Hindawi
Journal of Chemistry
Volume 2022, Article ID 2610852, 7 pages
https://doi.org/10.1155/2022/2610852

Research Article

An Insight into Pathway and Health Risk Assessment of Toxic Metals in Herbal Medicine

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Received 2 September 2021; Accepted 3 March 2022; Published 23 March 2022

Academic Editor: Andrea Mastinu

Introduction. Along with and in competition with orthodox medicines, herbal medicines have converted into a popular form of cure. While cumulative investigation reports on adverse effects by herbal drug uptake are few, systematic review along with deep insight into other relevant topics (carcinogenic and noncarcinogenic risk assessment, mechanism of toxicity, and entering toxic metal from source to herbal drug) is sporadic. *Methods*. Therefore, existing research and their published outputs pointing safety assessment of herbal medicines in terms of toxic metals have been reviewed systematically and information synthesized thematically while suggesting mechanism of toxicity, consequence of prolong exposure, and pathway of toxic metal from source to herbal drugs. *Result and Discussion*. Our study suggests that most of the herbal medicines were unsafe to consume although claimed harmless. Possible pathways regarding migration of toxic metals into herbal medicine are discussed. *Conclusion*. There should have appropriate screening from herb collection, and manufacturing to selling of finished herbal medicine by authority concerned is backed.

1. Introduction

Our exhaustive and unhealthy lifestyle prompts to diseases like diabetes, chronic alcoholism, high blood pressure, neurologic diseases, and erectile dysfunction ([1, 2], British Journal of Nursing, 2005; Korenman, 2004; [3–5]). Dissatisfaction with allopathic drugs is due to high cost and reported side effects (WHO 2001, Kamatenesi-Mugisha et al., 2005, [1, 6]), taking some patients on searching for some plant-based remedies, and thus, acceptance of herbal medicine is on rise in developing world (Zamir et al., 2019).

Unlike allopathic drugs, herbal drugs are not going through screening procedure, and monitoring on drug quality and safety is often lax. However, metal toxicity in herbal medicine is not new [7–12], and in recent years, focus has been given on the toxicity of metals on human health where plants are considered as bridging substance in mitigating toxic metals from the contaminated soil to humans [13] through food chain. Although documents on adverse effects and drug events by consuming herbal drugs are being reported, cumulative investigation of these reports is very few and a detail insight behind the cause and mechanism of metal toxicity is rare. This study is a first systematic review on herbal drugs' metal toxicity investigation which searches statistical formulation of risk, mechanism of toxicity, and trail of this contamination.

2. Methodology

2.1. Publication Search and Inclusion Criteria. Two bibliographic databases (PubMed and Google Scholar) were selected for this investigation. Literatures were searched systematically in PubMed and Google Scholar. The purpose was to identify the relevant information. Safety assessment of herbal drugs was searched, as text word search strategy ensures maximum selectivity as well as without compromising specificity, and

