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# AN INSIGHT INTO TOXIC METAL IN HERBAL MEDICINE: PATHWAY AND ITS CONSEQUENCE- A REVIEW

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## Abstract

Herbal medicines are becoming increasingly popular, thereby being used in a vast amount. Prime reasons for this ample amount of popularity are clever marketing techniques fed on perceived safety. However, without proven clinical trial these claims come undone. This poses a threat to public health and drug safety as well. As a result, the whole health system falls into peril. With the increasing of urbanization and industrialization for ensuring development, geologic and anthropogenic activities have increased which is polluting soils with toxic metals. Consequently, contamination in herbal plants and their finished formulations due to toxic metal is not rare and being reported in different articles. However, the mechanism behind the metal availability in herbal medicine and their mother plant and the consequence in terms of mechanism and different mathematically understanding is little discussed. Therefore, in this review, efforts have been given on obtainability of toxic metal in herbal medicine from the point of source as back as how the herbs may have been exposed to toxic metals and subsequent mitigation of toxic metals and the factors governing behind the up-taking. Human health risk assessment is explained for assessing the potential risk of exposure.

**Keywords**: *herbal medicine1, drug safety2, toxic metal3, human health risk assessment4.*

## Introduction

Metals are naturally occurring and omnipresent. Both natural and anthropogenic activities release toxic metals into the environment. For ensuring development, urbanization and industrialization is necessary. And these two processes are continuous. These processes affect human livelihoods and environmental quality negatively around the world (1,2). High levels of metal contamination in the soil are happening in consistence with this (3-6). Some of them are toxic even at very lower concentration, result in metal toxicity. Metals like As, Cd, Cr, Cu, Pb, Hg, Ni, Fe, Mn, and Zn are commonly known as toxic metal for their toxicity in low concentration of exposure.

Consumption of herbal medicine has a millennium old history. Recently, consumption of herbal medicine is increasing. It is believed, the global market of herbal medicine valued at US$107 billion (7). Herbal medicines are prepared from herbs, which are natural. Due to their natural origin, they are assumed safe (8,9). This concept of safety allows herbal medicines to reach to users as over the counter (OTC) product. Same senerio of OTC selling is viewed in Europe, North America and Australia and Asia. With this follow-through along with licensed medicine, vendors are often found selling non- certified or unlicensed herbal products (10). End users are not provided with patient information leaflets with the medicine being sold (11), builds concern about a lack of information to consumers. Therefore, safe use of these products is in question. As a result, in different investigations adverse effect of herbal medicines is due to metal toxicity often come out (12-14).

This review summarizes the concepts of outcome of metal toxicity and their possible entry pathway to herbal medicine. To do so, this review compile and describe concisely the factors govern toxic metal uptake from source of contamination to soil and soil to medicinal plant. This review would unravel some of the parameters which must be counted in choosing plants for medicinal purposes, followed by processing hacks to be considered for converting medicinal plants into finished products. Additionally, researchers would get information for assessing finished herbal products in terms of safety due to metal toxicity for prolong exposure.

## Methods

Literature were searched in bibliographic database PubMed and Google Scholar. This was done by identifying relevant information focusing on the mechanism behind the metal availability in herbal medicine and their mother plant and the consequence in terms of mechanism and different mathematical formula. Therefore, text word search strategy was adopted to safeguard maximum selectivity by not compromising specificity. Information were collected independently from the finally included studies by dint of a protocol (15). The discrepancies during data extraction process were fixed by accord between investigators.

## Discussion

*Mitigation of toxic metal from source of contamination to soil*

Toxic metals enter soil indirectly as a result of industrial activities. However, through municipal wastes fertilizer, or other soil additives direct exposure of toxic metals to soil takes place (16-18) .Contamination of soil also takes place through atmospheric deposition. Toxic metals, regardless of their sources, have the potential for being integrated by the plant by means of processes (foliar or root absorption) (19). These all adds up in total availability of toxic metal in soil. The readiness of toxic metals in soil can be formulated as:

$$M_s = P_1 + P_2 + P_3 + P_4 + P_5 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where '$M_s$' is the toxic metal, '$P_1$' is the parent material, '$P_2$' is the atmospheric deposition, '$P_3$' is the agrochemical sources, '$P_4$' is the organic waste sources, '$P_5$' is the inorganic pollutants.

