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Cadmium contamination in medicinal plants: Bioaccumulation, phytochemical alterations, and implications for human health

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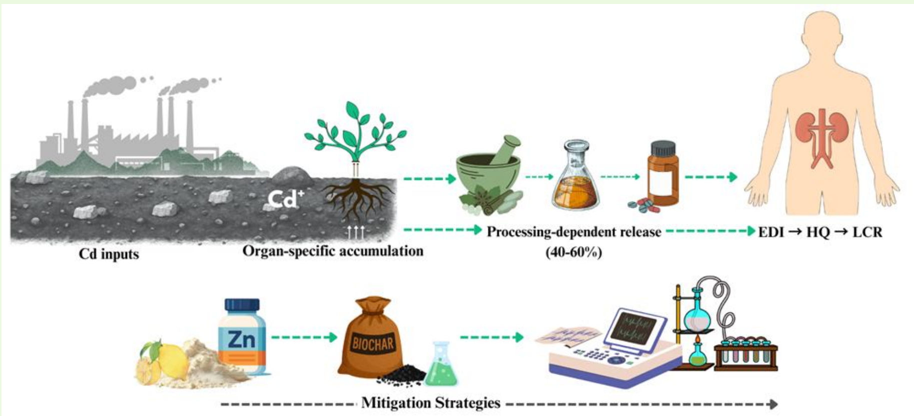
Abstract

Cadmium (Cd) contamination in medicinal plant systems is a critical concern because it can affect both toxicological safety and the biosynthesis of bioactive phytochemical that determine therapeutic efficacy. Unlike staple food crops, medicinal plants are frequently cultivated in marginal or contaminated soils, processed into concentrated preparations, and consumed chronically or in polyherbal formulations, thereby generating exposure dynamics distinct from those of conventional dietary pathways. This review synthesizes current evidence on Cd sources in cultivation systems, soil factors regulating bioavailability, molecular uptake mechanisms involving zinc-regulated transporter/iron-regulated transporter-like protein (ZIP), natural resistance-associated macrophage protein (NRAMP), and heavy metal ATPase (HMA) transporters, and species-specific accumulation patterns across leaf- and root-based medicinal taxa. Reported Cd concentrations in selected species, including *Panax notoginseng* and *Salvia miltiorrhiza*, exceed the WHO (World Health Organization) benchmark of 0.3 mg/kg in certain regions, with hazard quotient (HQ) and lifetime cancer risk (LCR) values approaching or surpassing acceptable thresholds. Processing methods further modify exposure, as *in vitro* digestion studies indicate 40-60% gastric bioaccessibility of plant-bound Cd, challenging reliance on total concentration-based risk estimates. In addition to toxicological implications, Cd exposure may alter phytochemical composition, thereby influencing pharmacological activity and therapeutic consistency of medicinal plant products. Current assessment frameworks predominantly employ deterministic models derived from food safety paradigms and may inadequately capture cumulative intake, preparation-specific extraction efficiencies, and long-term toxicokinetic burden. Integrated mitigation strategies, including low Cd fertilizer selection, soil pH optimization, competitive nutrient management, phytoremediation, cultivar screening, and supply-chain monitoring, provide actionable pathways for exposure reduction. Advancing phytomedicine-specific exposure modelling that links soil chemistry, plant physiology, processing effects, and human toxicokinetic is essential for safeguarding the safety, regulatory credibility, and global sustainability of medicinal plant-based therapeutics.



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1. Introduction

Medicinal plants remain foundational to global healthcare systems, with an estimated 70-80% of populations in developing regions relying on plant-based remedies for primary health management (Ekor, 2014). The global phytomedicine market continues to expand rapidly, driven by increased consumer preference for natural therapeutics and integrative medicine approaches. However, the safety and quality of medicinal plant materials are increasingly challenged by environmental contamination, particularly by Cd, a non-essential and highly toxic heavy metal (Clemens *et al*., 2016; Luo *et al*., 2021). Importantly, Cd contamination not only introduces toxicological risk but may also influence the biosynthesis and stability of bioactive phytochemical constituents, potentially altering the pharmacological efficacy of medicinal plants. Such interactions between metal stress and secondary metabolism are critical in phytomedicine, where therapeutic outcomes depend on the integrity and consistency of bioactive compounds.

Cd is characterized by long environmental persistence, high mobility under acidic conditions, and an exceptionally long biological half-life in humans. Chronic exposure is associated with nephrotoxicity, skeletal demineralization, cardiovascular dysfunction, and carcinogenic potential. While Cd contamination in staple food crops has been extensively investigated, comparatively less integrative attention has been directed toward medicinal plant systems.

Unlike food crops, medicinal plants are often cultivated in marginal soils, harvested from wild populations in industrially influenced areas, or processed into concentrated powders, decoctions, and extracts that may amplify contaminant exposure per unit intake. Furthermore, polyherbal formulations and long-term therapeutic consumption patterns introduce cumulative exposure scenarios that are rarely accounted for in conventional risk assessment models (Lekeux *et al*., 2019). These characteristics distinguish medicinal plants from general dietary crops and warrant system-specific evaluation.

Existing studies largely focus on isolated measurements of Cd concentration in plant tissues or single-product risk assessments (Zheng *et al*., 2026; Tchounwou *et al*., 2012). However, important gaps persist, including limited species-specific bioaccumulation comparisons, insufficient consideration of bioaccessibility under processing conditions, underrepresentation of cumulative exposure frameworks, and a lack of integration between soil chemistry, plant physiology, and human health risk models.

This review synthesizes current evidence on Cd contamination in medicinal plant systems, integrating soil-plant transfer dynamics, molecular uptake mechanisms, species-specific accumulation patterns, processing-induced bioavailability changes, quantitative risk assessment approaches, regulatory frameworks, and mitigation strategies to support evidence-based quality assurance strategies in phytomedicine and to ensure both safety and pharmacological consistency of medicinal plant-based therapies. By specifically linking Cd bioaccumulation patterns in medicinal plants with preparation-dependent exposure pathways and human health risk assessment frameworks, this review provides an integrated phytomedicine-focused perspective that is often overlooked in conventional heavy metal contamination studies. However, existing studies primarily focus on environmental contamination and toxicological assessment, with limited integration of phytochemical alterations and pharmacological implications in medicinal plant systems, highlighting a critical research gap addressed in this review. Plant names used in this review are reported in accordance with accepted botanical nomenclature based on standard taxonomic databases. The information presented in this review is synthesized from peer-reviewed research articles, review papers, and relevant reports focusing on Cd contamination, plant uptake mechanisms, phytochemical responses, and human health implications in medicinal plant systems. Emphasis was placed on studies providing quantitative data, mechanistic insights, and relevance to phytomedicine.

