

Heavy Metal Contamination in Medicinal Plants: Sources, Plant Defense Mechanisms, and Implications for Human Health

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ABSTRACT

Medicinal plants are employed extensively in traditional and contemporary healthcare systems, but heavy metal contamination seriously threatens their safety and effectiveness. The fact that both organic and inorganic materials from the air, soil, and water may be easily absorbed by plants and subsequently transferred up the trophic chain to humans makes this study important. The World Health Organization estimates that 65-80% of people worldwide rely on herbal items as their main source of medical care. This study explores the primary sources of heavy metal pollution, including industrial discharge, agricultural runoff, and atmospheric deposition, that contribute to the accumulation of toxic elements in therapeutic plant habitats. The synthesis of phytochelatins, the activation of antioxidant enzymes, and changes to root architecture are only a few of the physiological and biochemical defense mechanisms that plants employ in response to metal-induced stress. Despite these adaptations, prolonged or high-level exposure can impair plant growth and reduce the concentration of therapeutic phytochemicals. Moreover, the consumption of contaminated medicinal plants can cause bioaccumulation of heavy metals (HMs) in humans, posing risks like increased cancer susceptibility, neurological disorders, and organ damage. Addressing this issue requires stringent quality control, pollution mitigation strategies, and public awareness to safely use medicinal plant-based remedies.

KEYWORDS

Antioxidant, pH, reactive oxygen species, secondary metabolites, pesticide, phytoremediation

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INTRODUCTION

A variety of plants are used by humans for their health benefits as major sources of natural nutrients and antioxidants, as well as an integral component of traditional medicine¹. Compared with chemical-based pharmaceuticals, medicinal plants are less expensive and are used to treat various diseases around the world, including cardiovascular issues, arthritis, diabetes, and inflammatory diseases². All traditional medical systems, including Ayurveda, Amazonian, Tibetan, African, Chinese, and Unani, that have incorporated phytotherapy into their philosophies utilize therapeutic plants. Herbs may be prepared in various ways to capitalize on their antioxidant qualities; infusion, decoction, maceration, and cataplasm are a few examples.



The beneficial effects of herbs for a range of medical conditions have been shown in several studies. For instance, Zuo *et al.*³ discovered that *Malva sylvestris* L. lowers the oxidative stress response and has a cardioprotective impact. *Nepeta menthoides* Boiss & Buhse, and *Melissa officinalis* L. have been shown to help treat anxiety, depression, and sleeplessness^{4,5}. while spirulina (*Spirulina platensis*) improved memory impairment by preventing oxidative stress⁶. The antioxidant properties of medicinal plants make them valuable in managing oxidative stress-related disorders, which are linked to conditions such as aging, PTSD, and Parkinson's disease⁷.

Because traditional medicine is accessible, affordable, and culturally acceptable, most people in underdeveloped nations still turn to it for their fundamental medical needs⁸. It was⁹ reports that more than 60% of the global population relies on herbal treatments with even higher usage in several regions. Furthermore, Zahra *et al.*¹⁰ estimate that the international trade of therapeutic plants could reach a value of \$5 trillion by the year 2050. However, with this growing demand, concerns regarding the safety of herbal products have emerged, particularly due to contamination by heavy metals¹¹.

The toxicity of HMs has a major impact on ecological, evolutionary, nutritional, and environmental processes, making them significant environmental contaminants. Medicinal plants can become polluted with heavy metals from various sources, such as areas that are regularly irrigated with either treated or untreated wastewater, or locations near tailings piles and waste disposal sites containing metals. The use of sewage sludge as a soil amendment, industrial waste, traffic emissions, prolonged application of phosphate fertilizers, and poor irrigation practices are the main causes of the trace amounts of toxic heavy metals. Toxic metals such as lead (Pb), copper (Cu), cadmium (Cd), nickel (Ni), zinc (Zn), cobalt (Co), chromium (Cr), and arsenic (As) found in soils world⁹. These metal ions are persistent environmental pollutants and can severely contaminate soil and water systems¹².

Often present as cations, heavy metals (HMs) have a strong interaction with the soil matrix and can become mobile due to environmental changes. Both roots and leaves accumulate more metals when the external medium's accessible metal concentration is higher¹¹. Exposure to heavy metals causes various physiological, metabolic, and genetic changes in sensitive plants. It causes symptoms such as stunted growth, delayed seed germination, drooping leaves, decreased fruit output, and several other abnormalities¹³. In response to HM stress, plants also produce specific proteins, stress hormones, and antioxidants to counteract the damage. Secondary metabolite (SM) production can be altered as a result of HM stress¹⁴. Due to their widespread environmental presence, heavy metals can enter medicinal plants and subsequently the food chain, increasing the risk of human exposure⁵. Even though the detrimental effects of heavy metals on human health have long been known, exposure to these hazardous substances is still occurring and is even rising in some areas. Because medicinal plants have the potential to accumulate heavy metals, thorough research is necessary to shield consumers from harmful exposure levels¹⁵.

Although numerous studies have investigated heavy metal contamination in plants, the available information is often scattered and lacks a comprehensive perspective. Most studies address contamination sources, plant defense responses, or human health risks separately, with limited integration of these aspects in the context of medicinal plants. In particular, the impact of heavy metals on plant growth and metabolic status, including alterations in physiological processes and secondary metabolite production, has not been sufficiently synthesized in a unified framework. In this context, the present review aims to provide an integrated understanding of heavy metal contamination in medicinal plants by examining the major sources and pathways of contamination, their effects on plant growth, physiological and metabolic status, plant defense, and the potential implications for human health. By bringing these aspects together, this study seeks to address existing gaps and contribute to the development of effective strategies for monitoring, management, and safe utilization of medicinal plants.

MATERIALS AND METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), the current scoping review was carried out. The search approach was carried out by three authors (PB, KC, and SKS). MEDLINE/PubMed, Google Scholar, SpringerLink, Scielo, and Redalyc were the database sources examined; the research were published between 2000 and 2025. "Medicinal plants," "herbal medicine," "Secondary metabolites," "plants," "traditional medicine," "plant extracts," "antioxidant," "oxidative stress," "anti-inflammatory," "inflammation," "oxidative damage," "human health" "heavy metal," and "toxicology," were the search terms employed. For possible studies, the review papers' reference lists were carefully filtered. Regardless of the type of experimental study (e.g., *in vitro* and *in vivo*), original experimental research on contamination of heavy metals involving the antioxidant studies published in English or Chinese were considered for inclusion.

Following the above-indicated search methodologies, 6765 experimental studies were found. The total researches were 45 that met the inclusion criteria and were included for analysis. The selection procedure for the included studies is described in full in Fig. 1. Data extraction was done separately for each of the chosen articles. The following factors were taken into account: (1) Plant scientific names, (2) Plant common names, (4) intervention type, (5) comparator, (6) population and sample size, (7) intervention duration, (8) primary outcomes on the scoping review questions, (9) author(s) and publication year, and (3) origin/country of origin.

