppm) for this instrument (Fig. 1), bromine was report at the low, safe concentration of 20.0 pm (Fig. 1 & 2). The comprehensive peak lists and X-ray emission data together with the high-quality measurement conditions documented, provide further confidence for these results. Overall, the anemia sample follows safety standards regarding hazardous substances indicating it is safe for use as intended.

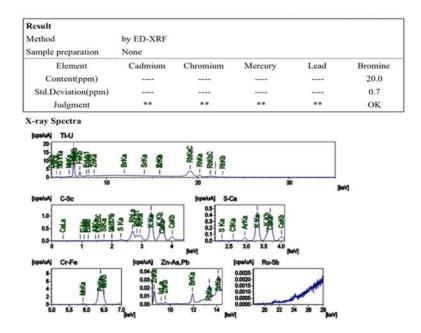


Figure 1. spectra of heavy metals present in anemia herbal medicine

Analyte	Result		[3-sigma]	ProcCal	c. Line	Int. (cps/uA
ĸ	3.090	•	[0.022]	Quan-FP	K Ka	4.6505
Ca	2.046		[0.014]	Quan-FP	CaKa	4.7741
Si	1.852	÷	[0.063]	Quan-FP	SiKa	0.2802
A1	0.887	•	[0.264]	Quan-FP	AlKa	0.0250
Fe	0.843		[0.005]	Quan-FP	FeKa	53.4536
C1	0.362	•	[0.014]	Quan-FP	ClKa	0.1223
3	0.351	÷	[0.021]	Quan-FP	S Ka	0.0455
P	0.222	•	[0.026]	Quan-FP	P Ka	0.1007
Ti	0.094		[0.003]	Quan-FP	TiKa	3.3191
Mn	0.026		[0.001]	Quan-FP	MnKa	1.0420
Cu	0.018		[0.001]	Quan-FP	CuKa	4.5708
V	0.008	•	[0.002]	Quan-FP	V Ka	0.4450
Zn	0.008	÷	[0.000]	Quan-FP	ZnKa	0.1238
Zr	0.005	•	[0.000]	Quan-FP	ZrKa	2.4546
Sr	0.003	•	[0.000]	Quan-FP	SrKa	0.2238
RЬ	0.002	•	[0.000]	Quan-FP	RbKa	0.1550
Br	0.002	•	[0.000]	Quan-FP	BrKa	0.1101
Ir	0.001	•	[0.000]	Quan-FP	IrLa	0.0073
Plastic	90.180		[]	-		

Figure 2. Quantitative result of anemia herbal medicine.

Blood Pressure sample

According to the elemental analysis of the "BP" sample (fig. 5.9) the sample is predominantly plastic (control sample, 79.686%), with elements such as potassium (5.213%), calcium (5.088%), silicon (3.154%), zinc (2.250%), aluminum (1.386%), iron (0.952%), chloride (0.844%), tin (0.659%), and sulfur (0.562%) as the principal elemental constituents. Additionally, trace amounts of titanium, manganese, copper, strontium, bromine, rubidium, chromium, zirconium, and vanadium were detected in very low concentrations. The hazardous materials analysis (fig. 3) showed no presence of cadmium, mercury, or lead, while chromium and bromine were found at 39.5 ppm (\pm 15.0 ppm) and 47.5 ppm (\pm 1.7 ppm), respectively, both within safe regulatory limits. With no highly toxic elements and very low chromium and bromine levels, it can be said that this sample meets standards for hazardous materials. Based on the thorough report of ED-XRF analysis and recorded instrument quality, you can assume that the "BP" sample is safe for its use.