2. Environmental sources influencing Cd entry and uptake in medicinal plants

2.1 Anthropogenic sources

Cd contamination in medicinal plant systems primarily originates from anthropogenic environmental inputs that influence metal availability for plant uptake. Among these, phosphate fertilizers represent the most significant contributor (McLaughlin *et al*., 1996). Phosphate rock, the primary raw material for fertilizer production, contains Cd at concentrations ranging from 0.1 to 170 mg/kg depending on geological origin. Repeated fertilizer application results in gradual soil Cd enrichment, with estimated annual loading rates of 1-10 g Cd/ha (Al-Khayri *et al*., 2023; Grant *et al*., 1998). In medicinal plant cultivation systems, phosphorus fertilizers are typically applied in the range of 40-120 kg P_2O_5/ha depending on crop type and management practices, which can contribute to cumulative Cd buildup over time, particularly under intensive cultivation conditions.

Industrial emissions constitute another major pathway. Non-ferrous metal smelting industries (particularly zinc and lead smelting), mining operations, battery manufacturing units, electroplating industries, and pigment production facilities are among the primary sources releasing Cd into the surrounding environment. These activities contribute to atmospheric deposition and localized soil contamination in adjacent agricultural areas, thereby increasing the risk of uptake by medicinal plants (Pacyna *et al*., 2009). Soil Cd concentrations in industrially impacted regions have been reported to exceed 10 mg/kg, substantially higher than natural background levels of 0.1-0.5 mg/kg (Ogbonna *et al*., 2018; Chernikova *et al*., 2025). Medicinal plants cultivated near such zones frequently exhibit elevated tissue Cd levels, indicating effective soil-plant transfer.

The application of sewage sludge as an organic amendment further contributes to Cd loading. Municipal sludge typically contains 2-15 mg Cd/kg dry weight; although industrial effluents can significantly elevate concentrations (Singh and Agrawal, 2008). While sludge improves soil organic matter and nutrient status, its long-term application may enhance heavy metal accumulation, particularly in systems lacking stringent monitoring (Al-Khayri *et al*., 2023; Hlihor *et al*., 2022). Irrigation water quality represents an additional, often underrecognized pathway. In regions affected by mining discharge, industrial effluents, or wastewater reuse, irrigation water may contain measurable Cd concentrations. Continuous irrigation with contaminated water can lead to progressive soil enrichment and increased plant uptake. This pathway is particularly concerning in water-scarce regions where treated wastewater is increasingly used for cultivation (Al-Khayri *et al*., 2023).

Collectively, these anthropogenic inputs create cumulative contamination pressures in medicinal plant cultivation systems. Unlike staple food crops, which are often cultivated under regulated agricultural frameworks, medicinal plants may be grown in marginal lands or wild-harvested from contaminated environments, increasing variability in Cd exposure risk.

2.2 Environmental factors

Environmental conditions such as temperature and humidity play a critical role in regulating contaminant dynamics and microbial activity in plant systems, influencing overall safety and quality of plant-derived products (Gupta *et al*., 2026). The uptake of Cd by medicinal plants is strongly influenced by environmental factors that regulate Cd mobility and availability in cultivation systems. Among these, soil pH is a dominant determinant of Cd solubility and plant uptake (Sauvé *et al*., 2000). Under acidic conditions, Cd^{2+} remains in more soluble and exchangeable forms, increasing its availability for root absorption, whereas neutral to alkaline conditions promote precipitation and adsorption processes that reduce Cd mobility (Hlihor *et al*., 2022; Yao *et al*., 2022).

Soil organic matter also plays an important role in modulating Cd behaviour through adsorption and complexation mechanisms (Zhao *et al*., 2013). Stable organic fractions generally immobilize Cd by binding metal ions, while dissolved organic compounds may increase mobility by forming soluble complexes (Al-Khayri *et al*., 2023). In addition, soil texture and cation exchange capacity influence Cd retention, with clay-rich soils typically exhibiting stronger adsorption than coarse-textured soils (Barbes *et al*., 2023; Hlihor *et al*., 2022).

Rhizosphere microbial communities play a critical role in regulating metal bioavailability by altering soil pH, producing chelating compounds, and influencing nutrient cycling processes, thereby affecting cadmium uptake in plants (Kumar *et al*., 2024). Competitive interactions with essential cations further regulate Cd uptake by medicinal plants. Zinc and calcium compete with Cd at root uptake sites due to chemical similarity (Smolders *et al*., 2001). Adequate Zn and Ca supply can therefore suppress Cd accumulation, whereas nutrient deficiencies may enhance uptake through non-specific transport pathways (Zhu *et al*., 2016; Hlihor *et al*., 2022). Collectively, these environmental factors determine the bioavailable fraction of Cd that ultimately controls accumulation in medicinal plant tissues.

3. Mechanisms of Cd uptake in medicinal plants

The mechanistic insights discussed in this section are synthesized from recent experimental and review studies focusing on Cd uptake, transport, and accumulation in medicinal plant systems. Cd uptake in medicinal plants occurs primarily through non-specific transport systems originally evolved for essential divalent cations (Tao and Lu, 2022). Following its presence in soil solution as Cd^{2+} , the metal is transported to root surfaces *via* mass flow and diffusion, where it may either bind to cell wall components or enter root cells through membrane transporters.

Unlike essential micronutrients, Cd has no dedicated uptake pathway. Instead, it exploits transporters involved in zinc, iron, and manganese acquisition (Figure 1). Members of the ZIP and NRAMP families play central roles in Cd entry into root cells (Al-Khayri *et al*., 2023; Hlihor *et al*., 2022, Huang *et al*., 2020; Tao and Lu, 2022). Under Zn or Fe deficiency, these transporters are often upregulated, inadvertently enhancing Cd uptake (Inoue *et al*., 2024; Huang *et al*., 2020). This competitive interaction partly explains the inverse relationship observed between soil Zn availability and plant Cd accumulation (Zhu *et al*., 2016).

A substantial proportion of absorbed Cd remains retained in roots through vacuolar sequestration and cell wall binding. However, a fraction is loaded into the xylem and translocated to aerial tissues. Xylem loading involves transporter proteins such as HMA2 and HMA4, enabling upward movement with the transpiration stream (Hlihor *et al*., 2022). The extent of translocation varies across species and is commonly quantified by the translocation factor (TF). Many medicinal plants exhibit TF values <1 (Huang *et al*., 2020; Niu, 2023), indicating preferential root retention, although shoot accumulation remains significant in certain species.

