
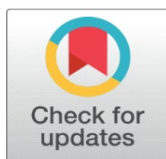
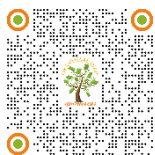


REVIEW ON COMPREHENSIVE HEAVY METALS ANALYSIS: A CRUCIAL TOOL FOR HEALTH ASSESSMENT WHEN USING HERBAL DRUGS/SUPPLEMENTS

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ABSTRACT

Heavy metals are a group of toxic elements that pose significant risks to human health when herbal substances are consumed as drugs/supplements. Due to their persistence and bioaccumulation potential, it is crucial to conduct regular heavy metals analysis to monitor their concentration, and potential sources. This review highlights the importance of heavy metals analysis in assessing & evaluating human exposure, and implementing effective mitigation strategies.

Keywords: Herbal Drugs, Supplements, Heavy Metals, Regulations, ICP-MS, ICP-OES, AAS

1. INTRODUCTION

- **Environmental Monitoring:** Heavy metals can enter the environment through various sources such as industrial discharges, agricultural practices, and natural weathering of rocks. Analyzing heavy metal concentrations in soil, water bodies, sediments, and air provides valuable insights into the extent of contamination and the potential ecological risks. Techniques such as atomic absorption spectroscopy (AAS), inductively coupled plasma-mass spectrometry (ICP-MS), and X-ray fluorescence (XRF)

spectroscopy enable precise and sensitive measurements of heavy metal concentrations.

- **Human Health Assessment:** Exposure to heavy metals can occur through multiple pathways, including ingestion, inhalation, and dermal contact. These toxic elements can accumulate in the human body, leading to various adverse health effects, including neurological disorders, kidney damage, and carcinogenesis. Analyzing heavy metal levels in biological samples, such as blood, urine, and hair, helps in evaluating individual exposure and identifying potential health risks. The drugs/supplements can be controlled throughout their manufacturing process before it reaches the consumer. Techniques like ICP-MS and graphite furnace atomic absorption spectroscopy (GFAAS) are commonly employed for accurate quantification of heavy metals in biological matrices.
- **Regulatory Compliance:** Regulatory bodies have established strict guidelines and permissible limits for heavy metal concentrations in various environmental matrices and consumer products. Heavy metals analysis plays a critical role in assessing compliance with these regulations, ensuring public safety, and preventing the release of harmful substances into the environment. Regular monitoring and analysis enable early identification of contamination sources, allowing prompt remedial actions to be taken.
- **Source Identification and Remediation:** Heavy metals can originate from diverse sources, including industrial activities, mining operations, and improper waste disposal. Analyzing the isotopic composition and speciation of heavy metals can aid in identifying their sources and tracking their migration pathways. This information is invaluable for developing targeted remediation strategies, minimizing further contamination, and restoring affected areas.
- **Emerging Trends and Technologies:** Advancements in analytical techniques and instrumentation have significantly improved the accuracy, sensitivity, and speed of heavy metals analysis. Novel approaches such as laser-induced breakdown spectroscopy (LIBS), voltammetry, and biosensors offer promising alternatives for on-site and real-time monitoring. Additionally, the integration of machine learning and data analytics enables efficient data processing and pattern recognition, facilitating a more comprehensive understanding of heavy metal contamination.

2. ANALYTICAL METHODS FOR HEAVY METALS ANALYSIS

The choice of method depends on factors such as the target elements, sample matrix, required sensitivity, and detection limits. Advances in technology continue to improve the accuracy, speed, and ease of heavy metals analysis.

- 1) **Atomic Absorption Spectroscopy (AAS):** AAS is a widely employed technique for heavy metals analysis. It measures the absorption of light by the atoms of the target element to determine its concentration. AAS is capable of detecting a wide range of heavy metals and offers good sensitivity and selectivity.
- 2) **Inductively Coupled Plasma-Mass Spectrometry (ICP-MS):** ICP-MS is a highly sensitive technique that combines inductively coupled plasma with mass spectrometry. It allows for simultaneous multi-element analysis and

can detect heavy metals at extremely low concentrations. ICP-MS is widely used for environmental and biological sample analysis.