The availability of metal in soil is affected by crop removal and losses by leaching and volatilization. These factors affect toxic metal availability in soil negatively.

Therefore, the equation 1 becomes,

$$M_s = (P_1 + P_2 + P_3 + P_4 + P_5)\text{-}(P_6 + P_7 + P_8) \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, $P_6$ is the process of crop removal, $P_7$lossess of toxic metal by leaching and $P_8$ is lossess of toxic metal by volatilization from soil (20,21).

Equation 2 can be written as,

$$M_s = P_{Addition} + P_{Substraction} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

From equation 3 it is evident that toxic metal in soil sample is highly influenced by anthropogenic activities (22). In soil, toxic metals can exist in both form as a separate entity or in combination with other soil components which constitute exchangeable ions sorbed on the surfaces of inorganic solids, nonexchangeable ions and insoluble inorganic metal compounds. Pollution or contamination problem is predominantly due to the metals that exists as separate entities than the metals that bound to silicate minerals (23,24). Toxic metal availability in soil is affected by different factors where it is believed that soil pH is the vital factor affecting metal availability in soil where increase of pH has been associated with decreasing availability of some toxic metals (Cd, Zn etc) in soil (25). pH dependency has also been observed in case of specific adsorption (26). The effect of pH on metal solubility can better understood in terms of its effect on precipitation–dissolution reactions. Presence of organic matter and hydrous ferric oxide also immobilize toxic metals, thereby decrease their availability in soil. However, factors like moisture content, certain soil colloids and water holding capacity of soil increases metal availability of soil (27,28). Soil colloids supply the large interface and specific surface areas which aid in controlling the concentration of heavy metals in natural soils (29). Factors like soil aeration and microbial activity also affect toxic metal availability in soils (30). Soil enrichment factor (SEF) provides information about availability of toxic metals in contaminated soil (31-33).

$$SEF = \frac{(\frac{M}{Al}\, contaminated\ soil}{\frac{M}{Al}\, control\ soil} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where, M and Al are concentrations of metal and Al respectively. Looking into the values of SEF, researchers can assume the source from where the metal has come into the soil body. SEF> 1 indicates a given metal may be entirely from crustal materials or natural weathering processes (34). SEF> 1.5 designates indication of human influence and (arbitrarily) SEF of 1.5–3, 3–5, 5–10 and >10 is considered the evidence of minor, moderate, severe, and very severe modification (35).

*Mitigation of toxic metal from soil to medicinal plant*

Soil contamination by toxic metals (equation 1-4) plays a key role in plant- metal uptake. Metal uptake by plants can be influenced by several factors like metal concentrations in soils, soil pH, cation exchange capacity, organic matter content, types and varieties of plants, and plant age where the metal concentration in soil is pivotal (36-38).

Plant- metal uptake is the process which gives us idea about metal mobility form soil to plant material. In plant- metal uptake process a fraction of toxic metals which are enthusiastically mobilized in the soil environment are taken up by plant roots. Plant- metal uptake is calculated by means of bioaccumulation factor (BF) (39). The amount of which a metal can be absorbed by a living organism (plant) and spread the systemic circulation of the living organism is called bioavailability (40). Total metal concentrations in soil do not necessarily correspond with metal bioavailability in plant. Estimation of the bioavailability of toxic metals in medicinal plant, necessitates the selection of an extractant which simulates the plant-available fraction of the element (41). The exchangeable fraction of elements in soil is estimated by Single extractions which assume toxicity deficiencies in palnts (42). However, some extractor work sequentially to assess toxic metal relationship with the different solid-phase components in sediments (43). Another approach determines the mitigation of toxic metal by plants from soil is transfer factor (TF) (44,45) where higher value of the TF indicates more mitigation of the toxic metal. Metal toxicity inside the plant system results in a series of physiological and metabolic disturbances (46).