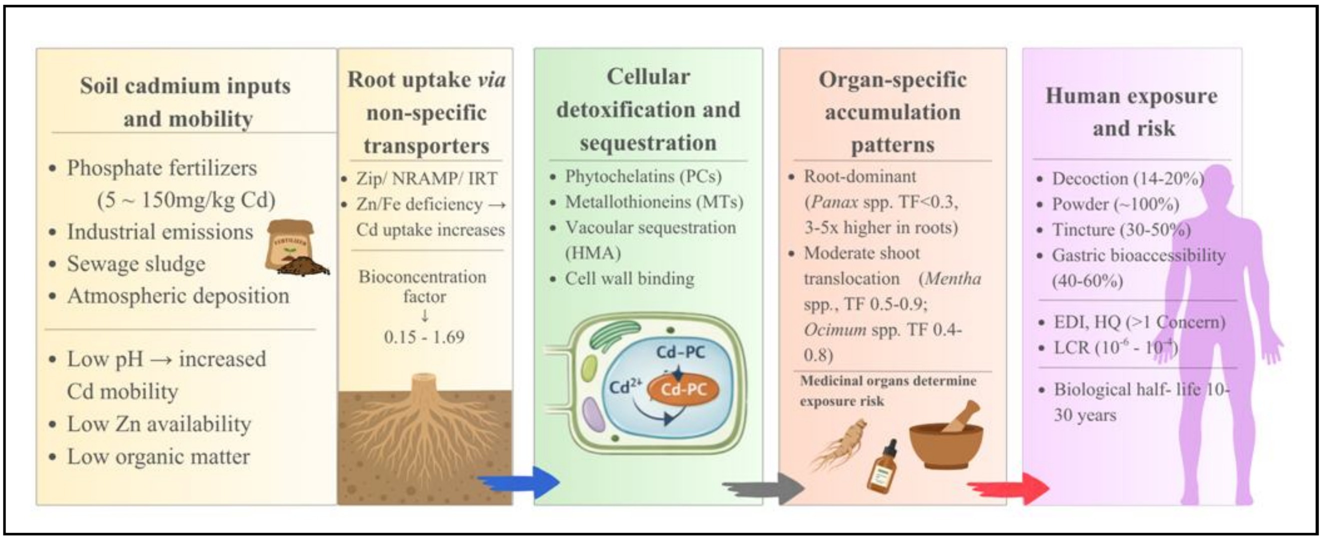

Figure 1: Schematic representation of Cd entry into medicinal plant systems, illustrating environmental sources, root uptake *via* non-specific divalent metal transporters (ZIP, NRAMP), intracellular sequestration and xylem translocation, organ-specific accumulation, and subsequent exposure pathways during processing and consumption.

The chemical form of Cd influences its mobility within plant tissues (Yu *et al*., 2024). Complexation with organic acids or amino acids enhances transport efficiency, whereas precipitation or strong binding to cell wall components limits redistribution. Species-specific variation in transporter expression, chelation capacity, and compartmentalization efficiency ultimately determines accumulation patterns in medicinal plant organs.

Overall, Cd dynamics in medicinal plants reflect an interplay between non-specific uptake systems, intracellular detoxification pathways, and differential translocation capacities-processes that collectively shape organ-specific accumulation and associated exposure risks (Tao and Lu, 2022; Huang *et al*., 2020). In addition to influencing metal accumulation patterns, Cd-induced stress may disrupt metabolic pathways involved in secondary metabolite biosynthesis, thereby affecting the composition and stability of bioactive phytochemicals that determine medicinal efficacy.

4. Species-specific bioaccumulation patterns in medicinal plants

The species-specific accumulation patterns summarized in this section are based on reported data from multiple experimental studies across different medicinal plant species. Cd accumulation in medicinal plants varies considerably across species, plant organs, and environmental conditions (Table 1) (Luo *et al*., 2021). Leaf-based medicinal species such as *Mentha* spp. and *Ocimum* spp. frequently exhibit moderate Cd accumulation in aerial tissues, reflecting active translocation from roots, whereas root-based medicinal plants, including *Panax* spp. and *Withania somnifera* often demonstrates substantial Cd retention in below-ground organs. Variability in bioaccumulation is influenced by soil Cd concentration, plant genotype, transporter expression, and detoxification efficiency (Bashir *et al*., 2020; Luo *et al*., 2021; Zhu *et al*., 2016; Liu *et al*., 2022; Yao *et al*., 2022). Importantly, several studies report Cd concentrations exceeding the WHO permissible limit of 0.3 mg/kg in marketed herbal materials, underscoring species-specific vulnerability and quality control challenges (Nath *et al*., 2020; Liu *et al*., 2023).

Table 1: Comparative synthesis of Cd concentration ranges, accumulation behavior, and exposure implications in selected medicinal plant species used in phytomedicine

Species	Plant part and medicinal use	Cd concentration (mg/kg)	BCF/TF	Accumulation behavior	Exposure implications and WHO status
P. notoginseng	Root; circulatory tonic (powder/decoction)	0.43 (mean)	TF < 0.3	Strong root retention (3-5× shoot)	Chronic root consumption may elevate exposure; the WHO limit exceeded (Zhu *et al*., 2016)
P. quinquefolium	Root; adaptogen (powder/extract)	0.06-0.40	BCF 0.15-1.69	Moderate root accumulation	Partial exceedance depending on cultivation conditions (Geng *et al*., 2023)
S. miltiorrhiza	Root; cardiovascular TCM herb	0.324 (category mean)	NR	Root-dominant accumulation	Market samples frequently exceed regulatory limit (Yao *et al*., 2022)
W. somnifera	Root/leaf; adaptogen (Ashwagandha)	Dose-dependent (50-1000 µM exposure)	TF 0.6-0.8	Moderate translocation	Root powders may contribute to cumulative intake (Al-Khayri *et al*., 2023)
M. arvensis	Leaf; digestive herb (infusion/oil)	0.165	TF 0.5-0.9	Moderate shoot translocation	Infusion-based exposure pathway (Mohammed *et al*., 2024)
Ocimum spp.	Leaf; immunomodulatory herb	Dose-dependent	TF 0.4-0.8	Moderate root retention	Decoction extraction may influence exposure (Al-Khayri *et al*., 2023)

Abbreviations: BCF, Bioconcentration Factor (Plant Cd concentration/Cd concentration in soil; Cd, Cd; HQ, Hazard Quotient; mg/kg, milligrams per kilogram; NR, Not Reported; TCM, Traditional Chinese Medicine; TF, Translocation Factor; WHO, World Health Organization.

Species-dependent variation highlights the importance of integrating transfer factor (TF) and bioconcentration factor (BCF) metrics when evaluating risk. Also root-dominant accumulation reduces aerial contamination but may pose higher risk in root-based herbal preparations (Figure 2). Conversely, efficient translocation to leaves elevates exposure potential in leaf-derived formulations. Such variability emphasizes the need for species-specific monitoring rather than uniform regulatory assumptions. In addition, differences in Cd partitioning between plant organs may influence the concentration and stability of bioactive phytochemicals, thereby affecting the therapeutic quality and consistency of medicinal plant preparations.