- 3) X-ray Fluorescence (XRF) Spectroscopy:** When an element is activated by an X-ray source, XRF spectroscopy analyzes the distinctive X-ray emissions from the element. It offers quick and non-destructive measurement of the levels of heavy metals in solid samples, such as soils, sediments, and rocks.
- 4) Graphite Furnace Atomic Absorption Spectroscopy (GFAAS):** This AAS variant improves sensitivity for trace metal analysis. The sample is atomized in a graphite furnace, which improves the detection limits for heavy metals. For the analysis of heavy metals in biological samples, GFAAS is frequently utilized.
- 5) Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES):** ICP-OES detects the emission of light from excited atoms using an inductively coupled plasma as the ionization source. It allows for concurrent multi-element analysis and provides accurate detection. Regulatory limits for heavy metals in pharmaceutical products vary depending on the country and specific regulations.

Here are some examples of regulatory limits for heavy metals in pharmaceutical products as per the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph. Eur.):

United States Pharmacopeia (USP):

- 1) Arsenic (As): Not more than 3 parts per million (ppm).
- 2) Cadmium (Cd): Not more than 5 ppm.
- 3) Lead (Pb): Not more than 10 ppm.
- 4) Mercury (Hg): Not more than 1 ppm.

European Pharmacopoeia (Ph. Eur.):

- 1) Arsenic (As): Not more than 3 ppm.
- 2) Cadmium (Cd): Not more than 5 ppm.
- 3) Lead (Pb): Not more than 5 ppm.
- 4) Mercury (Hg): Not more than 1 ppm.

It's important to note that these are general limits, and specific pharmaceutical products or dosage forms may have additional or modified limits. Additionally, different regulatory bodies and regions may have their own specific guidelines and limits for heavy metals in pharmaceutical products. [Boominathan \(2013\)](#)

These limits are established to ensure the safety and quality of pharmaceutical products, as heavy metals can have harmful effects on human health, especially when consumed over an extended period or in high concentrations. Compliance with these limits is essential to minimize the risk of heavy metal toxicity and ensure the safety of pharmaceutical products for patients. [Chan et al \(2020\)](#)

Herbal drugs, which are derived from plants and used for therapeutic purposes, are gaining popularity due to their perceived natural and holistic properties. However, it is crucial to ensure the quality and safety of herbal drugs, including assessing the presence of heavy metals. Here's some information on the importance of heavy metals analysis in herbal drugs:

- 1) Contamination Sources:** Herbal drugs can be susceptible to heavy metal contamination due to several factors. Plants may absorb heavy metals

present in the soil or water, especially if they are grown in polluted environments or near industrial areas. Contamination can also occur during the processing, packaging, or storage of herbal drugs, where they may come into contact with materials containing heavy metals. Consequently, heavy metal analysis is necessary to identify potential contamination sources and mitigate risks.

- 2) **Potential Health Risks:** Heavy metals, even in trace amounts, can have detrimental effects on human health. Prolonged exposure to heavy metals like lead, mercury, cadmium, and arsenic can cause various health issues, including organ damage, neurological disorders, developmental abnormalities, and even carcinogenesis. Herbal drugs are often consumed for therapeutic purposes, and if they contain high levels of heavy metals, they can pose a significant risk to consumers. Conducting heavy metals analysis helps in identifying potential health risks associated with herbal drugs and ensuring consumer safety.
- 3) **Regulatory Compliance:** Regulatory authorities have established guidelines and maximum permissible limits for heavy metals in herbal drugs to protect public health. These limits vary depending on the country and specific regulations. Analyzing herbal drugs for heavy metals is essential to comply with these regulations and ensure that the products meet the required safety standards. Regulatory compliance also contributes to building consumer trust and maintaining the integrity of the herbal drug industry.
- 4) **Quality Control:** Heavy metals analysis is an integral part of quality control for herbal drugs. It helps to assess the overall quality and purity of herbal products. By analyzing heavy metal content, manufacturers can identify any potential contamination issues and take corrective actions to ensure that their products meet the defined quality standards. Quality control measures, including heavy metals analysis, contribute to consistent product quality, efficacy, and safety.
- 5) **Consumer Safety and Confidence:** The presence of heavy metals in herbal drugs can undermine consumer safety and confidence in these products. Conducting rigorous heavy metals analysis reassures consumers that the herbal drugs they consume are safe and free from harmful contaminants. It also demonstrates the commitment of manufacturers and regulatory authorities towards ensuring the quality and safety of herbal drugs.

