The Safety Evaluation of Toxic Elements in Medicinal Plants: A Systematic Review

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A R T I C L E   I N F O

A B S T R A C T

Background: Despite the widespread use of medicinal plants in the food basket of many families, using healthy herbs with safe nutritional standards is one of the necessities.

Methods: In this review, the required data and related keywords (such as "latest methods of measuring and analyzing toxic elements in medicinal plants and foods, etc.) were collected from databases such as Google Scholar, ScienceDirect, Scopus, SID, PubMed, Elsevier, Springer, etc. Then we focused on accurate works related to toxic elements and medicinal plants.

Results: First, we introduced the issue of toxic elements in foods, especially medicinal plants, with a new perspective. Then, some tools related to measuring toxic elements in herbs and some recent research were investigated. Further, an attempt was made to show the importance of the issue. Finally, the effects of toxic elements on various parts of the human body were discussed.

Conclusion: An overview of using safe medicinal plants was presented while providing effective solutions such as identifying contaminated areas, using soil stabilizers, and preventing the leaching of toxic elements into farmland.

1. Introduction

All human societies are encouraged to use herbal drugs to treat disorders. Medicinal plants generally have no serious adverse side effects [1]. Furthermore, herbs are consumed in all parts of the world, especially some of which are rich raw material sources for medical applications. On the other hand, heavy metals are a group of mineral pollutants that have occupied a considerable part of environmental pollution [2]. Herbs mostly absorb toxic elements from water, soil, or the atmosphere. The capability of different species of herbs to absorb the toxic elements geochemically varies, which relates to special features depending on soil varieties [3]. Plants play a significant role in preparing crucial features in bio-systems. It is impossible to live a second without plants [4]. Using herbs for various purposes like remedies for disorders dates back to ancient lifestyles. Since humans reached an effective way against their health troubles, using different herbs was the first and latest choice for cure [5]. It could be said that more than a tenth of the herb species (over 5000) are being consumed in medical and non-medical applications. However, the distribution and application of

herbs worldwide are not transparent [6], and herbs are extensively collected from natural regions. Increasingly, the demand for nature has added by 8%-15% per year in European countries, North American regions, and Asian countries in coming years and, regarding drugs and the popularity of herbal medicines, some research on safety and positive effects are being restricted by several reasons [7]. After globalization, it is important for medicines and other related organizations to obtain information about the safety of herbs [8].

Various sources have been known for toxic elements in the environmental media. These sources can be natural or anthropogenic. Toxic elements are mainly introduced into groundwater by agricultural and industrial applications, landfilling, mining, and transportation. Although the geological background of toxic elements in herbs is low, soil, water, air, and plants are polluted by metals with human activities and even affect human health throughout the food chain [9]. Contamination with toxic metals belongs to phytotherapy research that relates to various sources, for instance, polluted irrigation water, industrial air pollution, contaminated soils, etc. [10]. Despite this, no study detects toxic metals in herbs by analytical methodology and assesses phytotherapeutic features [11]. Toxic metals cause severe disorders that need to be guided. "Heavy metals," "Toxic materials," and "Toxic elements" are phrases applied for a bunch of elements such as lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), iron (Fe), copper (Cu), Chromium (Cr), Zinc (Zn), etc. that are claimed to be reasons of toxicity in different shapes and at various concentrations [12].

This review provided a new perspective for better consumption and addressed this issue by introducing the subject of toxic elements. Moreover, some analytical and experimental tools were suggested for evaluating and measuring toxic elements in medicinal plants. Finally, the effects of toxic elements on the body were shown, and a positive approach was taken to the health of medicinal plants in this field and future decisions.

2. Materials and Methods

This research was conducted by collecting all the qualitative and quantitative research and review studies as well as some other related information in recent years, especially in the last decade in the world. Nearly 93 studies were selected and reviewed after the pilot study to identify the eligible ones. In this paper, based on the subject that can be cited and trusted from a database such as Google Scholar, ScienceDirect, Scopus, MagIran, SID, PubMed, Elsevier, Springer, etc., as well as keywords or phrases such as "latest methods of measuring and analyzing toxic elements in medicinal plants and foods, medicinal plants and toxic elements, the effects of toxic elements on body parts and other related expressions". First, a comprehensive collection of measurement methods was compared. Then we focused on research related to toxic elements, medicinal plants, and some related reports of their results. Finally, accurate

information on the negative effects of some toxic elements on human body parts was gathered.