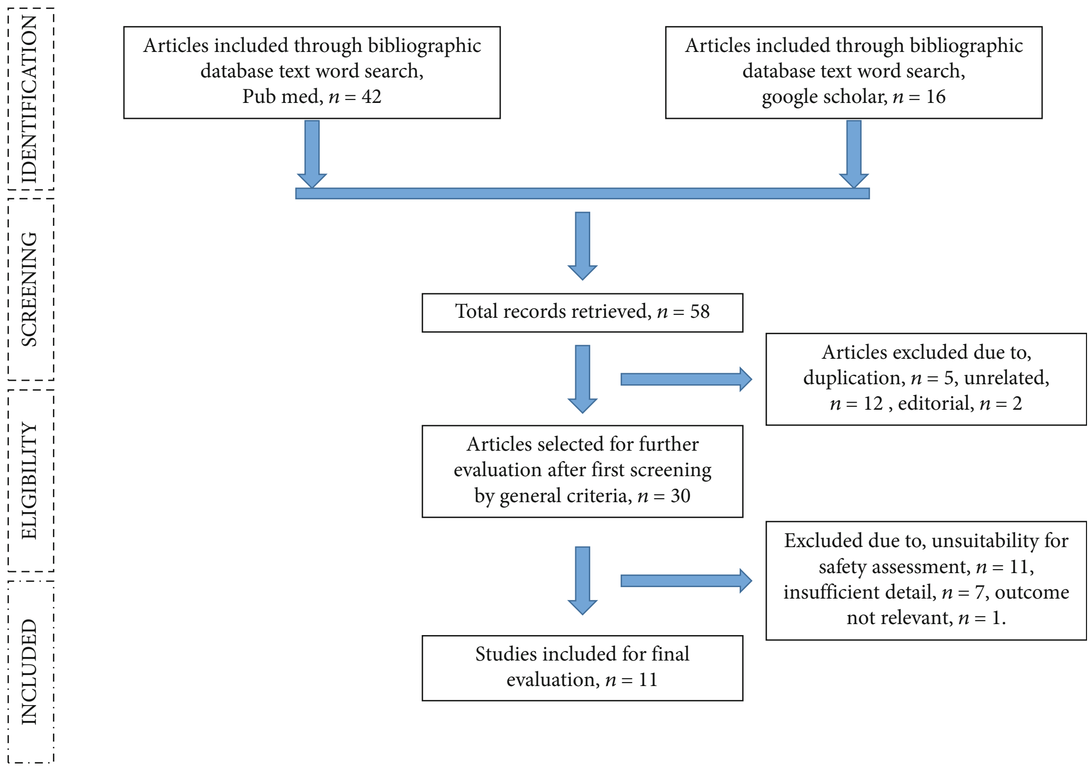

Figure 1: Article selection protocol.

the strategy was adopted in this study. Word and group of words like "herbal drugs," "herbal preparations," "complementary and alternative medicine (CAM)," "metal toxicity," "safety assessment," "drug safety," and "public health safety" were searched. Searches were concentrated to metal toxicity among all contaminants reported in herbal drugs. To increase the number of relevant articles, references of the initially identified articles were also searched. Thesis dissertations, conference proceedings, etc., were excluded from searching to eliminate the risk of bias.

2.2. Data Extraction. All data were collected independently from the finally included studies by means of a standardized protocol, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This was meant to aid the systematic reviewers transparently giving testimony behind the causation of the review and explicitly mentioning authors' effort towards the review and subsequent findings. Articles were through read manually, and relevant data were extracted. The discrepancies aroused during data extraction process were fixed by accord between investigators. Each study was studied, and the following were extracted: author and co-author, year of publication, reference, and toxic metals showed adverse effects and nature of adverse effects. The research synthesis protocol behind article searching using text word article search strategy is shown in Figure 1.

2.3. Qualitative Assessment. Relevant data from each study was extracted by two different reviewers working on this review manuscript write-up.

2.4. Outcome of This Review Investigation. The primary efficacy outcome of this systematic review was confirmation on metal toxicity by consuming herbal drugs.

2.5. Article Selection Protocol for Safety Assessment. In the first step of systematic review, identification of the relevant publications in a systematic and comprehensive way [14] was done. Two bibliographic databases (PubMed and Google scholar) were searched using prior mentioning text word searching strategy. Without including any subjective judgement, discrimination was maintained between relevant and irrelevant papers which provided potentially relevant papers. In order to ensure selectivity in a manner that no article slip passes our inclusion criteria, the screening process was performed twice. While doing this, to increase the specificity of searches through text word search strategy, titles and abstracts of the false positives were analyzed (Figure 1). In the first screening of general criteria, 28 articles were excluded out of 58 articles from the study due to duplication, unrelated articles, and selection of editorials instead to full articles. From 30 eligible articles, 11 were included for final assessment of safety assessment.