Quality assessment and risk of bias: The included papers' methodological quality was assessed using accepted guidelines for experimental rigor and best practices in phytopharmacological research. The quality of the studies varied quite a bit. Many studies lacked thorough phytochemical characterisation,

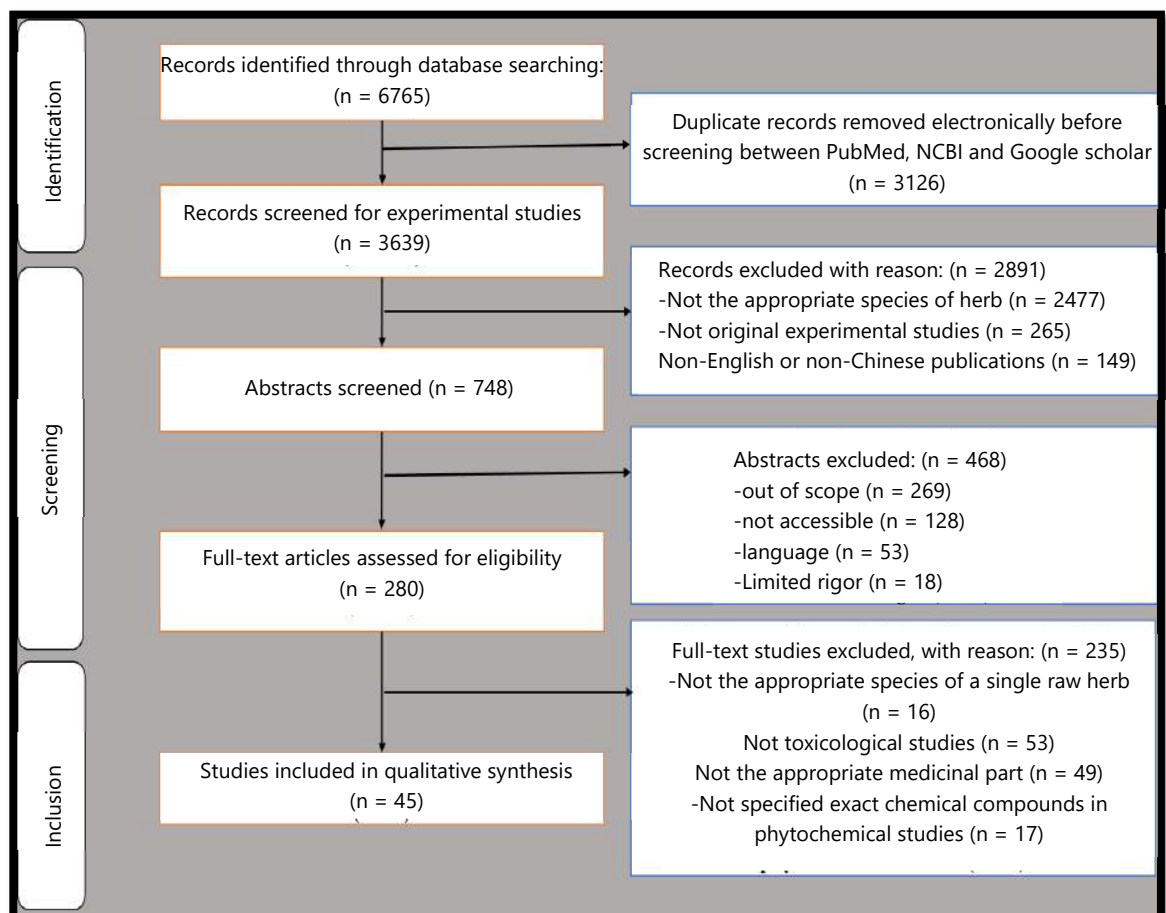


Fig. 1: Prisma flow chart depicting inclusion and exclusion criteria

extract standardisation, and botanical authentication, even when some reported suitable controls and statistical analyses. Limited disclosure of the rationale for blinding, randomization, and sample size raises the possibility of bias in several instances. These methodological flaws highlight the need for more standardized and properly planned future research and may have an impact on the repeatability and translational applicability.

Sources of heavy metal contamination: Heavy metal contamination poses a major threat to human health and the environment. There are several natural and man-made ways that these harmful substances enter ecosystems. Developing successful mitigation and prevention methods requires an understanding of these sources. Below is a list of the main causes of heavy metal contamination.

Natural sources: Although human activity introduces a lot of heavy metals, environmental contamination can also come from natural sources. For instance, significant concentrations of HMs like Hg and Pb can be released into the atmosphere during volcanic eruptions. As rocks and minerals deteriorate naturally, trace metals are also progressively discharged into surrounding soils and water bodies (Fig. 2). High quantities of heavy metals are natural in some geological formations, causing localised pollution without the need for human intervention¹⁶.

Industrial activities: Mining and metal smelting are two major industrial activities that contribute to heavy metal contamination. When ore is extracted, refined, and waste is disposed of, these operations release dangerous elements into the environment, such as As, Cd, Pb, and Hg. Levels of contamination are further increased by emissions and effluents from the chemical, electrical, and metallurgical production sectors. Leaks and spills at industrial sites are examples of accidental discharges that frequently cause serious environmental harm. Additionally, construction and demolition projects have the potential to unearth and release previously buried heavy metals, and building materials themselves may contain hazardous elements. Industrially impacted soils frequently contain heavy metal contaminants such as lead (II), Arsenic (III), Chromium (VI), Zinc (II), Copper (II), Mercury (II), Cadmium (II), and Nickel (II)¹⁸.

Agricultural practices: The other major way that heavy metals enter the environment is through agriculture. Metals like cadmium and mercury are frequently found in fertilizers and pesticides, and they gradually build up in the soil. These pollutants can enter adjacent water bodies through runoff from

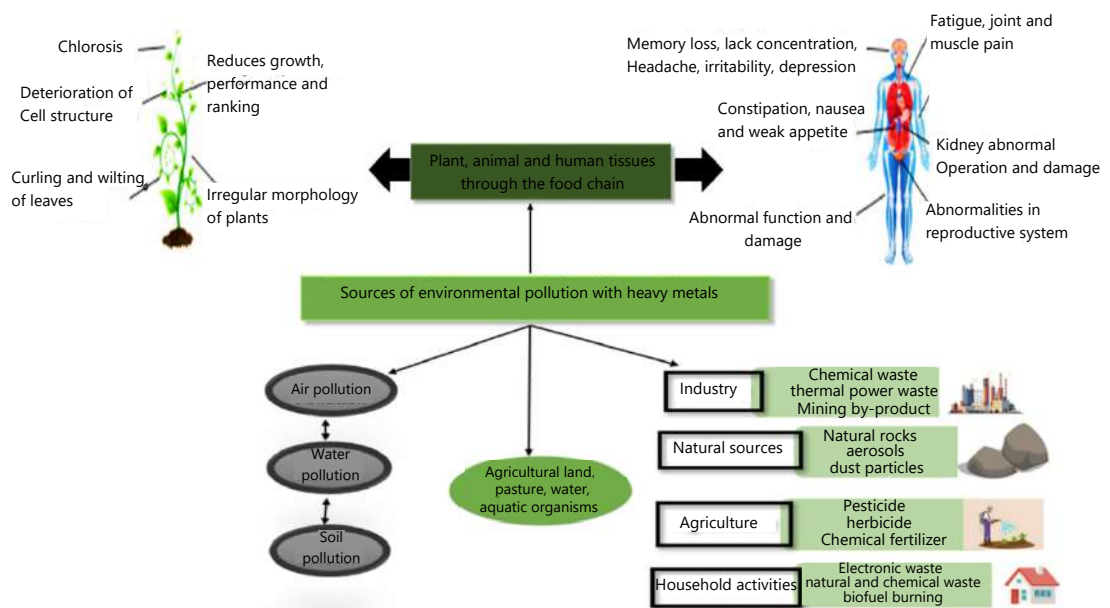


Fig. 2: Sources and effects of heavy metals¹⁷

Table 1: Heavy metal types, their impacts on human health, and the acceptable exposure limits²⁵