5. Human health implications

5.1 Health effects of Cd exposure

Cd is a cumulative toxicant with a biological half-life of approximately 10-30 years in humans, leading to progressive accumulation primarily in the kidneys and liver (Nordberg *et al*., 2018). Beyond its direct toxicological effects, Cd exposure through medicinal plants may also influence the composition of bioactive phytochemicals, thereby affecting both safety and therapeutic efficacy. Chronic exposure, even at low doses (<1 µg/kg body weight/day), has been associated with measurable renal and skeletal effects in exposed populations (Hlihor *et al*., 2022; Satarug, 2019).

5.1.1 Renal toxicity

The kidney is the principal target organ of Cd toxicity (Doccioli *et al*., 2024). Approximately 30-60% of absorbed Cd accumulates in renal cortex tissues, where concentrations exceeding 200 µg/g wet weights have been linked to tubular dysfunction in chronically exposed individuals (Nordberg *et al*., 2018; Luo *et al*., 2021). Cd-metallothionein complexes are filtered and reabsorbed in proximal tubular cells, inducing oxidative stress and cellular damage. Epidemiological studies report increased proteinuria (Jiang *et al*., 2019) and reduced glomerular filtration rate in populations with urinary Cd levels >2 µg/g creatinine.

5.1.2 Skeletal effects

Cd exposure disrupts calcium metabolism and vitamin D activation, contributing to bone demineralization. Long-term exposure has been associated with increased risk of osteoporosis and fracture, particularly in populations with urinary Cd concentrations exceeding 5 µg/g creatinine (Hlihor *et al*., 2022; Wallin *et al*., 2016). Severe manifestations, such as Itai-Itai disease, were historically observed in individuals chronically exposed to contaminated food sources.

5.1.3 Cardiovascular and metabolic effects

Chronic Cd exposure has been associated with elevated blood pressure and increased risk of cardiovascular morbidity (Verzelloni *et al*., 2024). Meta-analyses suggest that individuals in higher Cd exposure categories exhibit a 1.2-1.6 fold increased risk of hypertension compared to lower exposure groups, although causality remains under investigation (Shi *et al*., 2020). Oxidative stress and endothelial dysfunction are proposed mechanistic pathways.

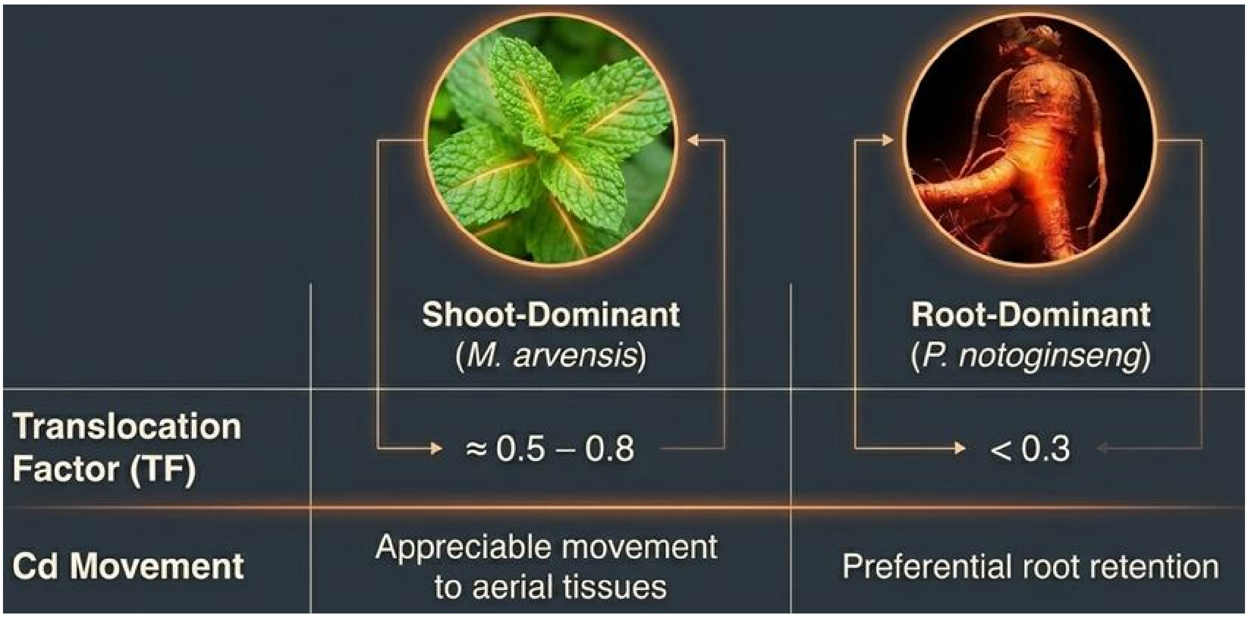

Figure 2: **Schematic representation of differential Cd partitioning in medicinal plant systems, illustrating contrasting translocation behaviour between shoot-dominant (*M. arvensis*) and root-dominant (*P. notoginseng*) accumulation patterns. Species exhibiting moderate translocation (TF~0.5-0.8) demonstrate appreciable Cd movement to aerial tissues, whereas low translocation (TF<0.3) results in preferential root retention. These accumulation dynamics directly influence exposure risk depending on the plant organ used for medicinal preparations.**

5.1.4 Carcinogenicity

Cd is classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (Rasin *et al*., 2025). Long-term occupational and environmental exposure has been linked to increased incidence of lung and renal cancers. Lifetime cancer risk estimates rise significantly when chronic intake exceeds established reference doses (Wang *et al*., 2021).

5.2 Quantitative risk assessment models

Human exposure to Cd through medicinal plant consumption is typically evaluated using estimated daily intake (EDI), hazard quotient (HQ), total hazard quotient (THQ), and lifetime cancer risk (LCR) frameworks (Kong *et al*., 2020; Geronimo *et al*., 2021). The EDI is calculated by integrating Cd concentration (mg/kg), ingestion rate, exposure frequency, and body weight. In several regional surveys of contaminated herbal products, reported EDI values ranged from 0.2 to >1.5 µg/kg body weight/day, with higher estimates exceeding the provisional tolerable intake levels recommended by international agencies (Nath *et al*., 2020).

The non-carcinogenic risk is assessed using the HQ, defined as the ratio of EDI to the oral reference dose (RfD). An HQ value greater than 1 indicates a potential health concern. Studies evaluating medicinal plant materials from industrially impacted regions have reported HQ values ranging from 1.2 to 3.5 for frequently consumed herbs, suggesting possible chronic risk under sustained intake scenarios (Liu *et al*., 2023). Carcinogenic risk is expressed as LCR, calculated using cancer slope factors. Acceptable LCR thresholds typically range between 10^{-1} and 10^{-4}. In certain contaminated herbal samples, estimated LCR values exceeded 10^{-4}, indicating elevated long-term carcinogenic probability under continuous exposure assumptions (Luo *et al*., 2021). However, most current assessments rely on total Cd concentration, introducing uncertainty where digestion-dependent bioaccessibility differs substantially from total content.