3. Results and Discussion

3.1. Some mentioned analytical & experimental tools for toxic elements measurement

Toxic element sources in different places relate to their role in various substances, especially in medicinal plants; therefore, it is crucial to adopt methods that can effectively and accurately detect the number of toxic elements in medicinal plants [13]. Increasingly, some remarked analytical ways used to detect toxic elements in herbs and their roles have been distinguished and summarized in detail. Detecting Pb concentration in herbs by pre-concentration flow injection analysis-Flame Atomic Absorption Spectrometry (FAAS) was developed in various materials such as herbs and vegetables that could prove the standard use [14]. Here are some analytical methods to detect and measure the toxic elements in some foods.

3.1.1. NexSAR HPLC-ICP-MS Speciation Analysis

In this method, some information like healthy liquids such as apple juice or some related medicinal plants is gathered. This work demonstrates a reversed-phase ion-pairing method to completely separate and accurately quantify the main and most toxicologically relevant arsenic species in commercially available materials like herbal drinks and juice. The NexSAR HPLC is a next-generation Speciation Analysis Ready (SAR) system engineered with a completely inert and metal-free fluid path, enabling laboratories to meet low chromatographic background requirements on the most challenging speciation applications. Plus, it is fully customizable, with the flexibility to select only the parts like herbs needed for the application(s) [15].

3.1.2. Analysis of Pb and Cd in the sample by application of Graphite Furnace Atomic Absorption (GFAA)

This method is declared as an official technique for measuring toxic elements like Pb and Cd and is graphite furnace atomic absorption spectroscopy (GFAAS, GB/T 5009. 12-2017, GB/T 5009-2017. 15 and EN 14083:2003). In this method, measurable amounts are prepared using different methods, including microwave, hot block, dry ashing, and hot plate digestions. It must be said that all expressed digestions are usually hard and consume long hours (2-4 h or even longer). Increasingly, the techniques of each one need to oxidize reagents [16].

3.1.3. The NexION 300/350 ICP-MS Analysis for some foods

The ability of various measurements and huge cases of inductively coupled plasma mass spectrometry (ICP-MS) is normally convenient for analyzing food materials. It would be known as a kind of demonstrative applicant with the ability of PerkinElmer's NexION 300/350X ICP-MS to

positively measure macro-level nutritional elements in the equal evaluation run as lower-level elements without having to dilute the samples [17].

3.1.4. The FAST Flame Atomic Absorption Analysis (FAA)

In this method, some major toxic elements (Cu, Fe, and Mn) are measured in some liquid samples with the capability of the PinAAcle 900 flame AA spectrometer to detect Cu, Fe, and Mn that the standard spray chamber used a high-power nebulizer. Demonstrative calibration is prepared by applying a single intermediate standard made in 2% HNO_3 /deionized water, diluted in line with the PerkinElmer FAST Flame. Operator errors would be decreased by applying the FAST Flame 2 sample automation accessory when diluting and meeting calibration standards, boosting sample throughput [18].