Pollutants	Sources	Effect on Human Health	Permissible levels
As	Metal smelters, fungicides, and pesticides	Poisoning, dermatitis, and bronchitis	0.02
Cd	Fertilizer, welding, pesticides and electroplating	Lung cancer, lung disease, kidney damage, bone abnormalities, bone marrow, and renal dysfunction	0.06
Cr	Origins of minerals and mining sites	Nervous system injury and irritability	0.05
Cu	Pesticides production, mining, and the chemical industry	Anaemia, gastrointestinal distress, and damage to the liver and kidneys	0.1
Hg	Pesticides, batteries, and the paper industry	Gingivitis, spontaneous abortion, tremors, protoplasm toxicity, and nervous system damage	0.01
Mn	Ferromanganese production, welding, and fuel addition	Central nervous system injury from inhalation or touch	0.26
Pb	Paint, tobacco use, pesticides, mining, coal combustion, and vehicle emissions	Childhood mental retardation, fatal neonatal encephalopathy, delayed development, kidney damage, long-term nervous system damage, and liver damage	0.1
Zn	Refineries, metal plating, and brass manufacture	Dermatitis and nervous system injury	15

agricultural areas, harming aquatic life and human health. Furthermore, animals that consume contaminated feed may collect heavy metals, which are subsequently added to soils by applying manure. de Vries *et al.*¹⁹ report that the routine use of fertilizers and animal manure in European farming contributes considerable quantities of lead, copper, cadmium, and zinc to the soil. Because of heavy metal contamination, approximately 137,000 km² of agricultural land around Europe is deemed unfit for food production²⁰.

Urbanization and traffic emissions: Traffic emissions and infrastructure development in urban areas are major contributors to the accumulation of HMs. Metals, including zinc, copper, and cadmium, are released by vehicle wear, including brake pad and tyre degradation. The burden is increased by the corrosion of metal infrastructure and engine parts. These pollutants enter storm drains and neighbouring habitats through urban runoff. Heavy metals are released by urban industrial zones through wastewater and exhaust gases. According to studies, roadside soils frequently have higher than WHO-recommended levels of lead and cadmium, especially in proximity to populated areas²¹.

Wastewater irrigation and sewage sludge: Large volumes of heavy metals can be released into the environment when sewage sludge and untreated or poorly managed wastewater are utilized in agriculture. High levels of hazardous metals have been found in e-waste and municipal garbage leachates, which can affect nearby soils and groundwater²².

Atmospheric deposition: Lastly, one important route for the long-distance movement of heavy metals is atmospheric deposition. Toxic metal-containing airborne particles are released by automobiles and industrial processes, and these particles eventually fall to land and water as precipitation. Particularly in agricultural regions close to industrial zones, this process is a significant cause of contamination in locations distant from the initial source of pollution²³. According to Favier *et al.*²⁴, all parts of the environment have become polluted with various contaminants, including heavy metals (HMs), due to interactions among environmental components and a variety of natural and human-related sources. As a result of this pollution, plants inevitably become contaminated, taking up metals from the soil, water, or air (Fig. 2). Heavy metals can build up in organisms and endanger human health because of the consumption of these plants along the food chain. The various forms of heavy metals, their effects on human health, and the acceptable exposure levels are shown in Table 1.

Uptake and accumulation in medicinal plants

Uptake of heavy metals: The HMs can enter the plant's body by foliar and root uptake. Soil-root transfer is the primary mechanism influencing the metal concentrations in the various plant organs when comparing the two exposure pathways. Both pathways can be used at the same time in places with a lot of traffic, mining activity, or industrial activity. Unlike the air-leaves-stem pathway, a lot of research has been done on the soil-root transfer²⁶.

Soil uptake: When heavy metals (HMs) occur in the soil, they initially attach to the surfaces of plant roots. Following this, water molecules naturally move into and diffuse through the metals. Another possible process involves active transport, where movement occurs along a concentration gradient. The physico-chemical properties of the soil, such as its particle size and cation exchange capacity (CEC), significantly influence metal availability. The solubility, bioavailability, and toxicity of heavy metals (HMs) all depend on the pH of the soil. At low pH values, metals are more readily available in their free ionic forms, but as the pH increases, they tend to form poorly soluble phosphates and carbonates²⁷. The bioavailability and biosorption of HMs can also be influenced by microbial activity. The distribution of metals within plant organs can further affect their presence and potential toxicity. The levels of several heavy metals (Ni, Zn, Fe, Cu, Mn, Cr, and Pb) in the stems, roots, and leaves of *Amaranthus spinosus* and *Datura stramonium* were measured in a study conducted by Olowoyo *et al.*²⁸. They observed a decreasing trend in metal concentrations from root to stem to leaf. Conversely, heavy metals can also accumulate in above-ground plant parts. Pehoiu *et al.*²⁹ explored the uptake and movement of HMs in therapeutic plants such as *Taraxacum officinale* and *Plantago major*, finding notable concentrations of Mn, Cd, and Pb in the leaves.

Foliar uptake: Airborne pollution is a comparatively under-discussed exposure mechanism. According to their aerodynamic size, atmospheric particulate matter (PM) is divided into three groups: ultrafine particles (UFPs) or PM_{0.1} fine particles (PM_{2.5}), and coarse particles (PM₁₀). These groups have sizes that range from 2.5 to 10 µm, less than 2.5 µm, and less than 0.1 µm, respectively. While the characteristics, fate, and toxicity of UFPs are still emerging issues, the PM₁₀ and PM_{2.5} fractions are more extensively studied and understood. The size of the particles is important because PM can adsorb potentially harmful substances, such as heavy metals. Smaller particles, especially fine particles, possess a larger surface area, allowing them to hold more contaminants and thus posing greater risks. Srivastava and Jain³⁰ discovered that the PM_{0.7} fraction contained most of the metal mass, including Ni, Mn, Cd, Pb, Cr, and Fe, in an urban sample. Similarly, Hu *et al.*³¹ observed that tiny particles had a higher concentration of lead than coarse particles when they examined the uptake of lead by plant leaves from nine distinct size-separated aerosol stages.