2.6. Thematic Analysis. Articles included through article selection protocol were synthesized thematically in a qualitative manner. This was an add-in tool employed with PSISMA article selection protocol to aid in identifying, finding, and interpreting patterns of different themes. Relevant information provided with different articles was made familiarized, transformed into coding, and searched for probable

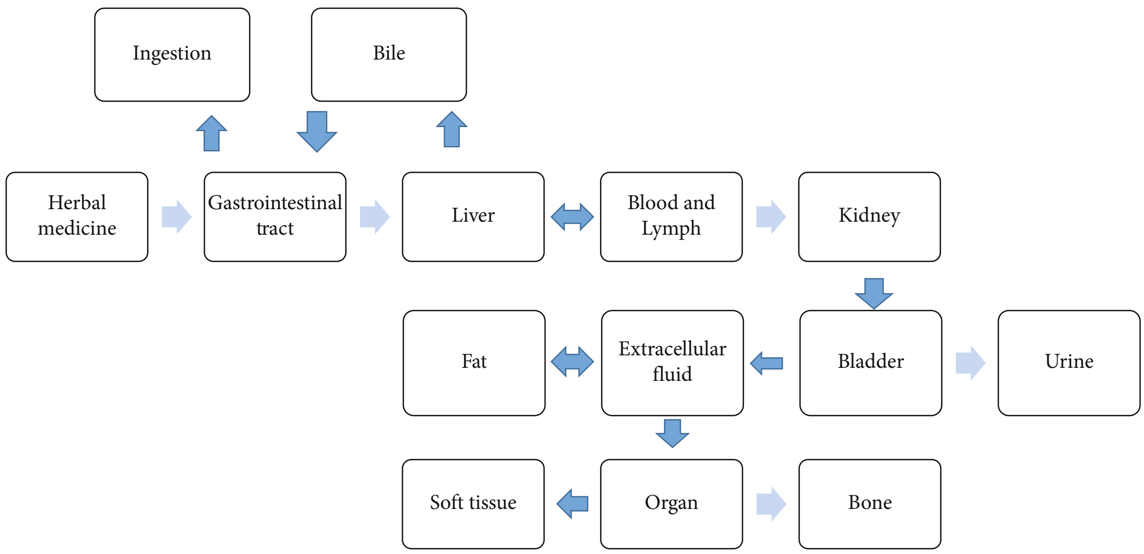

FIGURE 2: Interaction and fate of toxic metal in human body through ingestion of herbal medicine (Encyclopedia Britannica, 1994).

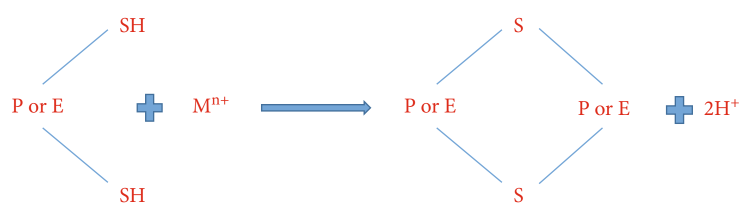

FIGURE 3: Enzyme suppression by toxic metal in human body.

patterns to group them. Patterns were reviewed, defined, and finally documented.

3. Result and Discussion

3.1. Safety Assessment. Having been of natural origin, herbal drugs are claimed safe. However, while exceeding safety limit as recommended by regulatory bodies, herbal drugs often causes adverse effects to human body. The research into adverse effects of metals consumed through herbal remedies began decades ago [15]. Different metals cause damage to different organs through deposition and mimic metabolic procedures.

Lead, cobalt, iron, and copper intoxication led to gastrointestinal (GI) symptoms [13, 16–19]. Chronic arsenic and mercury poisoning is associated with organ damage [20, 21]. Zinc and cadmium causes toxicity [22–24]. Distress is associated with excess calcium intake [25].

Interaction and fate of toxic metal in human body ingested through herbal medicine can be represented as Figure 2.