Result						
Method by ED-XRF						
Sample preparation						
Element	Cadmium	Chromium	Mercury	Lead	Bromine	
Content(ppm)		39.5			47.5	
Std.Deviation(ppm)		15.0			1.7	
Judgment	**	OK	**	**	OK	

X-ray Spectra

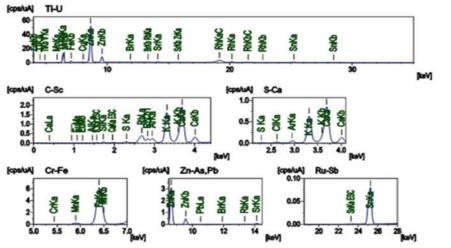


Figure 1. spectra of heavy metals present in anemia herbal medicine

Dyspnea

The elemental analysis of the "Dyspnea" sample revealed it to be composed primarily of plastic (69.786% by weight) with macronutrients distributed as potassium (18.245%), calcium (7.903%), chlorine (1.727%), silicon (0.743%), phosphorus (0.563%), iron (0.466%), and sulfur (0.435%). trace and minor elements detected included titanium, manganese, zinc, rubidium, strontium, and bromine. No hazardous elements such as cadmium, chromium, mercury or lead were detected below instrument detection limits (i.e. maximum allowed concentrations were below the lower detection limits for ED-XRF analysis (fig. 4). There was bromine at a low level and concentration of 12.1 ppm (\pm 1.3), well within acceptable and safe limits for potential exposure scenarios. The analysis was also documented with the peak lists and X-ray spectra, and all instrument parameters were recorded as well, leaving nothing lacking in terms of reliability and reproducibility analysis. Given the lack of considerable hazardous materials and only a very small amount of bromine, the results indicate that the "Dyspnea" sample meets safety standards as safe for future analysis or for the indicated application.

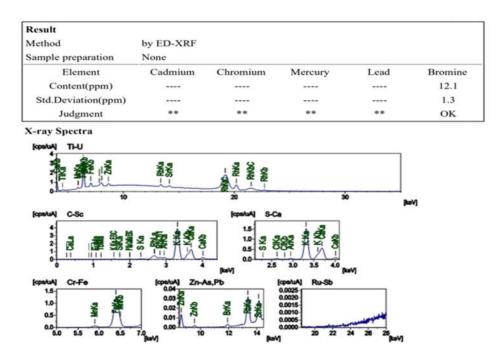


Figure 4. spectra of heavy metals present in dyspenia herbal medicine

Gass (flatulence)

Elemental analysis of the "Gass" sample resulted with the identification of its constituent materials with chloride (with the highest content of 9.949%), potassium (2.142%), and calcium

(0.845%) as major elemental additives, with significant amounts of aluminum, silicon, iron, sulfur, phosphorus, titanium copper, manganese, bromine, strontium, zinc and rubidium. Special attention was paid to hazardous elements, and ED-XRF analysis confirmed, non-detection of cadmium, chromium, mercury, and lead, as their concentrations were below the detection limits of the instrument (fig. 5). Bromine was present at 37.4 ppm (\pm 1.0), which is environmentally acceptable. The X-ray spectra and associated diagrams confirmed the identification and intensity of detected elements, and I carefully kept records all the instrument setups to ensure reproducibility. There are no identified harmful substances, and only a trace amount of bromine for the "GASS" sample and no regulatory standards for this sample means that the samples comply with environmental regulations and are deemed safe for their intended use.