The presence of heavy metals in herbal drugs can pose several risks to human health. Here are some of the key risks associated with heavy metals in herbal drugs:

- 1) **Toxicity and Health Effects:** Even at low concentrations, heavy metals including lead, mercury, cadmium, and arsenic are known to be harmful to human health. Using herbal medications that contain these metals over an extended period of time can have a number of negative health impacts. They have the potential to build up in tissues and organs, harming the neurological system, kidneys, the liver, and other crucial systems. Mild discomfort to serious ailments, such as neurological disorders, kidney damage, respiratory problems, and even cancer, can be the outcome of heavy metal exposure.
- 2) **Cumulative Effects:** The potential for bioaccumulation of heavy metals is one of the major issues with these substances. Heavy metals in herbal remedies can build up in the body if they are frequently used over a long

period of time. The progressive buildup of heavy metals in tissues and organs is known as bioaccumulation, and it can increase toxicity and pose long-term health hazards. Consistently consuming even modest amounts of heavy metals can have cumulative effects that may not be immediately noticeable but may grow more serious over time. Synergistic Effects: Heavy metals can interact with each other and other chemical compounds present in herbal drugs, leading to synergistic effects. Synergism occurs when the combined effects of two or more substances are greater than the sum of their individual effects. In the case of heavy metals, the presence of multiple toxic metals in herbal drugs can amplify their toxicity, leading to heightened health risks. This makes it crucial to consider the overall heavy metal content in herbal drugs and assess the potential for synergistic effects.

- 3) **Vulnerable Populations:** Some groups are especially vulnerable to the harmful effects of heavy metals, including pregnant women, young children, newborns, and those with weakened immune systems or pre-existing medical disorders. They may be more susceptible to the hazardous consequences because their bodies may not be able to remove heavy metals from the body as well. Heavy metal contamination in herbal medications can increase the hazards for these people, raising the possibility of developmental problems, cognitive problems, or other health issue.
- 4) **Lack of Standardization:** Because herbal medicines are frequently derived from many geographic locations and employ various cultivation and production techniques, their quality and safety might vary greatly. The likelihood of heavy metal contamination in herbal medications is increased by the absence of defined guidelines and quality control procedures. Consumers may unknowingly eat products with high quantities of heavy metals without sufficient examination and control, endangering their health. To mitigate these risks, it is crucial to implement rigorous quality control measures, including regular heavy metals analysis, during the manufacturing and distribution of herbal drugs. This helps ensure that herbal drugs meet the required safety standards and minimize the potential health hazards associated with heavy metal contamination.

Present trends in herbal analysis for heavy metals involve the adoption of advanced techniques and methodologies to enhance the accuracy, sensitivity, and efficiency of heavy metal detection in herbal drugs. Here are some notable trends:

- 1) **Advanced Instrumentation:** Analytical instrumentation has significantly improved, enabling more accurate and sensitive heavy metal analysis in herbal medicines. The accessibility and detection limits of methods like atomic absorption spectrometry (AAS), inductively coupled plasma-mass spectrometry (ICP-MS), and inductively coupled plasma-optical emission spectroscopy (ICP-OES) have improved. These tools assist discover tiny quantities of heavy metals and provide accurate quantitative assessments.
- 2) Heavy metal analysis of herbal medications is beginning to place more emphasis on speciation analysis. It entails identifying the heavy metal species or chemical forms that are present in the herbal matrix. Different heavy metal species could have varied levels of toxicity and bioavailability. It is possible to accurately analyze the potential health concerns posed by these species and implement effective risk management techniques by identifying and measuring them.
- 3) **Sample Preparation Methods:** For heavy metal analysis to produce accurate and representative results, effective sample preparation methods

are crucial. In order to increase extraction efficiency, decrease matrix interference, and improve the recovery of heavy metals from herbal medications, novel sample preparation techniques have been developed. These techniques include microwave-assisted digestion, ultrasound-assisted extraction, and solid-phase microextraction. These methods streamline the analytical procedure, reduce sample contamination, and save time.

- 4) **Quality Assurance and Standardization:** Strong quality assurance standards and standardization in herbal analysis for heavy metals are being implemented, and both are gaining traction. This includes participating in proficiency testing programs, using certified reference materials, and developing and validating analytical methods. It is easier to compare and assess the quality of herbal drugs when heavy metal analysis results from various laboratories are standardized to assure uniformity, precision, and dependability.
- 5) **Nanotechnology advancements:** Methods based on nanotechnology are being investigated for heavy metal analysis in herbal medicines. The sensitivity and selectivity of detection techniques are improved by the use of nanomaterials like nanoparticles and nanocomposites. Heavy metals can be selectively bound with by functionalized nanomaterials, which helps with quantification and detection. For quick and on-site analysis of heavy metals in herbal medicines, nano sensors and nanoprobos are also being developed.
- 6) **Chemometrics and Data Analysis:** Heavy metal analysis of herbal medications is increasingly using chemometrics, including multivariate analysis and data mining approaches. These techniques allow for efficient data processing, pattern detection, and outlier identification. Chemometric methods make it easier to find intricate connections between heavy metal concentrations, sample properties, and suspected sources of contamination. This aids in figuring out what influences the amount of heavy metal in herbal medications and helps to direct quality control tactics.