5.3 Exposure complexities in medicinal plant consumption

Risk assessment models for Cd exposure are generally adapted from food safety frameworks. However, medicinal plant consumption patterns differ substantially from conventional dietary intake. Herbal materials are commonly consumed as concentrated powders, decoctions, tinctures, or extracts, processing methods that can modify metal solubility and bioavailability (Figure 3). Thermal extraction during decoction may increase Cd release into aqueous fractions, potentially elevating systemic exposure compared with raw plant materials (Kong *et al*., 2020).

Unlike staple foods with relatively standardized consumption rates, medicinal plants are often used chronically for therapeutic purposes, sometimes over extended periods. Even when individual doses contain relatively low Cd concentrations, prolonged use may lead to cumulative intake. This concern is particularly relevant for root-based formulations, where Cd retention is frequently higher. Polyherbal preparations further complicate exposure estimation because simultaneous consumption of multiple contaminated ingredients may produce additive intake levels not reflected in single-herb HQ calculations.

Processing characteristics also influence effective exposure. Powdered herbal formulations theoretically deliver the full Cd content of the plant matrix, whereas alcoholic extracts may release only a portion of the total metal depending on solvent composition and extraction duration (Liu *et al*., 2023). In addition, in vitro gastrointestinal digestion studies indicate that approximately 40-60% of plant-bound Cd becomes bioaccessible under simulated gastric conditions (pH 1.5-2.0), suggesting that total concentration alone may not accurately represent systemic exposure (Zhang *et al*., 2022; Luo *et al*., 2021).

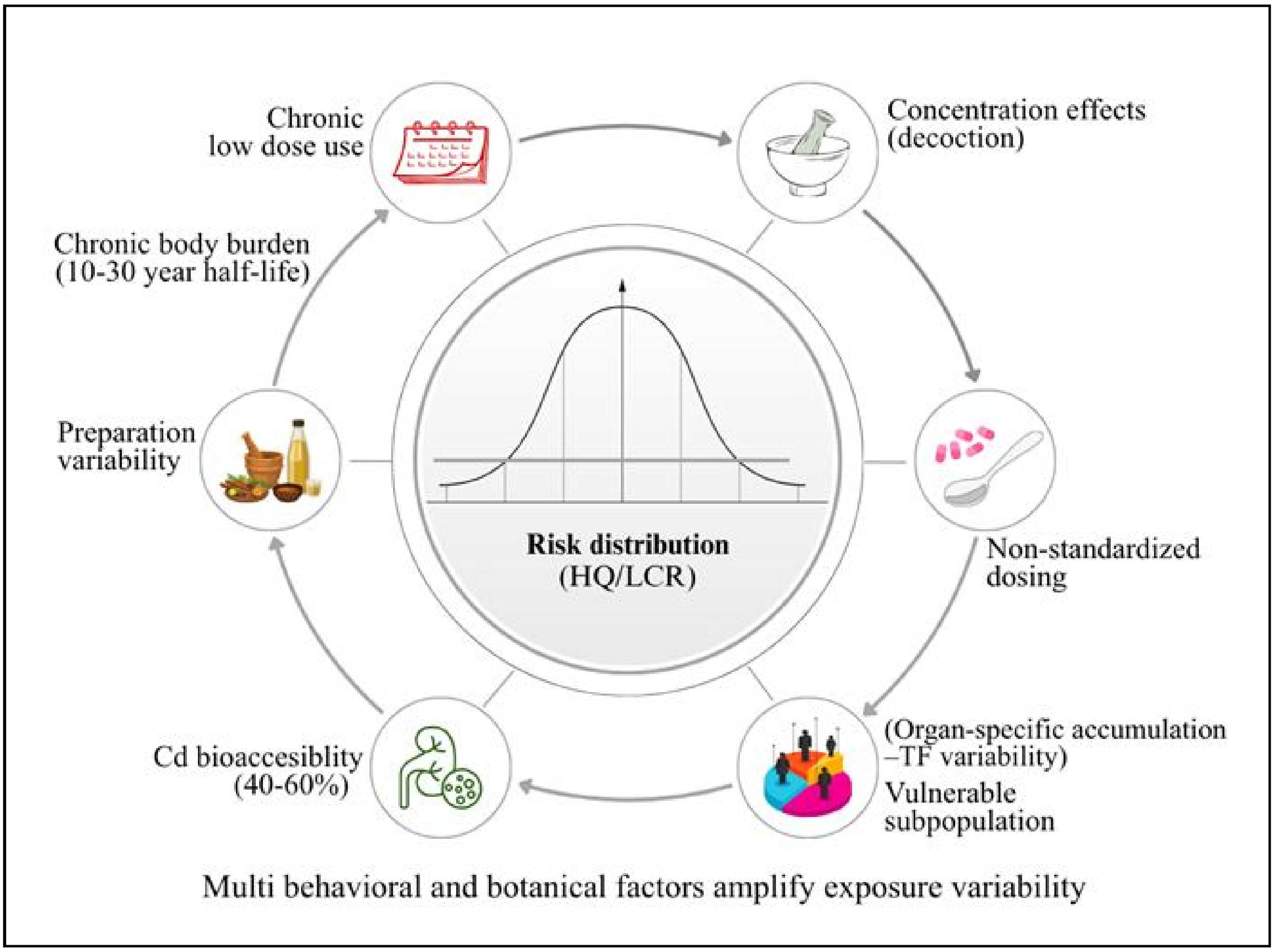

Figure 3: Conceptual model illustrating behavioural and preparation-related determinants that influence variability in Cd exposure and resulting risk distribution metrics (HQ, LCR). Factors including chronic therapeutic use, preparation variability (decoction, powder, extract), non-standardized dosing, phytochemical-metal interactions, and population susceptibility contribute to heterogeneity in exposure outcomes beyond deterministic point estimates.

5.4 Impact of Cd on phytochemical composition and pharmacological activity

Cd exposure not only contributes to metal accumulation in medicinal plants but also influences the biosynthesis of key phytochemical constituents that determine their therapeutic properties. Cd-induced oxidative stress can stimulate the production of secondary metabolites such as phenolics and flavonoids as part of the plant's defence response. While moderate increases in these compounds may enhance antioxidant capacity, excessive Cd stress can disrupt metabolic balance and reduce the overall quality and consistency of bioactive constituents (Al-Khayri *et al*., 2023; Faizan *et al*., 2024).