There are two possible sources of atmospheric heavy metals: natural (forest fire) and anthropogenic (mine, waste incineration, etc.). Brake dust is another significant source of Pb and Cd continue to be the most common elements in atmospheric aerosols that have the potential to be harmful. The possible toxicity of atmospheric PM is further influenced by the presence of redox-active trace elements as Cr, Co, As, and Ni. However, there is a seasonal pattern in the HMs content of atmospheric PM; for instance, Pb, which is mostly sourced from human activity, is present in higher amounts between the spring and winter³². Much less study has been done on the intake of heavy metals via air fallout than on soil-to-root transmission. Plants may be exposed to airborne particulates by wet or dry deposition; in the latter case, the particles are removed by rain, snow, or fog. For a variety of heavy metals, Pan and Wang³³ investigated the importance of both dry and wet deposition fluxes and discovered that dry deposition was the most prevalent mechanism for many of them. However, the relative contributions of wet and dry deposition fluxes differed by sampling location for several heavy metals, including lead, cadmium, nickel, zinc, and arsenic.

Table 2: Factors associated with the mechanism by which plants absorb heavy metals¹⁷

Characteristics	Factors	Description
Soil characteristics	pH levels	The availability of metals to plants is significantly influenced by the pH of the soil. While elements like Cd and Pb are frequently more accessible in acidic soils, metals like Ni and Zn may be more mobile in alkaline soils. Metal speciation is impacted by soil pH, which also impacts the solubility and absorption of metals
	Soil texture	Whether the soil is sandy, loamy, or clayey, its texture has an impact on drainage and water retention. For instance, sandy soils may let metals leach more readily since they often have a lower cation exchange capacity (CEC). Higher CEC clay soils have the potential to hold onto metals, which affects their availability
	Organic matter content	Metals' mobility and bioavailability may be impacted by binding with organic materials in the soil. While low organic matter may increase metal mobility, high organic matter tends to decrease metal absorption by forming complexes
Metal characteristics	Chemical form	The chemical composition or speciation of metals in the soil affects how readily available they are to plants. Metals can be complexes, free ions, or bonded to soil particles, among other forms. Free metal ions are more likely to be absorbed by plants than complexed or precipitated metal ions.
	Redox potential	The speciation of metals is affected by the soil's redox potential, which reflects its oxidative or reductive state. Metals like Fe and Mn become more soluble under reduced conditions, which affects their availability for plant absorption
Plant-related factors	Plant species	A variety of plant species have different affinities for particular metals. Certain species may accumulate large amounts of specific metals without becoming noticeably poisonous because they are hyperaccumulators. For the purposes of phytoremediation and sustainable land management, it is essential to comprehend the metal absorption properties of certain plant species
	Root characteristics	Metal absorption is influenced by the shape and structure of plant roots. Extensive root systems enable plants to more efficiently obtain metals and explore wider soil volumes. Metal absorption can also be improved by mycorrhizal symbiosis and root filaments
	Physiological responses	When plants experience metal stress, several physiological mechanisms are activated. Plants produce substances called glutathione, phytochelatins, and metallothioneins that chelate and detoxify metals, reducing any possible negative effects
Environmental conditions	Temperature and moisture	The soil's chemical reactions and microbiological activity are influenced by environmental factors, including moisture and temperature. These variables then affect metal availability and absorption. Microbial activity may be increased by warmer temperatures, which might affect metal reactions.
	Aeration	Microbial activity and root respiration depend on adequate soil aeration. The mobility and uptake of specific metals can be influenced by reducing environments created by waterlogged conditions, which are frequently linked to low oxygen levels
	Competing ions	To be absorbed by plant roots, metal ions may compete with other ions in the soil solution. The bioavailability and absorption of heavy metals can be impacted by the presence of large concentrations of other ions or vital minerals

According to Muezzinoglu and Cizmecioglu³⁴, wet deposition generally exhibits seasonal variability and is highly dependent on the local precipitation pattern. Metals involved in the deposited particles can be absorbed by stomatal penetration and internalization through the cuticle. Different species will show varying degrees of HM absorption efficiency since leaf shape significantly affects how much PM plants can absorb and retain. The most important morphological traits are the thickness, size, form, roughness, and presence or absence of leaf hairs in the epicuticular wax layer³⁵.

Accumulation of heavy metals: According to research, the amount of heavy metals (HMs) that accumulate in the tissues of medicinal plants varies depending on the metal and plant species. Medicinal plants possess adaptive mechanisms that allow them to thrive in highly polluted environments. For

instance, it was³⁶ discovered that *Lavandula spica* leaves had substantial amounts of Pb, Zn, and Cd, but *Ocimum basilicum* roots had large quantities of the same elements. *Lavandula angustifolia* was shown to accumulate metals mostly in its stems and roots in a study conducted by Bai *et al.*³⁷. However, Dinu *et al.*³⁸ found that *Ocimum basilicum* retained heavy metals in its organs in a different way: Zn(II), Cu(II), and Ni(II) were concentrated in the flowers, while Cd (II), Cr (III), Co (II), and Pb (II) mostly accumulated in the roots. The study also found that Cr (III) and Pb (II) levels in the roots exceeded permissible limits. Similarly, Fattahi *et al.*³⁹ found that the leaves and roots of *Ocimum basilicum* had higher concentrations of lead (II) and Cd(II) than other plant components, with the leaves having higher levels of Cd(II) and Pb(II) than the roots. When exposed to Cd (II) stress, Hashemi *et al.*⁴⁰ found that *Lavandula stoechas* L., accumulated ions primarily in the aerial portions, especially the leaves. According to a different study on *Lavandula spica* L., the roots were better able to absorb Cd than other areas, and accumulation increased as the content of Cd (II) in the soil increased. These results emphasize how crucial it is to take plant species into account when evaluating heavy metal contamination. The effects of heavy metal exposure on the synthesis of secondary metabolites in medicinal plants require more research. The medicinal qualities of plants may be impacted by differences in the amount and quality of these substances. Therefore, understanding the effects of HM's contamination on secondary metabolite formation is critical⁴¹.

Factors affecting accumulation in medicinal plant species: Multiple factors across the environmental and physiological ranges of plants affect the complicated and dynamic process of heavy metal uptake by plants. Developing an understanding of these elements is crucial for controlling and minimising possible contamination as well as for understanding the complexity of metal uptake. Table 2 discusses some of the major elements affecting the absorption process.

Significance of medicinal plants' antioxidant properties and their relationship to heavy metals: According to estimates, abiotic stress can reduce global crop production by up to 70% annually, which is worrying given the population increase. Various forms of environmental pollution enhance the stress that abiotic forces exert on plants. It is essential to comprehend how medicinal plants react to abiotic variables, particularly HMs, to improve crop yields in terms of both quality and quantity. This knowledge allows for effective intervention. If the antioxidant systems do not adequately respond to the level of abiotic stress the plant experiences, these stressors can damage plant tissues and ultimately threaten the plant's survival. Plants employ various complex survival strategies. For instance, when exposed to high levels of stress, plants may activate PCD (programmed cell death) as a genetically controlled mechanism to endure the stress²⁷. The ROS (Reactive oxygen species), which serve as mediators of the stress response, tend to accumulate in higher concentrations along the PCD pathway. The type of metal ion and the tolerance of the plant species can affect the defense responses of the plant. The accumulation of heavy metal ions generally begins in the soil and is absorbed by the roots, from where signals are sent to other plant tissues to produce compounds capable of neutralizing the metals. For example, the epidermis's secretory cells and epidermal trichomes release essential oils. Specialised cells found within the plants, such as laticifers, idioblasts, or epithelial cells, also produce lipophilic compounds in addition to trichomes⁵.