3.1.5. Analysis Method of GB 5009.11-2014 to Safety

HPLC-ICP-MS is the suitable analytical technique with five samples of various items using a gradient anion-exchange method per GB 5009.11. The analysis is carried out using PerkinElmer NexSAR™ HPLC-ICP-MS speciation solution, consisting of a NexSAR inert HPLC coupled to a NexION® ICP-MS. It is also performed for various toxic elements, especially in confirmation of daily foods like rice safety standards or herbs [19]. Different methods included: I) X-ray diffraction (XRD), which is often famous for both amount and qualification features of crystalline phases in different samples, and specific XRD are used for better analysis, II) Scanning electron microscopy (SEM), the range of useful signals which generated by electrons is used [20]. III) Energy dispersive X-ray analysis (EDX) is an analytical technique used for the elemental analysis or chemical characterization of a sample. It relies on the interaction of some source of X-ray excitation and a sample [21], VI) X-ray photoelectron spectroscopy (XPS) is a surface-sensitive quantitative spectroscopic technique based on the photoelectric effect that can identify the elements that exist within a material (elemental composition) or are covering its surface, as well as their chemical state [22], V) infrared spectroscopy (IR), is measuring the interaction of infrared radiation by absorption, emission, or reflection. It is used to study and identify chemical substances or functional groups in solid, liquid, or gaseous forms [23], VI); thermogravimetry (TG) is a method of thermal analysis in which the mass of a sample is measured over time as the temperature changes. It provides information about physical phenomena, such as phase transitions, absorption, adsorption, and desorption, as well as chemical phenomena, including chemisorptions, thermal decomposition, and solid-gas reactions (e.g., oxidation or reduction) [24]. In addition, the surface area is measured to compare the relationships between some measured elements. The collected conclusions were drawn to properly coordinate the analytical methods and tools with the following goals in samples.

3.2. Assessment of toxic elements in herbs

The necessity of medicinal plants is growing because of their lower negative side effects and popularity among different groups. Increasingly, it is known as one of its nature in applications, purity, and qualification of medicinal plants according to its security and application. When the concentration of toxic elements exceeds bio-organisms, it could cause severe impacts on different items of life and bio-ecosystems. The United States and other developed countries have increasingly shown growing toxic metals in various media [25]. The concentration of toxic elements, namely Pb, Cd, Cu, and Zn was estimated in the market as well as standard samples of pointed herbal drugs of India. These plants included *Alpinia galanga, Artemesia parviflora, Butea monosperrma, Coleus forskohlii, Curcuma amada, Euphorbia prostrate, Leucas aspera, Malaxis accuminata*, and *Pueraria tuberose*.The amount of Pb and Cd was beyond the WHO permissible limits in most samples [26]. Bio-concentration of toxic metals in five local species of herbs and five mangrove species in India was studied. The average amount of Pb in mangrove samples was 1.75 times that of Inland plants, and mercury was 11.31 times that of Inland plants [27]. Detecting toxic metals like Cd, Pb, Zn, Nickel (Ni), and Molybdenum (Mo) in twenty-seven cases of herbs by Flame AAS and Pulse polarography and stripping voltammetry was done. The samples were collected from different regions in Bielsko Biata [28]. Analytical methods of medicinal plant and extracting them by the disposable electrochemical sensor was followed, and the efficacy of this method for the monitoring of toxic elements assessment in herbal medicines was carried out. The amount of Cd and Pb were assessed [29]. Measuring Cd, Pb, and Zn concentration by 2 digestion protocols named microwave-assisted total digestion and an *Aqua regia* extraction procedure based on the international organization for standardization 11466 method (specific method for extracting with aqua regia of trace elements from soils and similar materialls containing less than about 20 % (m/m) organic carbon) were validated and declared a fast, low-paid, and automated digestion way for showing toxic element concentration in natural outside samples [30]. Some toxic elements included Fe, Zn. Pb, Cd, and Se (Selenium) amounts in herbs by X-Ray Fluorescence analysis and Galvanostatic stripping chronopotentiometric analysis in five species *Melissa officinalis L, Agrimonia eupatoria L, Hypericum perforatum L, Salvia officinalis L.,* and *Achillea millefolium L* were detected [31]. Furthur, As amounts in different parts of Typha latifolia using chromatography and mass spectrometry was detected. Those results recommended that As and Fe elements are accumulated in the skin part of T. latifolia, which was proven by previous research [32]. High toxic metals concentrations in ten Chinese crude herbs marketed in Italy included *Radix ginseng, Radix astragali, Rhizoma coptidis, Rhizoma atractylodis, Radix bupleuri, Radix rehmanniae, Radix alba, Pericarpium citri, Radix polygalae,* and *Radix salviae* was analyzed. The toxic metal amount was around the limit standard for *Rhizoma coptidis* [33]. Measuring the