In several medicinal plant species, Cd exposure has been associated with alterations in essential oil composition, alkaloid content, and secondary metabolite profiles, potentially affecting pharmacological activities such as antimicrobial, anti-inflammatory, and antioxidant functions. For example, Cd stress in *Mentha* spp. has been reported to modify monoterpene biosynthesis pathways, which may influence therapeutic effectiveness despite apparent changes in metabolite concentration (Azimychetabi *et al*., 2021).

These observations highlight a dual concern in phytomedicine: Cd contamination not only introduces toxicological risk but may also alter pharmacological performance through changes in phytochemical composition. Therefore, evaluation of heavy metal contamination in medicinal plants should extend beyond concentration-based risk assessment to include its effects on phytochemical integrity and therapeutic efficacy. In addition to qualitative changes in phytochemical profiles, Cd exposure may also influence the quantitative balance between primary and secondary metabolites, leading to inconsistencies in therapeutic potency. Variability in stress response across species further complicates the predictability of such changes, highlighting the need for standardized evaluation of phytochemical integrity in contaminated medicinal plant systems.

6. Regulatory limits and safety standards

Regulatory authorities worldwide have established permissible limits for Cd in herbal materials. However, these thresholds are largely derived from food safety paradigms and may not fully reflect phytomedicine-specific exposure dynamics. However, allowable thresholds, monitoring rigor, and enforcement mechanisms vary across jurisdictions (Table 2). Differences in analytical protocols and exposure assumptions further complicate harmonization efforts.

Table 2: Comparison of permissible Cd limits, regulatory scope, and framework characteristics across international authorities relevant to medicinal plant materials and herbal preparations

Region / authority	Permissible Cd limit (mg/kg)	Scope (Raw material/ finished product)	Key limitation	Regulatory body
WHO	0.3	Raw medicinal plant material	Non-binding guidance	WHO
India	~0.3 (aligned)	Herbal drugs and ASU (ayurveda, siddha, and unani) formulations	Enforcement variability	Ministry of AYUSH
China	0.3-1.0 (varies by category)	Herbal raw materials and preparations	Category-specific limits	Chinese pharmacopoeia
European Union	0.1-0.3 (food/ dietary basis)	Dietary supplements	Not phytomedicine-specific	EFSA
United States	Not unified; dietary supplement limits vary	Supplements	No dedicated herbal metal standard	FDA guidance

Notably, none of the existing regulatory frameworks explicitly incorporate bioaccessibility-adjusted thresholds or cumulative exposure from polyherbal formulations, despite increasing evidence of preparation-dependent metal release (Luo *et al*., 2021).

Despite established benchmarks, most regulatory frameworks focus primarily on finished products rather than contamination occurring during cultivation. Variation in permissible limits and testing protocols reduces global harmonization and complicates international trade of herbal materials. Moreover, most standards remain concentration-based and do not explicitly integrate bioaccessibility-adjusted exposure models, cumulative intake across multiple herbal products, or toxicokinetic persistence parameters (Luo *et al*., 2021; Nordberg *et al*., 2018). Strengthening traceability systems and aligning permissible limits with phytomedicine-specific consumption patterns remain critical for ensuring safety.

7. Risk assessment approaches

7.1 Estimated daily intake (EDI)

EDI quantifies Cd exposure from medicinal plant consumption and is calculated as:

$$EDI\ (\mu g/kg/day) = C \times IR/BW$$

where C is Cd concentration (mg/kg), IR is ingestion rate (kg/day), and BW is body weight (kg).

Reported EDI values vary across medicinal plants. For *P. notoginseng*, EDI ranged from 0.0010-0.0012 µg/kg/day in pharmaceutical users and 0.011-0.013 µg/kg/day in health product consumers, corresponding to 1-13% of the WHO provisional tolerable intake (Zhu *et al*., 2016). In *S. officinalis* from Turkey, Cd intake was substantially lower (3.86×10^{-1} mg/day) (Ogbonna *et al*., 2018). Monte Carlo simulations of Iranian medicinal plants indicated mean EDI values below tolerable limits for both adults and children, although uncertainty ranges were wide (Zuo *et al*., 2021).

While EDI provides a primary exposure estimate, it assumes complete absorption and relies on standardized intake rates, which may not reflect variable medicinal dosing practices.

7.2 Hazard quotient (HQ) and target hazard quotient (THQ)

Non-carcinogenic risk is evaluated using the HQ:

$$HQ = EDI/RfD$$

where, RfD is the oral reference dose. For Cd, the USEPA RfD is 1.0 µg/kg/day [USEPA integrated risk information system (IRIS), Cd (Oral RfD)], while WHO's provisional tolerable monthly intake approximates 0.83 µg/kg/day.

HQ <1 indicates negligible risk; HQ >1 suggests potential health concern.

The target hazard quotient incorporates exposure duration:

THQ = (C × IR × EF × ED)/(Rfd × BW × AT)

where EF is exposure frequency, ED is exposure duration, and AT is averaging time.

For *P. notoginseng*, HQ values (0.0010-0.013) suggested low average risk, but probabilistic analysis showed 36-42% of health product consumers exceeding acceptable intake thresholds (Zhu *et al*., 2016). In Indian herbal medicines, 24% of marketed samples exhibited THQ >1 despite overall mean values below unity (Nath *et al*., 2020). Romanian samples reported hazard index (HI) values <1, indicating acceptable cumulative risk (Chernikova *et al*., 2025).

Importantly, HQ/THQ frameworks were originally developed for staple food commodities and may inadequately capture concentrated herbal preparations or simultaneous multi-product intake scenarios. Although widely applied, HQ/THQ frameworks assume threshold-based toxicity and do not account for cumulative multi-product exposure or inter-individual susceptibility. However, HQ-based assessments assume standardized consumption rates and do not account for variability in bioavailability or combined exposure from multiple herbal formulations, which may influence the accuracy of risk estimation in medicinal plant systems.

7.3 Lifetime cancer risk (LCR)

Carcinogenic risk is expressed as:

LCR = (C × IR × EF × ED × CSF)/(BW × AT)

Although, oral CSF values remain debated, some risk assessments apply a slope factor of 0.38 (mg/kg-day)$^{-1}$ based on route-to-route extrapolation (USEPA IRIS). Acceptable LCR values range between 1×10^{-1} and 1×10^{-4} (USEPA, RAGS). Studies of Iranian medicinal plants reported total carcinogenic risk below 1×10^{-4} (Liu *et al*., 2023). Romanian herbal materials showed carcinogenic risk values near or below 1×10^{-4} (Chernikova *et al*., 2025), and assessments of Chinese herbal medicines indicated Cd-related risks within acceptable limits, with arsenic contributing a greater carcinogenic burden (Yao *et al*., 2022). Furthermore, route-to-route extrapolation of inhalation-derived slope factors introduces additional uncertainty in oral carcinogenic risk estimation for Cd in medicinal plant matrices. Similarly, lifetime cancer risk (LCR) estimations rely on fixed exposure parameters and may not adequately reflect variations in preparation methods, long-term therapeutic usage patterns, or differences in individual susceptibility. Values exceeding 1×10^{-4} warrant regulatory attention and exposure mitigation.