3.2. Human Health Risk Assessment. Impact of metal on human body for prolong exposure is evaluated according to the United States Environment Protection Agency (USEPA) guideline [26–29]. The impact of prolong exposure prediction model takes Hazard Quotient (HQ) for the metals in interest. If $HQ < 1$, there is no concern for noncarcinogenic effects, and if $HQ > 1$, there is reason for noncarcinogenic anxiety.

$$HQ = \frac{CDI}{RfD}, \quad (1)$$

where CDI is the daily dose of toxic metal (mg/kg) to which patients might be exposed.

$$CDI = \frac{C \times IR \times EF \times ED}{(BW \times AT)}, \quad (2)$$

where C (mg/kg) is the concentration of toxic metals in the ESHDs, IR (kg/day) is the ingestion rate (dosage of drug taken), EF (days/year) is the exposure frequency, ED (years) is the exposure duration, BW (kg) is the body weight, AT ($ED \times 365$) (days) is the averaging time ([29]; USEPA, 2006), and RfD is the reference dose that enables individual to sustain the level of exposure over a long period of time without experiencing any harmful effects [30].

3.3. Mechanism of Metal Toxicity. Usually herbal remedies enter human body through oral exposure. Through herbal remedy, toxic metals found their way to the ingestor. Human stomach contains gastric juice. The metals are oxidized to their various oxidative states while reaching in stomach.

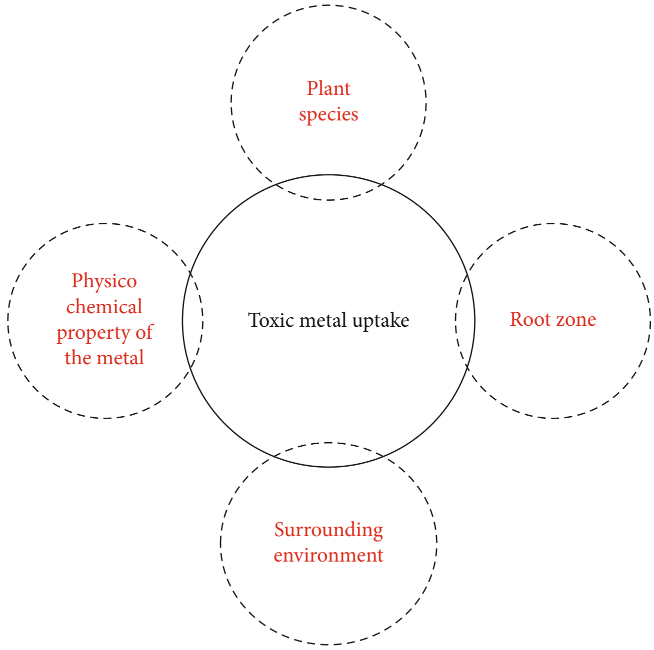

FIGURE 4: Plant contamination factors by toxic metals.

Let the oxidative state be M^{n+}, where M is toxic metal and $n+$ is its oxidative state. M^{n+} can bind with proteins and enzymes. The most common functional group that toxic metals bind is the thio groups (SH group of cysteine and SCH_3 group of methionine) (Engwa et al., 2019) (Figure 3). As a result, stable and strong bond forms.

If toxic metal M^{n+} reacts with sulphydryl groups (-SH) of proteins (P) or enzymes (E) then M^{n+} replaces the hydrogen of the SH group. As a result, the function of the protein (P) or activity of the enzyme (E) is suppressed. The concept is represented in Figure 3.

3.4. Pathway of Toxic Metals from Source to Herbal Medicine. Environmental sources are responsible behind the contamination of natural herbs by toxic metals. Toxic metals are naturally occurring and widely distributed in soil, water, and air where Cd, Cr, Cu, Hg, Pb, and Zn are most common of these [31]. Anthropogenic activities are known potential contributor in producing toxic metals which are released into surrounding environment. For instance, soil, water, and air can be contaminated by means of deposition of toxic metals from different sources by different industrial activities ([32–34], Maobe et al., 2012, [35–38]). As a result of industrial activities, waste water and industrial effluent releases which carry toxic metals may contaminate surrounding environment [39].