Medicinal plants react differently to abiotic stresses such as heavy metals. The first step involves detecting the stressor, which is then translated into a signal and sent to the cell receptors. Following this, the plant initiates a series of processes aimed at counteracting the stressor. The kind and severity of the stressor, as well as the plant's capacity to lessen it by changing its molecular, physiological, and biochemical states, all influence these responses. Although heavy metals can cause stress to medicinal plants, the degree of harm varies based on the metal's concentration and type. Naturally, the result is also influenced by the plant's capacity to withstand these shocks. In the literature, HMs have been found to disrupt the normal functioning of therapeutic plants through a number of mechanisms. These include: substituting essential elements, which results in enzyme dysfunction; disrupting protein function by binding to functional sites;

or overwhelming the plant's capacity to cope by producing excessive reactive oxygen species (ROS). Through the Fenton and Haber-Weiss reactions, redox-active metals like Fe and Cu can directly increase the formation of ROS²³. Medicinal plants are susceptible to abiotic stresses that damage tissues at the cellular level, which can impact plant growth, productivity, or even life. As previously stated, these stressors cause ROS to accumulate, which interacts with metabolites and cell components to cause irreversible metabolic abnormalities and necrosis. By triggering the apoptotic signal through lipid peroxidation, enzymatic activity inhibition, nucleic acid damage, or protein oxidation, elevated ROS generation might also result in cell death⁴¹.

Oxidative stress occurs when the impact of HMs is severe enough to disrupt the balance of the redox system. In such cases, the plant's antioxidant defense system becomes overwhelmed, leading to an increase in the production of ROS. Certain HMs that fall within the category of non-redox active metals, like Pb, Zn, and Cd, also indirectly enhance the concentration of ROS. The suppression of enzymes that are a component of the plant's cellular antioxidant defense system is one instance of indirect ROS development²³. The ratio of ROS generation to clearance determines how much ROS builds up in medicinal plants. Numerous environmental conditions, including soil salinity, water availability, temperature fluctuations, light intensity, and the presence of pesticides or HMs, affect this balance. Heavy metals can also restrict CO₂ fixation in chloroplasts, which is another harmful consequence and a major source of ROS formation, in addition to the excessive decrease of the electron transport chain (ETC) in photosynthesis²⁷.

Plants experiencing oxidative stress due to heavy metal pollution require metalloenzymes with antioxidant properties to maintain optimal growth and development within the context of ROS metabolism. Key metalloenzymes involved in this process include catalase (CAT), superoxide dismutase (SOD), xanthine oxidoreductase (XOR), and ascorbate peroxidase (APX). As previously mentioned, trace elements are essential for living organisms in small amounts, but when these elements exceed the plant's required threshold, they can induce oxidative stress. For example, the synthesis of CuZn-SOD (copper-zinc superoxide dismutase), which is necessary for healthy plant growth, requires copper (Cu) as a cofactor. However, excessive Cu levels can become a stressor, leading to several negative effects on plants⁴².

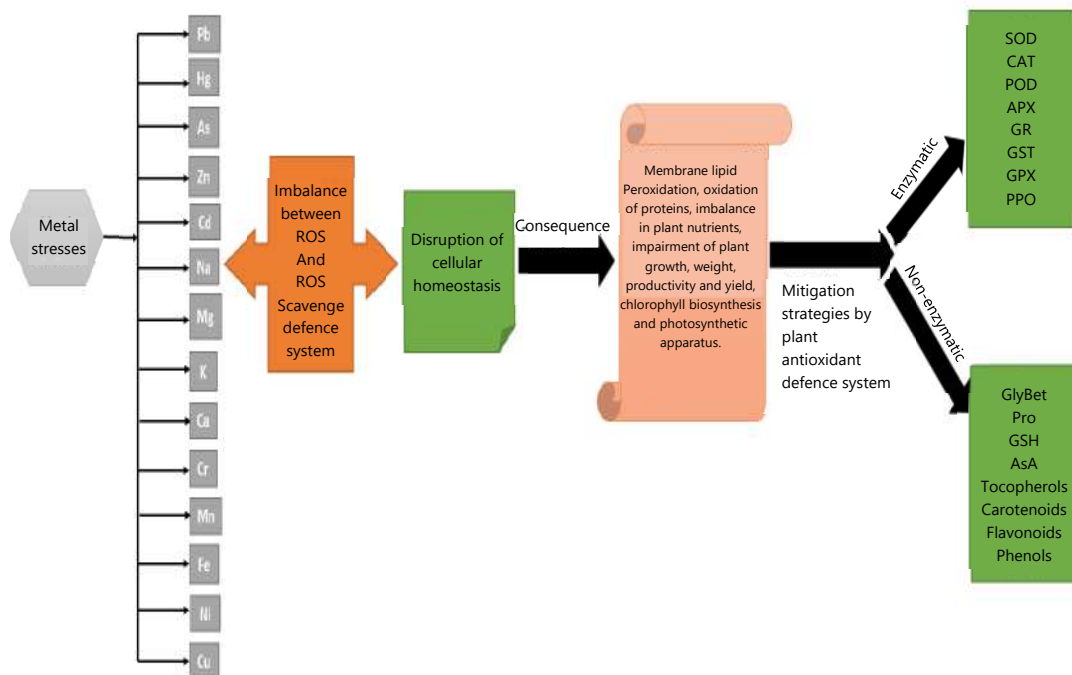


Fig. 3: Different types of metal stresses and their nonenzymatic and enzymatic responses⁴³

Plants mitigate oxidative damage from heavy metals (HMs) by activating their ROS-scavenging mechanisms through the production of antioxidant enzymes and non-enzymatic antioxidants (Fig. 3). To mitigate the toxicity of accumulated metal ions, their bioavailability in plant cells is reduced through chelation or complexation with ligands. Ahmad *et al.*⁴³ observed that in *Ocimum basilicum* L., both the MDA (malondialdehyde) content and nitro oxidative response increased with rising concentrations of HMs (Zn, Cu, Ni) in the soil. A strong correlation was found between hydrogen peroxide (H₂O₂) levels and the activity of SOD, APX, and CAT. Additionally, as heavy metal concentrations increased, levels of chlorophylls, anthocyanins, and carotenoids decreased when compared to control plants. Other studies investigating the impact of different heavy metal concentrations in growth systems on enzymatic and non-enzymatic antioxidants, in particular medicinal plants, are compiled in Table 3.

Heavy metals' impact on medicinal plant growth and metabolic status: Oxylipins are produced as a result of lipid oxidation processes carried on by heavy metal stress. The signal transduction process for the plant defence system is initiated by oxylipins. One of the main defence mechanisms of plants is the activation of biosynthesis and accumulation of secondary metabolites, including terpenoids, alkaloids, and phenylpropanoids⁴⁴. An understanding of the complex signalling network brought on by different environmental stresses and their patterns of similarities is shown in Table 4⁴⁵.