concentration of toxic elements in local Chinese drugs produced by various factories or providers using ICP-MS (Inductively coupled plasma mass spectrometry) was done, and the capabilities of various sample digestion ways were compared. The amount of several elements like Pb and Cd varied extensively with various providers, recommending that their origination is basically from external sources. Reviewing toxic elements and undeclared medicines in some Asian countries showed that some Asian herbal drugs have toxic elements, or undeclared prescription medicines might be due to the mentioned health issue. The number of toxic elements, mainly Fe, Mn, Zn, and Cu in herbal substances, are not assessed legally. Following these ways and the WHO guidelines, the permissible Pb level in herbs is 10 mg kg^{-1} d.w. Based on the Polish Pharmacopoeia, the regulations are more limited, and they identify the limit values of Pb concentrations below 5.0 mg kg^{-1} d.w. in medicinal plants [34]. The plant species of the family of Lamiaceae, described by *T. serpyllum*, include the species known as toxic metal hyperaccumulators [35], which, in the aboveground parts, can accumulate 10 to 500 times more metal than the same species growing in the uncontaminated stands. The group also includes the plants for which the ratio of metal content in the aboveground parts to the content in roots and soil is higher than 1 [36]. The number of toxic elements varied from plant to plant. Pb was the highest in *Calotropis procera* root in heavy traffic area locations [37]. Some toxic elements in various species of Berberis and its bazaar samples were evaluated, in which 10 cases were procured from various places in India. It was discovered that market samples were more polluted than actual samples [38]. Heavy metal detection in *Hypericum perforatum* pharmaceutical derivatives by atomic absorption and emission spectrometry was performed in which measurable amounts of Calcium (Ca), Cu, Potassium (K), Lithium (Li), Magnesium (Mg), Manganese (Mn), Sodium (Na), Ni and Zn were detected. This way also allows complete demonstration of mineral sizes in pharmaceutical quality control of medicinal plants [39]. Managing the concentration of the toxic element in herbs and vegetables introduces the main agent for assessing the qualification. It is clear that these herbs originated from various places and have had huge varieties in the absorption items, and doses of toxic elements in tissues of herbs could be distinguished [40]. The raised amounts of toxic metals in some herbs decrease their potential to gather special elements. Meanwhile, increased absorption could be discovered in cultured places in mountain regions because of special features of pointed soils like acidity and/ or the existence of metal-bearing minerals that claimed the mobility of toxic elements in soil and plants [41]. Based on some systems, some medicines include the term of metal in its mixed oxides. Data around Pb encephalopathy caused by herbal medicines was provided. It showed big concerns for health care providers around this issue that the potential of herbs can extend the concentration of these hidden tiny enemies [42].

3.3. Health-related issues and toxic elements

The concentration of toxic metals in the long period of application, as well as direct exposure, could cause several serious issues for various body organs (Fig1). As mentioned in different literatures, mostly their negative effects appear by the change of concentrations, immunological features, abilities for detoxification, etc. [43].
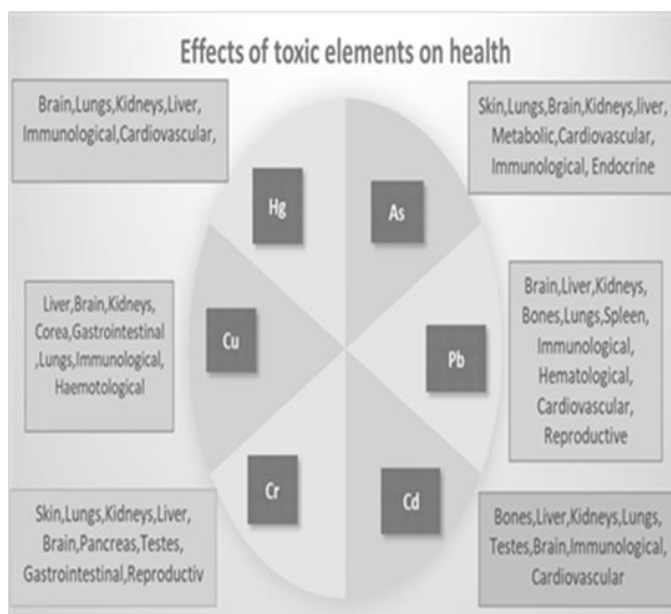

Figure 1: Some important effects of toxic elements in body.