Toxic metal uptakes by plants have been discussed in different findings where plants act both as accumulators and excluders [40]. Contamination of plants by metals relies on the source of metal releasing (like the soil) and the receiver which is receiving the toxic metals (like the plant). Some properties of the metals make them vector for moving from source to receiver [33, 41, 42]. To put it into perspective, let us take the metal arsenic. Toxicity of the metal depends on its speciation, and the pH, redox conditions, surrounding mineral composition, and microbial activities affect the form (inorganic or organic) and the oxidation state. Inorganic species like As^{3+} and As^{5+} are the predominant species in environments [43, 44]. Soil depth plays a role in lead contamination. The metal accumulates in the upper eight inches of soil. There lead remains in insoluble form, and the contamination is highly immobile [45, 46] (Figure 4).

The availability of toxic metals in soil can be formulated as follows:

$$M_{\text{total}} = M_p + M_a + M_f + M_{\text{ag}} + M_{\text{ow}} + M_{\text{ip}} - (M_{\text{cr}} + M_l), \quad (3)$$

where "M" is the heavy metal, "p" is the parent material, "a" is the atmospheric deposition, "f" is the fertilizer sources, "ag" are the agrochemical sources, "ow" are the organic waste sources, "ip" are other inorganic pollutants, "cr" is crop removal, and "l" is the losses by leaching, volatilization, and so forth [47, 48].

To evaluate the magnitude of contaminants in soil, enrichment factor (EF) is used [49]. EF provides information about anthropogenic influences on toxic metals in sediments [50].

$$\text{EF} = \frac{C_M/C_{\text{Al}}\ \text{sample}}{C_M/C_{\text{Al}}\ \text{background}}, \quad (4)$$

where C_M/C_{Al} sample represents the ratio of concentration of toxic metal (C_M) to that of aluminum (C_{Al}) in the soil sample, and (C_M/C_{Al}) background is the same reference ratio in the background sample.

If EF > 1, then a given metal may be entirely from crustal materials or natural weathering processes [51].

If EF > 1.5, then it is indicative of human influence and (arbitrarily).

EF of 1.5–3, 3–5, 5–10 and >10 is considered the evidence of minor, moderate, severe, and very severe modification [52].

By determining metal mobility, the effect of soil contamination on plant-metal uptake can be presumed. Plant-metal uptake is understood by the bioaccumulation factor (BF) and the transfer factor (TF). From these factors, the degree of metal accumulation in the plants grown at the farm site close to the metal-scrap dumpsite is calculated [53].

$$\mathrm{BF} = \frac{\text{Concentration of metal in plant}}{\text{Concentration of metal in soil}},$$
$$\mathrm{TF} = \frac{\text{Concentration of metal in plant shoot}}{\text{Concentration of metal in plant root}}. \tag{5}$$

Postharvest treatment of herbs like application of fumigants can possibly contaminate the substance with toxic metals [54]. Local herbs are often marketed by Layman who does not maintain hygiene. As a result, possibility of toxic metal contamination from environment increases. Different manufacturing stages act as entry route of toxic metals into herbal formulations. These steps include open-air drying, processing of drugs in vessel, conversion stage (e.g., organic solvent residue), and preservation [55–57].

4. Conclusion

This study is first systematic review on metal toxicity in herbal drugs incorporating risk assessment modeling, mechanism of toxicity, and pathway together suggesting probable health risk of herbal medicine consumption with prolong ingesting and exceeding permissible limit. Adverse health effect on human after consumption of toxic metals contaminated herbal formulations is likely. Culpability goes to polluted soils where the herbs grow, production house and its utensils where the herbal medicines are manufactured, and improper legislation which made the way of lax law enforcement behind ensuring safety of herbal medicines. Therefore, prior to selling of these medicines, there should have proper screening from herb collection, and manufacturing to selling by authority concerned is advocated. In addition, scientific community should carry on lab-based research and their accumulation as review to notify the presence of toxic metals exceeding safety limit along with predicting risk through modeling to ensure drug safety.

Data Availability

Data is provided within the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

We would like to acknowledge the contribution of the International Science Program (ISP) through Swedish International Development Cooperation Agency (Sida) for their financial support.

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