When exposed to heavy metals, plants react differently in terms of the synthesis and accumulation of bioactive molecules. The biosynthesis of secondary metabolites is adversely affected by heavy metal stress in certain species, such as *Matricaria recutita*. On the other hand, under comparable circumstances, other plants show increased production of these chemicals. Research has reported that heavy metals can stimulate secondary metabolite synthesis in specific medicinal plants (see Table 5)⁴³. However, the safety of using heavy metals to boost metabolite production depends on which part of the plant is intended for consumption¹¹.

Human health risks: When consumed, inhaled, or, in certain situations, applied topically, heavy metals like arsenic, cadmium, lead, chromium, mercury, silver, selenium, and barium can be extremely harmful to one's health. Although naturally occurring, industrial processes and environmental contamination can result in hazardous amounts of some metals. Exposure to plants is especially dangerous since pollutants can be ingested through smoking (tobacco or jimson weed), burning plant components (smudging), or volatilization in enclosed areas like sweat lodges. Exposure can also happen when contaminated plant materials are used in handicrafts, tonics, or other everyday activities. When harvested from contaminated locations, many plants known as hyperaccumulators pose a risk because they easily take heavy metals from the soil. Yet, soil particles that adhere to plant surfaces frequently pose a bigger risk than internal metal build-up, particularly for crops that grow in or near the soil, such as leafy greens and root vegetables³⁶.

Serious health consequences such as neurotoxicity, nephrotoxicity, and carcinogenicity can result from long-term exposure to HMs. The CNS (central nervous system) is disrupted by metals like lead and mercury, which may result in cognitive decline and illnesses like Parkinson's and Alzheimer's¹⁶. Lead and cadmium are especially detrimental to kidney function because they cause oxidative stress and hinder cellular repair. Long-term exposure to these chemicals is also linked to a higher chance of developing cancer because of mechanisms like DNA damage and disruption of cellular replication¹. Organizations like the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) have set exposure limits based on toxicological evidence in order to reduce these risks. For instance, in raw materials, the WHO suggests maximum allowable levels of 0.3 mg/kg for cadmium and 10 mg/kg for lead. Although several important components can also become harmful at high doses, many still lack well-defined limits¹¹.

Table 3: The impact of heavy metals on both enzymatic and non-enzymatic antioxidants in medicinal plants^{26,43}

Plant names	Metal	Amount of heavy metals	Plant Component	Plant growth system	Common enzymatic response	Common non-enzymatic response
<i>Artemisia annua</i> L.	As, Cr, Na	0-500 μ M, 0-160 mM	Root and shoot	Hydroponic culture	CAT \uparrow , SOD \downarrow	TBARS \downarrow
<i>Bacopa monnieri</i> (L.) Pennell	Cd	50-100 μ M	Shoot and root	Hydroponic culture	SOD \uparrow , GPX \uparrow , CAT \uparrow , APX \uparrow	AsA \downarrow , Cysteine \downarrow , Cysteine \downarrow , NPSH \downarrow , NPSH \downarrow , TBARS \downarrow
<i>Bruguiera gymnorrhiza</i> (L.) Lam.	Na, Cd, Pb, Hg	750 μ M	Root and leaves	Soil	CAT \downarrow , CAT \downarrow , LPO \downarrow , POD \downarrow , SOD \downarrow	-
<i>Camellia sinensis</i> (L.) Kuntze	Cu (II)	50-600 μ M	Leaves and roots	Hydroponic culture	APX \uparrow , CAT \uparrow , SOD \uparrow , POD \uparrow	Phenol \uparrow , MDA \uparrow
<i>Cardaminopsis arenosa</i> (L.) HAYEK	Fe, Cu	2,632.5 and 74.1 mg/kg	Leaves	Hydroponic culture	NPSH \uparrow , GSH \uparrow	-
<i>Cleome gynandra</i> L.	Cu, Cd	200mg/ 1000 kg	Plant	Soil	CAT \uparrow , SOD \uparrow	GSH \uparrow , Phenolics \downarrow , Proline \downarrow
<i>Coriandrum sativum</i> L.	Pb	0-1500 mg/kg	Plants	Soil	SOD \uparrow , POD \uparrow , CAT \downarrow	Flavonoid \uparrow , MDA \uparrow , Vitamin C \downarrow , Soluble proteins
<i>Egeria densa</i> (Planch.) Casp.	Cd	100 μ mol	Leaves and Shoots	Hydroponic culture	CAT \uparrow , SOD \downarrow	Carotenoids \downarrow , PSH \downarrow , NPSH \downarrow
<i>Erigeron annuus</i> (L.) Desf.	Cd	0-200 μ M	Leaves, shoot, and root	Hydroponic culture	POD \uparrow , CAT \downarrow , SOD \downarrow	GSH \uparrow , MDA \uparrow , PC \downarrow , NPT \downarrow , Proline \downarrow
<i>Glycyrrhiza uralensis</i> Fisch. ex DC.	Cd	100 mg/L	Leaves, shoot, and root	Soil	CAT \downarrow , POD \downarrow , SOD \downarrow	-
<i>Helianthus annuus</i> L.	Cr	0.25 mM	Plant	Soil	CAT \downarrow , GSH \downarrow , SOD \downarrow	Vitamin A, B, C \downarrow , Proline \uparrow , β -carotene \downarrow
<i>Hypericum Perforatum</i> L.	Cd	0-10 μ M	Shoots Root	Hydroponic	PAL \downarrow , PAL \downarrow	Ascorbic acid \downarrow , Epicatechin \downarrow , Glycine \downarrow , Flavonols \downarrow , MDA \uparrow , GSH \downarrow , GSSG \downarrow , Procyanidins \downarrow , Proline \downarrow , Total soluble phenols \downarrow , Epicatechin \downarrow , Flavonols \downarrow , Procyanidins \downarrow , Total soluble phenols \downarrow
<i>Jatropha curcas</i> L.	Al	3 mM	Seedling	Hydroponic culture	CAT \downarrow , CAT \downarrow , PAL \downarrow , POD \downarrow , SOD \downarrow	-
<i>Kandelia candel</i> (L.) Druce	Pb, Cd, Hg	0.2-1.0 mg/L	Root and leaves	Soil	CAT \downarrow , SOD \downarrow , CAT \downarrow	-
<i>Lemna minor</i> L.	Co	0-1 mM	Plants	Hydroponic culture	SOD \downarrow	TBARS \downarrow
<i>Lonicera japonica</i> Thunb.	Cd	0-200 mg/kg	Leaves	Soil	APX \uparrow , GR \uparrow , DHAR \uparrow , MDHAR \uparrow	GSH \uparrow , GSSG \downarrow , H ₂ O ₂ \uparrow , NPT \downarrow , Proline \downarrow
<i>Matricaria chamomilla</i> L.	Mn	0 and 1000 μ M	Shoots	Soil	APX \uparrow , CAT \uparrow , GR \downarrow , GPX \downarrow	AsA \downarrow , NPT \downarrow , Soluble phenols \downarrow , Soluble proteins \downarrow ,
<i>Mentha piperita</i> L.	Ni	100-500 μ M	Leaves and roots	Hydroponic system	APX \uparrow , POD \uparrow , CAT \uparrow , SOD \uparrow	Carotenoids \downarrow , MDA \uparrow , H ₂ O ₂ \uparrow , Protein \downarrow
<i>Mentha spicata</i> L.	Cr, Ni	0-30,512 μ g/g, 0-60 μ g/g	Stem, root, and leaves	Soil and sludge	SOD \uparrow , POD \uparrow , CAT \uparrow ,	MDA \downarrow , Proline \downarrow