The concentration of toxic elements can have a huge negative effect on the human body. We must declare that some essential elements also are known as an actor in the body system. As it is known a toxic factor that surprisingly causes a lack of vitamin A in our body, followed by heart issues and night blindness [44]. It was found that acute toxicity appears with serious symptoms within just 30 min of ingestion and leads to some other symptoms mouth dryness, difficulty in swallowing, nerve pain, vomiting, nausea, stomach pain, and diarrhea. Additionally, exposure leads to some disorders like skin pigmentation, skin cancer, hyperkeratosis of the feet and hands, and liver failure [45]– exposure to Cd remarkably induced renal damage, cancer, and pulmonary fibrosis. Cd is categorized as a carcinogenic agent. It is investigated that a serious element in low doses cause of its role compared to other essential elements such as Zn, Ca, Cu, and Fe [46]. The variety of impacts of Al (aluminum), Pb, Cr, etc., contains neurological disease, Alzheimer's, cardiovascular, and brain disorders [47]. Some researchers also have demonstrated toxic elements in herbs,

which were measured by various methods. Their important accessible data leads us to reach better choices; also, we could take a good note of the role of the toxic elements in various foods, especially medicinal plants. As it is evident, food security is one of the significant factors in every society. The status of medicinal plants as a valuable factor can guarantee people's health since they are used to treat various diseases and can increase the health of their daily consumption, especially in the case of toxic elements and in preventing many problems. In this review paper, we first tried to examine the common methods of measuring toxic elements. HPLC-ICP-MS Speciation Analysis was first used to measure toxic elements, especially in apple juice. The well-known and reliable method called The NexION 300/350 ICP-MS Analysis was used to measure toxic macro elements, which showed good results. Methods such as The FAST Flame Atomic Absorption Analysis (FAA) are more cost-efficient and are used based on the type of food and its ingredients. However, the accuracy of the recently used devices increases the reliability of the results. Although, in other methods coupled to a NexION® ICP-MS via NexSAR inert HPLC, the accuracy of the measurements can also be increased. On the other hand, an attempt was made to introduce using the sample varieties with accurate results [48]. Furthermore, we examined the results of articles related to the measurement of toxic elements and medicinal plants, and it was concluded that according to different regions (severity of contamination, number of samples, time and type of sampling regions, etc.), the variety of methods and measuring devices can have different results, especially in recent years. ICP-MS device that is used for various samples and measuring a range of toxic elements such as Pb, Cd, Cr, Fe, and As can be of higher importance due to diseases associated with their accumulation in the body [49]. For example, Pb, a dangerous toxic metal, leads to disorders in hemoglobin release and porphyrin metabolism by bounding to the enzymes. Pb accumulation in the human body causes brain injuries and mental retardation. Other findings showed the effects of various toxic elements on the human body, such as the liver, lungs, kidneys, and vascular system. Their hematological and immunological effects can be the most significant [50].

4. Conclusion

It is reasonable to conclude that a path is needed to improve nutrients and supplements and raise our awareness. Medicinal plants are widely used in food; therefore, they must follow the world's suitable standards. This review proposed a new approach to introduce toxic metals in herbs. Furthermore, by briefly explaining the measurement tools and some recent related research in this area, a new overview of the healthy use of herbs in our daily food basket, especially in medicinal plants, was provided. Finally, we outlined some effective strategies such as identifying contaminated areas, using soil stabilizers, preventing leaching, less use of chemical fertilizers and pesticides in

agriculture, using more resistant and more productive cultivars, raising the knowledge of medicinal plants and the potential of each to absorb toxic elements, using safe agricultural water away from municipal wastewater, and raising public awareness of using healthier medicinal plants that could make a good overview for the future.

Authors' Contributions

Ebrahim Alinia-Ahandani: Study design; Project management; collecting data; Manuscript preparation; Revising the manuscript. Habibollah Nazem, Ali Akbar Malekirad, Mohammad Fazilati: Collecting data; Revising manuscript.

Conflict of interest

The Authors declare that there is no conflict of interest.

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