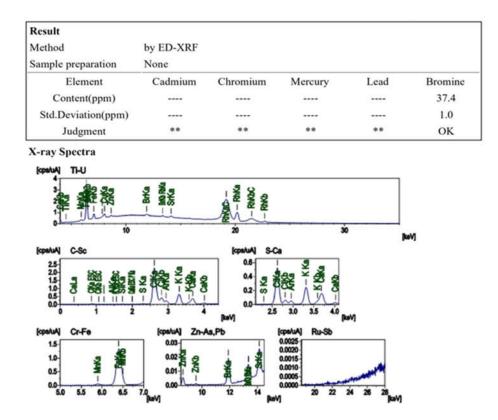


Figure 5. spectra of heavy metals present in flatulence herbal medicine

Pain Relief

The scientific analysis of the "pain Relief" sample revealed it was elements were silicon (0.280%), aluminum (0.260%), sulfur (0.096%), cesium (0.017%), copper (0.009%), chlorine (0.009%), holmium (0.009%), potassium (0.008%), calcium (0.006%), scandium (0.003%), and iron (0.001%). Small amounts of zinc and chromium were also detected but all others were below quantifiable levels. The analysis also focused on hazardous elements and found that cadmium, mercury, lead, and bromine were not detected. While chromium was detected, it was at negligible and considered a safe concentration of 2.9 ppm (\pm 1.0) (fig. 6). The complete X-ray spectra and element peak lists confirmed this and all instrument settings were documented to repeat the methods and preserve results. The "pain Relief" sample is safe for its intended application because there are no hazardous properties detected or are they below detection.

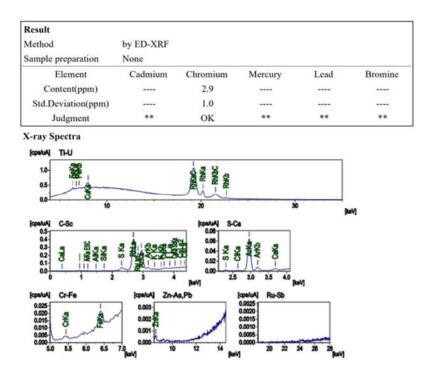


Figure 6. spectra of heavy metals present in pain relief herbal medicine

Weakness

The "Weakness" sample was made up of some key elemental concentrations: Calcium (Ca) = 12.256%, Potassium (K) = 1.630%, and Chlorine (Cl) = 0.579%. There was also recorded trace elements of silicon (Si) (0.153%) and sulfur (S) (0.067%) on a dry weight basis. What contained bromide was recorded at 7.6 ppm (SD = 1.0 ppm), and this was within acceptable

limits (fig. 7). In qualitative data, the individual peak for Calcium, Sulfur and Iron were particularly strong. Overall, the results, energy dispersive X-ray fluorescence analysis (ED-XRF), provides a good account of the elemental content of the sample's content and gives confident results to enable further analysis of the material properties and potential uses.

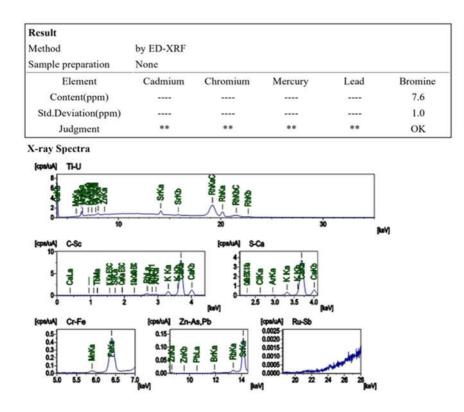


Figure 7. spectra of heavy metals present in weakness herbal medicine

Vata Roga

In the analysis of the "vataroga" sample, the major elemental additives were potassium (6.094%), calcium (5.692%), chlorine (1.301%), silicon (0.893%), Sulphur (0.645%), iron (0.490%), and phosphorus (0.197%). Other minor and trace elements (precisely titanium, manganese, copper, strontium, zinc, vanadium, rubidium, bromine, and zirconium) were less than 0.1%. Hazardous elements received special attention in the interpretation. The ED-XRF analysis showed that cadmium, chromium, mercury, and lead were present below detection limits (fig. 8). Bromine was detected at 36.8 ppm (\pm 1.2) which is acceptable. The identification of these elements and their relative intensities were supported by the X-ray spectra and peak lists documented, and instrument settings were checked in detail to determine reliability. The absence or extremely low concentrations of hazardous constituents suggest that the "vataroga" sample ultimately does meet safety standards and is suitable for application.