Table 3: Continue

Plant names	Metal	Amount of heavy metals	Plant Component	Plant growth system	Common enzymatic response	Common non-enzymatic response
<i>Nicotiana tabacum</i> L.	Cd	0-500 µM	Plants	Hydroponic culture	APX↑, SOD↑, GPX↑, CAT↑	GSH↑, GSSG↑, Proline↑
<i>Ocimum basilicum</i> L.	Cd (II) and Al (III)	0-100 mg/kg	Epigeal parts	Soil	DPPH↑	Flavonoids↓, Flavanols↓, Phenols↓
<i>Olea europaea</i> L.	Cd	0.25 µg/g	Leaves and root	Soil	CAT↑, GPX↑, SOD↑	TBARS↑, Proline↑
<i>Origanum vulgare</i> L.	Cu	0-1000 ppm	Leaves	Soil mixed with	-	Anthocyanins↓, Proline↑, MDA↑, Carotenoids↓, Total Phenols↓
<i>Parthenium hysterophorus</i> L.	Pb	4.30 to 9.56 mg/kg	Root	Soil	-	Citric acid _R ↑
<i>Pfaffia glomerata</i> (Spreng.) Pedersen	Cd	50 µM	Leaves and root	Hydroponic culture	APX _L ↑, APX _R ↓, CAT _L ↓, GPX _L ↑, GPX _R ↑, GR _L ↑, GR _R ↓, SOD↑	-
<i>Plantago lanceolata</i> L.	Cu, Pb	2964 mg/kg	Leaves	Soil	-	NPSH↑, GSH↑
<i>Polygonatum sibiricum</i> F.Delaroche	Cd	0-54.60 mg/kg	Aerial parts and roots	Soil	CAT↑, SOD↑, POD↓	Polysaccharide↑
<i>Salicornia brachiata</i> Roxb.	Cd, As	3 mg/kg, 150 mg/kg	Flower	Soil	CAT↑, SOD↑	Proline↑
<i>Salvia officinalis</i> L.	Pb	0-400 µM	Leaves	Hydroponic culture	GPX↑, APX↑, GR↑, SOD↑	H ₂ O ₂ ↑, Protein↓, MDA↑
<i>Silybum marianum</i> (L.) Gaertn.	Cd	30 mg/kg	Seedling	Hydroponic culture	-	Proline↑
<i>Solanum nigrum</i> L.	Cr	0-1 mM	Leaves roots	Soil	SOD↑, POD↑	Proline↑ Malic acid↓, Citric acid↑
<i>Trifolium resupinatum</i> L.	Cd	0.5 mM	Root and shoot	Soil	CAT↓, POD↑	-
<i>Urtica dioica</i> L.	Cd	0-0.09 mM	Stem, root, and leaves	Hydroponic culture	GR↑, GST↑, GSH-Px↑	GSSG↑, GSH↑, LPO↑
<i>Withania somnifera</i> (L.) Dunal	Fe	25, 50, 100 and 200 µM	Root and leaves	Hydroponic culture	CAT↑, GPX↑	-
<i>Zygophyllum album</i> L.f.	Al, Cu, Zn, Fe	100 µM	Shoot	Soil	APX↑, ASO↑, CAT↓, GPO↑, LPO↑, SOD↑	-

Enzymatic antioxidants: POD: Peroxidase, SOD: Superoxide dismutase, CAT: Catalase, GPX: Guaiacol peroxidase, APX: Ascorbate peroxidase, GR: Glutathione reductase, GST: Glutathione S-transferase, DPPH: Radical scavenging activity, GPO: Guaiacol peroxidase, DHAR: Dehydroascorbate reductase, MDHAR: Monodehydroascorbate reductase, PAL: Phenylalanine ammonia-lyase activity, NR: Nitrate reductase, GSH-Px: Glutathione peroxidase, PPO: Polyphenol oxidase, p5CS: Pyrroline-5-carboxylate synthase, Non-enzymatic antioxidants: MDA: Malondialdehyde, H₂O₂: Hydrogen peroxide, AsA: Ascorbic acid, NPT: Non-protein thiols, GSH: Reduced glutathione, GSSG: Oxidized glutathione, NO: Nitrite-derived nitric oxide, DHASC: Dehydroascorbate, ASC: Ascorbate, LPO: Lipid peroxidation, TBARS: Thiobarbituric acid reactive substances, PC: Phytochelatin, "↑": Increase, "↓": Decrease, "↑" indicates an increase in the parameter and "↓" indicates a decrease in the parameter

Detection and monitoring of heavy metals

Since HMs remain in the environment and pose health hazards, it is imperative that they be detected and monitored. Numerous analytical methods and sampling procedures are used to provide precise measurement and quality control. Although Atomic Absorption Spectroscopy (AAS) is a portable and affordable technique that can be used to detect low quantities of heavy metals, it might not be sensitive enough for some metals¹⁷. Although it can be costly, Inductively Coupled Plasma Mass Spectrometry (ICP-MS), which is known for its great sensitivity and capacity to examine numerous elements at once, is perfect for examining complicated matrices. X-ray fluorescence (XRF), a non-destructive approach that makes it easier to analyze solid samples quickly and is particularly helpful for *in-situ* monitoring, is another

Table 4: An overview of certain signals caused by heavy metals in relation to other environmental stressors^{12,26,43}

Heavy metal	Signal	Other stress conditions	Cellular responses
Cu	Calcium fluxes	Drought, salinity, and cold	2nd signalling molecules, Phosphoprotein cascades
Cd, Cr	Mitogen-activated protein kinase	Pathogen interaction and osmotic stress	Stress-responsive genes and transcription factor activation
Fe	pH shifts	Pathogen interaction	Secondary metabolism induction
Co, Zn	Ethylene or abscisic acid	Drought, salinity, and cold	Calcium signaling and guard cell regulation (water balance)
Cd, Cu	Jasmonic acid (JA)	Sugar, pathogen interaction, salinity, and drought	Stress response, formation and stimulation of secondary metabolism
Nearly all heavy metals at higher concentrations, including redox-active metals	ROS	Contact with pathogens, drought, salinity, cold, and intense light	Stress-responsive genes, phosphoprotein cascades, transcription factors, and antioxidant defense are all activated