Researchers and regulators can increase the precision, effectiveness, and dependability of heavy metal detection in herbal medications by implementing these current developments in herbal analysis for heavy metals. As a result, consumer safety is improved, product quality is ensured, and the responsible use of herbal medicines is supported.

Speciation analysis in heavy metal analysis involves identifying and quantifying different chemical forms or species of a particular heavy metal. Here are some examples of speciation analysis for commonly studied heavy metals:

- 1) **Arsenic (As):** Speciation analysis of arsenic is crucial due to the varying toxicities of its different forms. Common arsenic species analyzed in herbal drugs include:
 - **Arsenate (As(V)):** This is the oxidized form of arsenic and is generally considered less toxic than other forms.
 - **Arsenite (As(III)):** This is the reduced form of arsenic and is considered more toxic and more readily absorbed by the body.
 - **Organic arsenic species:** In addition to its inorganic forms, arsenic can also exist in organic forms like arsenobetaine and arsenocholine, which are typically regarded as less dangerous than the former.

- 2) **Mercury (Hg):** Because the toxicity of mercury changes depending on its form, speciation study is significant. Typical mercury species found in traditional medicines include:
- **Inorganic mercury (Hg(II)):** This is mercury that has undergone oxidation, making it more dangerous than other forms.
 - Methylmercury is an extremely hazardous organic form of mercury that can be produced by microbial activities in the environment.
- 3) **Selenium (Se):** Because the different forms of selenium can have variable bioavailability and physiological consequences, speciation analysis of selenium is important. Typical selenium species found in plant medicines include:
- **Selenite (Se(IV)),** an oxidized form of selenium, is typically regarded as being less bioavailable.
 - **Selenate (Se(VI)):** A more accessible form of selenium, this compound is an oxidized form known as selenium.
 - Selenomethionine is a naturally occurring organic form of selenium that is less harmful than inorganic forms and is frequently found in plant-based materials.

These illustrations show how speciation analysis is crucial for comprehending the toxicological significance and bioavailability of various heavy metal forms in herbal medicines. Researchers can create more thorough understandings of heavy metal behavior and effective risk management measures by identifying and quantifying particular species. [Kašpárková et al. \(2017\)](#)

Many official texts concern heavy metals in herbal drugs:

USP: United States Pharmacopeia Through its General Chapters, the USP offers recommendations for heavy metal limitations in herbal medicines. Several pertinent chapters are:

Basic Chapter 231 Heavy Metals: This chapter outlines criteria for the maximum allowable levels of heavy metals in pharmaceutical preparations, including herbal medicines, such as arsenic, cadmium, lead, and mercury. The upper and lower limits are given in parts per million (ppm) or micrograms per gram (g/g) of the active ingredient in the herbal medication.

The European Pharmacopoeia (Ph. Eur.): Through its monographs, the European Pharmacopoeia specifies upper limits for heavy metals in herbal medicines. Several pertinent monographs are:

The "Heavy Metals" monograph offers broad principles and restrictions for the presence of heavy metals in herbal medicines. The upper and lower limits are given in parts per million (ppm) or micrograms per gram (g/g) of the active ingredient in the herbal medication.

The maximum allowed levels of heavy metals are listed in Monograph 01/2011:2040 on "Herbal Drugs and Herbal Drug Preparations" for particular herbal remedies and their preparations. Based on the probable toxicity of the heavy metals and the intended use of the herbal drug, it sets unique limitations for these metals, such as arsenic, cadmium, lead, and mercury. [Zhang et al. \(2015\)](#)

The purity and security of these goods are ensured by the pharmacopoeial details, which establish precise rules and limits for heavy metals in herbal medicines. For the most recent and detailed information regarding heavy metal limits in herbal remedies, it is crucial to check the relevant pharmacopoeias.

The maintenance of public safety depends on regulatory compliance, and heavy metals analysis assures adherence to the allowable limits set by regulatory agencies. Regular analysis and monitoring aid in locating the origins of contamination, permit quick corrective action, and protect the environment and human health.

Overall, heavy metals analysis is essential for regulatory compliance, quality assurance, consumer safety, and assessments of the environment and human health in the contexts of both conventional and herbal medicines. Improvements in analytical methods and the use of speciation analysis lead to better heavy metal monitoring, mitigation, and responsible usage, safeguarding the environment and human health. [Zhang et al. \(2018\)](#)

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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