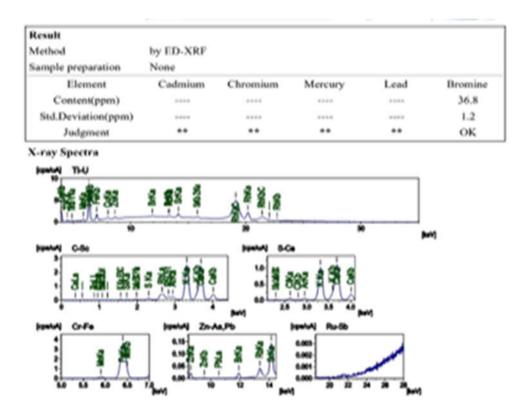


Figure 8. spectra of heavy metals present in vata roga herbal medicine

Urine Infection

The scientific analysis of the "urine infection" sample determined that the main matrix material represented potassium (4.863%), calcium (4.572%), silicon (1.190%), iron (0.582%), sulfur (0.536%), chlorine (0.506%), phosphorus (0.090%), and titanium, manganese, copper, zinc, strontium, rubidium, bromine, and iridium were found in lower concentrations or trace amounts under 0.1%. Hazardous elements were monitored closely and ED-XRF analysis showed that cadmium, chromium, mercury, and lead were not detected and were below instrument detection limits and bromine was detected at a safe level of 13.2 ppm (\pm 0.6) (fig.9). With hazardous substances absent or at an extremely low determination, the "urine infection" sample does meet the safety requirements and is considered safe for the intended use.

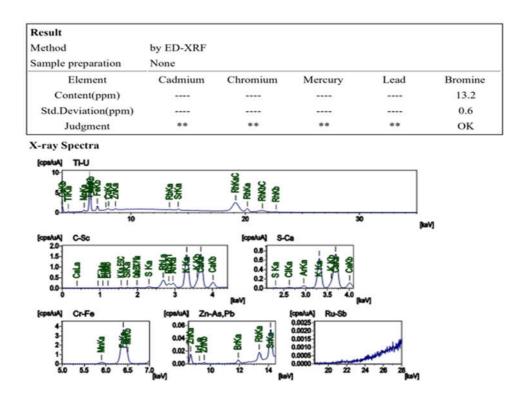


Figure 9. spectra of heavy metals present in herbal medicine for urine infection

Tapeworm

Qualitative analysis of the tapeworm sample showed dozens of elements, and six elements with reasonable abundance. The predominant elements, with concentrations were, potassium (K) 1.478%, calcium (Ca) 1.092%, sulfur (S) 0.636%, silicon (Si) 0.404%, chlorine (Cl) 0.124%, and iron (Fe) 0.099%. Trace and minor elements included titanium (Ti), strontium (Sr), copper (Cu), manganese (Mn), zinc (Zn), rubidium (Rb), bromine (Br), and zirconium (Zr), all below 0.01% of the sample amount. Hazardous elements, which we lack detection of were cadmium (Cd), chromium (Cr), mercury (Hg), and lead (Pb). These concentrations must have been below the detection limits of the instrument, while Br was present at a low and safe amount of 9.9 ppm (\pm 0.5) (fig. 10). Therefore, the tapeworm sample is free or at negligible concentration of hazardous materials and meets standards for safety for these applications.

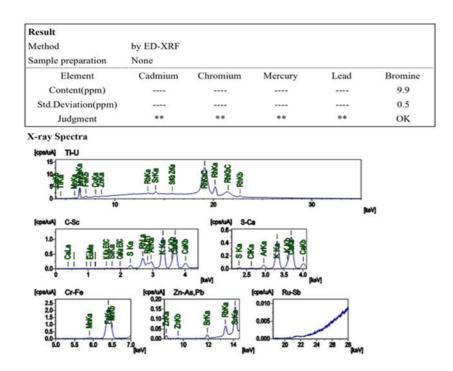


Figure 10. spectra of heavy metals present in tapeworm herbal medicine

CONCLUSION

This study systematically explored the potential of heavy metals in herbal medicines obtained from unlicensed apothecaries located in Chhattisgarh, India. Although Energy-Dispersive X-Ray Fluorescence (EDX-RF) was the main analytical method utilized1, focus was on specifically detecting toxic elements including lead (Pb), cadmium (Cd), arsenic (As) and mercury (Hg) across nine different herbal preparations used for medicinal purposes. EDX-RF is especially ideal supporting evidence guidelines due to its non-destructive technique, lack of sample preparation and rapid multi-element analysis. The EDX-RF was highly effective as previous studies reported sample batch sizes of elemental levels in herbal medicines. Successful control experiments confirmed there were no hazardous contaminants introduced via laboratory setup, testing materials (i.e. Mylar) on detection ranges that interfaced the acceptable limits the lab would use for detecting unwanted contaminants directly inferring dependable results.