Table 5: The secondary metabolites of several plants increase under HM stress

Plant species	Heavy metal	Compound	Medicinal properties	References
<i>Artemisia annua</i> L.	As (5, 7.5 µg/mL)	Artemisinin	Antimalarial, antifungal, and anti-inflammatory	Ahmad <i>et al.</i> ⁴³
<i>Bacopa monnieri</i> (L.) Pennell	Zn (0.12 mM)	Bacoside A	Neuroprotection against amnesia, dementia, Alzheimer's disease, and schizophrenia	Hlihor <i>et al.</i> ²⁶
<i>Camellia sinensis</i> (L.) Kuntze	Cd (100 µmol/L)	Polyphenols	Anti-carcinogenic, anti-inflammatory, and anti-mutagenic effects	Ghafoor <i>et al.</i> ⁴¹
<i>Catharanthus roseus</i> (L.) G. Don	Cd (0.05-0.4 mM)	Ajmalicine	Anticancer and antidiabetic properties	Izah <i>et al.</i> ⁴²
<i>Hibiscus sabdariffa</i> L.	Co (20 mg/kg), Ni (25 mg/kg)	Flavones and anthocyanins	Intestinal infections, arteriosclerosis, and diseases of the stomach and liver	Ghafoor <i>et al.</i> ⁴¹
<i>Hypericum perforatum</i> L.	Cr (0.1 µM)	Hypericin and pseudohypericin	Wounds, nerve pain, and skin diseases	Zhang <i>et al.</i> ³²
<i>Jatropha curcas</i> L.	Pb (63.31 ppm), Hg (0.03 ppm)	Alkaloids, flavonoids, and phenolic compounds	Anti-inflammatory and insecticidal properties	Bin <i>et al.</i> ³⁷
<i>Matricaria chamomilla</i> L.	Cu, Cd (60-120 µM)	Umbelliferone, herniarin, and sesquiterpenes	Spasmolytic and anti-inflammatory properties	Maleki <i>et al.</i> ²⁷
<i>Mentha piperita</i> L.	Pb (300 and 600 ppm)	Menthol	Used for digestive issues such as bloating, irritable bowel syndrome (IBS), and indigestion	Safarian <i>et al.</i> ⁴⁴
<i>Nicotiana tabacum</i> L.	Cd	Alkaloids and flavonoids	Antioxidant	Alam and Sharma ²⁰
<i>Ocimum tenuiflorum</i> L.	Cr (20 µM)	Eugenol	Antispasmodic and antibacterial effects	Maleki <i>et al.</i> ²⁷
<i>Ononis arvensis</i> L.	Ni, Co, Cr	Flavonoids (6.3 µmol)	Anti-inflammatory, cardioprotective, antiproliferative, and antioxidant properties	Hu <i>et al.</i> ³¹
<i>Phyllanthus amarus</i> Schumach. and Thonn.	Cd (0.1-1 mM)	Hypophyllanthin	Hepatoprotective and diuretic properties	Pehoiu <i>et al.</i> ²⁹
<i>Rheum palmatum</i> L.	Cd (10 µM)	Anthracene derivatives	Antioxidant properties	Srivastava and Jain ³⁰
<i>Salvia officinalis</i> L.	Cr (20-100 ppm)	Rosmarinic acid	Relieves stress, aids digestion, and promotes memory	Ramakrishnan and Nagella ⁴⁵
<i>Salvia miltiorrhiza</i> Bunge	Cu, Ag, Fe, Zn, Mn (15-40 µM)	Tanshinone	Coronary artery dilation and broad-spectrum bactericidal activity	Pan and Wang ³³
<i>Solanum nigrum</i> L.	Zn (46 and 90 µg/g d.wt.), Pb (71 and 89 µg/g d.wt.)	Flavonoids and phenols	Antioxidant, anti-inflammatory, and anti-tumor properties	Ghafoor <i>et al.</i> ⁴¹
<i>Thalictrum rugosum</i> Poir.	Cu (20-500 µM)	Berberine	Treatment of infectious diarrhea and dysentery	Pan and Wang ³³
<i>Withania somnifera</i> (L.) Dunal	Cd (0-200 ppm), Pb (0-2000 ppm), and Hg (10-100 ppm)	Withanolides	Antioxidant and anxiolytic effects	Saebo <i>et al.</i> ³⁵

often-used technology. Digestion or extraction procedures are often used in effective sample protocols to remove contaminants and concentrate analytes, guaranteeing reliable results. Furthermore, using blanks and duplicates, as well as routine calibration with established standards, helps preserve the accuracy and dependability of analytical data¹⁴.

Mitigation strategies: To manage contamination from sources like industrial pollutants and agricultural practices, mitigation strategies are crucial. To efficiently manage heavy metal pollution, several strategies have been devised. According to Alzoubi *et al.*⁷, microbial strategies employ microorganisms to detoxify heavy metals through enzymatic conversion, protein binding, and metal exclusion to less toxic forms. To decrease the bioavailability of heavy metals in the soil, phytoremediation uses plants to stabilize and absorb the metals. Furthermore, organic and inorganic substances like lime, compost, and charcoal can be used as soil amendments and chelators to improve the immobilization of heavy metals and further reduce their bioavailability. Furthermore, enforcing regulations and safety standards for herbal products is crucial; governments and organizations must establish and monitor permissible levels of heavy metals in agricultural soils and herbal products; compliance with these standards is crucial to prevent health risks, including chronic conditions linked to heavy metal exposure⁴². Good Agricultural and Collection Practices (GACP) also play a crucial role in minimizing contamination, ensuring that herbal products are grown and harvested with appropriate soil management and heavy metal level monitoring^{14,42}.

CONCLUSION

Exposure to heavy metals (HMs) in medicinal plants induces stress responses that activate defense mechanisms to mitigate physiological and biochemical damage. While some metals serve as essential micronutrients, their excess leads to toxicity, resulting in overproduction of reactive oxygen species (ROS) and oxidative stress. Plants counteract this through enzymatic and non-enzymatic antioxidant systems, though their efficiency depends on the intensity and duration of exposure. Prolonged stress can disrupt the balance between ROS generation and antioxidant defense, ultimately affecting plant metabolism and medicinal quality. This study highlights that heavy metal accumulation varies with plant species, metal type, and exposure pathways, influencing antioxidant activity and secondary metabolite composition. These biochemical changes underscore the importance of stringent quality control and avoiding cultivation or collection from contaminated areas to ensure the safety and efficacy of plant-based medicines. Future research should focus on expanding studies across diverse medicinal species, elucidating genetic and molecular mechanisms underlying stress tolerance, and examining the impact of heavy metals on key bioactive compounds such as flavonoids and phenolics. Integrating approaches like transcriptomics, phytoremediation, and sustainable management strategies will be essential to protect medicinal plants and support their long-term therapeutic value in polluted environments.

SIGNIFICANCE STATEMENT

This study highlights the dual role of medicinal plants in tolerating heavy metal stress while maintaining the production of bioactive compounds with therapeutic value. By systematically linking specific plant species, heavy metal exposure levels, and associated phytochemicals, the study provides insight into how stress conditions influence medicinal properties. These findings are significant for phytoremediation strategies, sustainable use of contaminated soils, and the pharmaceutical potential of stress-adapted plants. Furthermore, the compiled data support future research on optimizing medicinal plant cultivation under environmental stress while ensuring safety and efficacy.

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