Plants uptake from soil takes place by means of a number of different plasma membrane localized transporters. The plant uptake depends on a number of plant factors. Plant factors which affect plant uptake of toxic metals can be classified as physical processes, biological processes and plant adaptability. Root intrusion, water, and ion fluxes and their relationship to the kinetics of metal solubilization in soils are physical processes. Plant root intrusion within the soil profile supplies an extensive rhizosphere for ion absorption. In the rhizosphere ion depletion is relieved to some degree by diffusion of ions. Induced transpirational demands of the plant also alleviate rhizosphere ion depletion by mass flow of both water and ions from surrounding soil (47). The kinetics of solubilization of ions sorbed to the solid phase of soil and the kinetics of removal by the plant root controls ion supply within the rhizosphere. Interaction between different ions, transportation through membranes and metabolic fate of absorbed ions are biological processes. Metabolically adaptation to changing metal stresses in the environment also affect plant uptake of toxic metal (19).

*Mitigation of toxic metal during processing of herbs into finished formulations*

The medicinal plants, during processing can also be exposed to toxic metals. Toxic metal exposure to herbal plant can be intentional or accidental. Intentional addition is known as adulteration. Adulteration of herbal medicine with toxic metals is evident where herbal medicines are replaced partially or fully with impure, extraneous or inferior metal containing substances during production, sampling, packaging or repackaging, storage or transport process (48-52). Accidental contamination takes place when herbs are gone through different processes like grinding, mixing for making into finished herbal medicine. The mentioned processes require heavy to light metal made equipment. As a result, these equipments can also release toxic metals into herbal medicine (53).

$$M_{HM} = M_{PR} + M_A M_{AR} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where $M_{HM}$ is toxic metal in herbal medicine, $M_{PR}$ is toxic metal in plant residue and $M_A$ is toxic metal for adulteration and $M_{AR}$ is toxic metal for accidental release during processing.

*General methods to evaluate the risk of metal toxicity in herbal medicine*

Toxic metals if exceeded safety limits, exerts harmful effect on human health. It took ling time to fathom the risk due to metal toxicity. Therefore, different models explain possible risks of metal toxicity for prolong exposure. Risk assessment is defined as an outcome variable of predictor variables (hazard and exposure). Methods have been developed for assessing risk on human health for prolongs exposure of toxic metals. The methods calculate the chance of happening of any given extent of the harmful health hazards occurred over a definite time period (54,55).

In risk assessment exposure pathway and exposure duration plays a role along with contamination. Exposure pathways represent the ways by which a person can come into contact with a hazardous substance. Inhalation, dermal absorption, ingestion and injection are four major exposure pathways for toxic metal entry into human body. In case of herbal drugs contaminated with toxic metals, ingestion is pivotal among the potential exposure pathways (56). Non-carcinogenic exposure equations are grounded on references supplied by an independent agency conduct environmental assessment (57-60). Estimation on potential non-cancer health risk through ingestion of individual toxic metal in the herbal drug is done after computing Hazard Quotients (HQ) through estimated daily intake of metal (EDIM). HQ values for all toxic metals under investigation are summed up to compute, Hazard Index (HI) (61-63).

$$HQ = \frac{EDIM}{ORD} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Where, EDIM is the daily dose of toxic metal to which patients might be exposed and ORD is the oral reference dose that enable individual to sustain the level of exposure over a long period of time without experiencing any harmful effects (64).

HQ values are positive integer and fraction where 1 is the cutoff point of HQ value where HQ<1 indicates no concern for non- carcinogenic effects and HQ> 1 directs cause for concern due to non-carcinogenic anxiety (65)

value for HI for several toxic metals is calculated according to the EPA guidelines for health risk assessment (66,67).

$$HI=\sum_{k=1}^{n} HQ = HQ_{M1} + HQ_{M2} \dots HQ_{Mn} \dots\dots\dots\dots\dots\dots\dots (7)$$

$M_1$, $M_2$ and $M_n$ are individual toxic metals present in herbal drug.

Recently, focus has been given on cancer risk for exposure of toxic substances. Statistical models are used to compute the probability of developing of cancer. Cancer risk is assessed by lifetime cancer risk formula. The prediction of risk of cancer due to exposure to a specified dose of toxic metal in herbal drug can be computed using the formula. ILCR stands for incremental probability of a person developing any type of cancer over a lifetime as a result of twenty-four hours per day exposure to a given daily amount of a carcinogenic element for seventy years (68).

*ILCR= CDI* CSF………………………..(8)*

Here, CSF is the cancer slope factor and is defined as the risk generated by a lifetime average amount of one mg/kg/day of carcinogen chemical and is contaminant specific.

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