Analysis of the herbal samples showed that for the specific cases reviewed (e.g., anemia and blood pressure remedies), hazardous heavy metals such as cadmium, mercury, and lead either were undetected or below the instrument detection level (<4.0 ppm), and all recorded levels were below internationally accepted levels (e.g., WHO guidelines). Other elements detected were at trace or safe levels, and no violations of regulatory limits for toxic metals were

PAGE NO: 1003

identified. Given the sample set, these findings indicate that the herbal medicines from unlicensed vendors did not contain hazardous heavy metals at levels that constituted an immediate risk to public health. Still, this study also reminds us of the public health risk associated with contamination within the unregulated world of unlicensed herbal medicine. The use of EDX-RF provides a powerful forensic method to rapidly screen and legally document the presence of heavy metal contamination with a view to supporting regulatory compliance and public health.

References

- Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. PMID: 22593937.
- Pandey, M. M., Rastogi, S., & Rawat, A. K. S. (2013). Indian Traditional Ayurvedic system of medicine and nutritional supplementation. *Evidence-based Complementary* and Alternative Medicine, 2013, 1–12. https://doi.org/10.1155/2013/376327
- Duffus, J. H. (2002). "Heavy metals"—A meaningless term? Pure and Applied Chemistry, 74(5), 793–807. <u>https://doi.org/10.1351/pac200274050793</u>
- Guzzi, G., & La Porta, C. A. M. (2008). Molecular mechanisms triggered by mercury. *Toxicology*, 244(1), 1–12. <u>https://doi.org/10.1016/j.tox.2007.11.013</u>
- 5. Clarkson, L. Magos, & G. Nordberg (Eds.), *Toxicology of metals* (pp. 355–367). Springer.
- Shen, Z. X., Chen, G. Q., Ni, J. H., Li, X. S., Xiong, S. M., Qiu, Q. Y., ... & Wang, Z. Y. (1997). Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): I. As₂O₃ exerts dose-dependent dual effects on APL cells. *Blood, 89*(9), 3345–3353. <u>https://doi.org/10.1182/blood.V89.9.3345</u>.
- Sun, H., Brocato, J., & Costa, M. (2001). Oral bismuth drugs and Helicobacter pylori: Mechanisms of action and resistance. *Metallomics*, 4(6), 589–598. <u>https://doi.org/10.1039/C2MT20025A.</u>
- Furst, D. E. (1997). Practical clinical pharmacology and drug interactions of low-dose methotrexate therapy in rheumatoid arthritis. *British Journal of Rheumatology*, 36(3), 12–15. <u>https://doi.org/10.1093/rheumatology/36.suppl_2.12</u>
- 9. Grandjean, P. (2010). Even low-dose lead exposure is hazardous. *The Lancet,* 376(9744), 855–856. <u>https://doi.org/10.1016/S0140-6736(10)61483-1</u>
- 10. Needleman, H. (2004). Lead poisoning. *Annual Review of Medicine*, *55*, 209–222. https://doi.org/10.1146/annurev.med.55.091902.103653.
- 11. Harada, M. (1995). Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution. *Critical Reviews in Toxicology*, 25(1), 1–24. <u>https://doi.org/10.3109/10408449509089885</u>

- 12. Nogawa, K., & Kido, T. (1993). Itai-itai disease and cadmium nephropathy. In T. W.
- 13. Thatte, U. M., & Rege, N. N. (2004). Phytopharmacology of metals: An Ayurvedic perspective. *Indian Journal of Pharmacology*, *36*(5), 269–275.