7.4 Probabilistic risk assessment

Deterministic models rely on point estimates and may obscure variability. Monte Carlo simulation incorporates parameter distributions for Cd concentration, intake rate, and body weight to generate probabilistic risk profiles.

In *P. notoginseng*, probabilistic assessment revealed that although mean HQ values were <1, 36-42% of high-end consumers exceeded tolerable intake (Zhu *et al*., 2021). Similar findings in Iranian medicinal plants demonstrated acceptable mean risk but wide uncertainty intervals (Rahati *et al*., 2025). Probabilistic approaches better capture high-risk subpopulations but require robust consumption and contaminant distribution data.

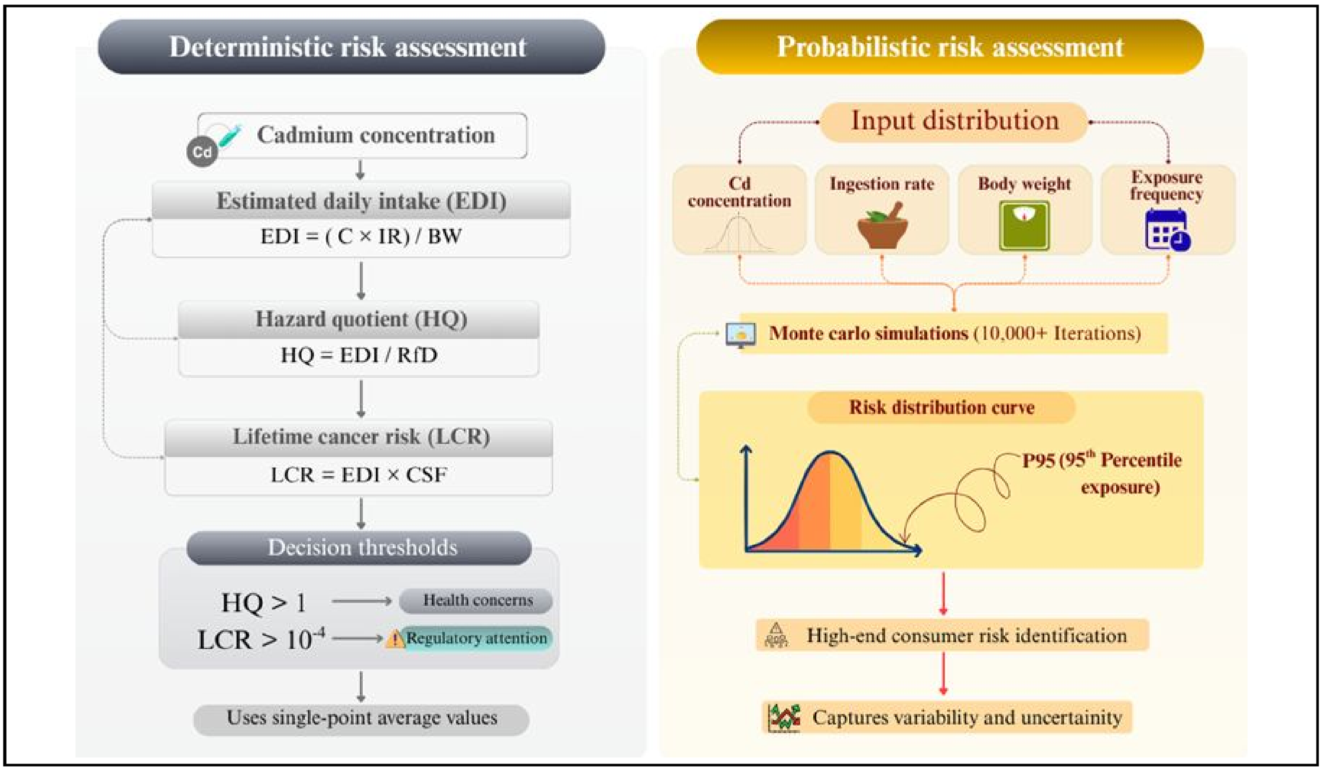

Figure 4: **Conceptual comparison of deterministic exposure modeling using point estimates (EDI, HQ, THQ, LCR) and probabilistic approaches incorporating parameter variability through Monte Carlo simulation to estimate population-level risk distributions in medicinal plant consumption scenarios.**

7.5 Limitations and refinements

The risk assessment approaches discussed in this section are adapted from established methodologies reported in food safety and environmental health literature (Figure 4). Current risk assessments for Cd in medicinal plants remain largely adapted from conventional food safety paradigms and may not adequately reflect phytomedicine-specific exposure dynamics. Although, such approaches provide screening-level evaluation, they may not reflect actual systemic exposure or long-term body burden.

Bioaccessibility studies indicate that a substantial fraction of plant-bound Cd becomes soluble under simulated gastric conditions (Zhang *et al.*, 2022), supporting the need for bioaccessibility-adjusted exposure estimation. In addition, cumulative intake modelling across multiple herbal products and incorporation of toxicokinetic parameters reflecting Cd's prolonged biological retention (Nordberg *et al.*, 2018) are essential for improving exposure realism and long-term risk characterization. However, these risk assessment models are subject to limitations, including assumptions of uniform consumption patterns, lack of consideration for bioavailability variations, and limited applicability to polyherbal formulations. Such constraints may lead to underestimation or overestimation of actual exposure risks in real-world scenarios.

8. Strategies for reducing Cd accumulation in medicinal plants

Effective mitigation of Cd contamination in medicinal plant systems requires integrated interventions spanning source control, agronomic management, biological strategies, and supply-chain oversight. Because Cd persists in soil and accumulates over time, preventive measures at the cultivation stage remain the most sustainable approach.

8.1 Cultivation and agronomic strategies

Source control begins with fertilizer management. Phosphate fertilizers derived from sedimentary rock typically contain 5-20 mg Cd/kg, whereas igneous sources may contain 50-150 mg/kg. Selection of low-Cd formulations and precision phosphorus application based on soil testing reduces long-term Cd loading (Liang *et al.*, 2024; Al-Khayri *et al.*, 2023; Hlihor *et al.*, 2022). Soil pH regulation through liming ($CaCO_3$ or dolomite at 1-4 t/ha) to maintain pH 6.5-7.5 can reduce Cd solubility by 50-80%, significantly decreasing plant uptake. However, pH adjustments must be balanced with species-specific agronomic requirements (Beigmohammadi *et al.*, 2023; Zhao *et al.*, 2020).

Organic amendments, particularly biochar (2-5% w/w), enhance Cd immobilization *via* surface adsorption and increased cation exchange capacity. Field studies report 30-60% reductions in plant Cd uptake depending on biochar characteristics and soil properties (Dghaim *et al.*, 2015; Geronimo *et al.*, 2021; Huang *et al.*, 2020). Compost and manure also increase Cd-binding capacity, though contamination of amendments must be monitored. Competitive ion supplementation further limits Cd absorption. Maintaining soil Zn:Cd ratios >100:1 and applying $ZnSO_4$ (5-25 kg/ha) can suppress Cd uptake by 20-40% through transporter competition (Cakmak *et al.*,2023; Zhu *et al.*, 2016). Calcium supplementation provides additional competitive inhibition and membrane stabilization.

Site selection remains fundamental. Avoiding cultivation near industrial zones, mining sites, or sludge-amended soils significantly reduces contamination risk. Controlled-environment cultivation (*e.g.*, greenhouse systems) provides maximal exposure control for high-value medicinal crops.

8.2 Biological and genetic mitigation approaches

Phytoremediation offers a biological strategy for contaminated sites. Hyperaccumulator species such as *Thlaspi caerulescens*, *Sedum alfredii*, and *Solanum nigrum* can accumulate >100 mg Cd/kg in shoots (Yan *et al.*, 2020; Li *et al.*, 2023). Repeated cultivation over 5-10 years can progressively reduce soil Cd levels, although the process is time-intensive (Al-Khayri *et al.*, 2023). Phytostabilization using low-translocation species provides an alternative where complete removal is impractical.

Arbuscular mycorrhizal fungi (AMF) may reduce Cd uptake by binding metals within fungal structures or modifying rhizosphere chemistry, though responses are strain- and host-dependent and require further field validation (Bushra *et al.*, 2024; Begum *et al.*, 2019).

Genetic variation in Cd accumulation enables cultivar selection. For example, allelic variation in NRAMP1 in *S. miltiorrhiza* has been associated with reduced Cd uptake, supporting marker-assisted breeding approaches (Yao *et al.*, 2022; Chen *et al.*, 2023). Advanced strategies include enhancing phytochelatin production, downregulating Cd transporters (ZIP/NRAMP), or increasing vacuolar sequestration. However, regulatory and consumer acceptance challenges limit widespread application of genetically modified medicinal plants.

8.3 Post-harvest and supply chain risk control

Post-harvest interventions can partially reduce consumer exposure. Washing and peeling root-based medicinal materials may reduce surface-associated Cd by 10-30%, though internalized Cd remains unaffected (Li *et al.*, 2023; Lee *et al.*, 2019). Segregation and rejection of batches exceeding the WHO limit of 0.3 mg/kg is preferable to dilution practices that mask contamination.

Routine heavy metal screening using ICP-OES (Inductively coupled plasma-optical emission spectroscopy) or ICP-MS (Inductively coupled plasma-mass spectrometry) at both raw material and finished product stages is essential (Satarug *et al.*, 2010). Implementation of good agricultural and collection practices (GACP) and good manufacturing practices (GMP), with heavy metal testing as a critical control point, strengthens traceability and prevents contaminated materials entering commercial supply chains. In addition to reducing Cd exposure, these strategies play a critical role in preserving phytochemical integrity and ensuring consistency in the pharmacological efficacy of medicinal plant-based products.

9. Research gaps and future directions

Despite increasing documentation of Cd contamination in medicinal plant systems, significant knowledge gaps continue to constrain accurate exposure assessment, risk modelling and regulatory alignment.

9.1 Methodological gaps in exposure assessment

Most investigations report total Cd concentrations without distinguishing between bioavailable and bioaccessible fractions.

In vitro digestion studies indicating approximately 40-60% gastric bioaccessibility suggest that reliance on total Cd content may misrepresent actual systemic exposure (Zhang *et al*., 2021). However, digestion methodologies remain non-standardized, with substantial variability in extraction protocols, solid-to-liquid ratios, and simulation parameters. This lack of methodological harmonization limits cross-study comparability and hinders integration of bioaccessibility-adjusted exposure models into routine risk assessment frameworks.

9.2 Limitations in risk modelling frameworks

Current assessments predominantly employ deterministic HQ and LCR models based on fixed intake assumptions. Such approaches inadequately reflect the variability inherent in medicinal plant use, including chronic therapeutic dosing, seasonal consumption patterns, and polyherbal formulations. Moreover, cumulative exposure modelling that integrates multiple herbal products and background dietary intake remains underdeveloped. Toxicokinetic considerations, particularly Cd's 10-30 years biological half-life is rarely incorporated into phytomedicine-specific risk evaluations, potentially underestimating long-term body burden (Nordberg *et al*., 2018).

9.3 Species-specific accumulation mechanisms

While interspecific variation in Cd accumulation is widely recognized, mechanistic understanding in medicinal plants remains comparatively limited relative to staple crops. Functional characterization of transporter families (ZIP, NRAMP, HMA) has been conducted in a narrow subset of species, restricting extrapolation across diverse medicinal taxa. Comprehensive germplasm screening and investigation of genotype-environment interactions are necessary to identify low-accumulating cultivars suitable for safe cultivation.

9.4 Regulatory and monitoring gaps

Existing permissible limits are largely adapted from food safety paradigms and do not fully account for concentrated preparations, long-term therapeutic intake, or cumulative polyherbal exposure. Inconsistencies across jurisdictions, combined with limited traceability of wild-harvested materials, impede harmonized quality assurance. Development of standardized surveillance systems and harmonized analytical criteria specific to phytomedicine supply chains remains a critical priority.

9.5 Translational and policy-level integration

A persistent disconnect exists between soil contamination research, plant physiological studies, toxicokinetic modelling and regulatory policy. Integrated frameworks that link soil chemistry, plant uptake mechanisms, processing-induced bioaccessibility changes, and human exposure modelling are scarce. Advancing multidisciplinary collaborations among agronomists, toxicologists, pharmacologists, and regulatory scientists will be essential to develop evidence-based, phytomedicine-specific safety strategies.

10. Conclusion

Cd contamination in medicinal plant systems represents a significant safety concern driven by organ-specific accumulation, preparation-dependent exposure, and variability across species, with root-based medicinal plants frequently exhibiting higher concentrations and documented exceedances of the WHO benchmark (0.3 mg/kg) in certain regions. Beyond direct toxicological risks, Cd exposure may influence the biosynthesis and stability of bioactive phytochemicals, potentially altering the pharmacological efficacy and therapeutic consistency of medicinal plant preparations. Quantitative risk assessments further indicate that hazard quotient and lifetime cancer risk values may approach or exceed acceptable limits under chronic or cumulative consumption scenarios, particularly when bioaccessibility is considered. These findings underscore the need for integrated strategies that combine improved cultivation practices, species-specific monitoring, and phytomedicine-oriented risk assessment approaches to ensure both safety and therapeutic reliability of medicinal plant-based products.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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