International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 08-02-2026, Accepted: 11-03-2026, Published: 26-03-2026
Volume 11, Issue 1, 2026, Page No. 120-130

Contaminants and impurities in Herbal Medicines: A comprehensive review of sources, toxicological impacts, analytical detection, and regulatory control

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Abstract
Background: Herbal formulations represent a significant segment of global healthcare, with over 80% of the world's population relying on traditional plant-based medicines as a primary or supplementary therapeutic resource.
Objectives: This review systematically examines the types and sources of impurities in herbal formulations, their toxicological consequences, analytical methodologies for their detection, and evidence-based quality control strategies.
Methods: A comprehensive literature search was performed across PubMed, Scopus, Web of Science, and WHO technical reports published between 2000 and 2024, focusing on peer-reviewed studies addressing contamination, standardization, and regulation of herbal products.
Results: Impurities in herbal formulations include microbial contaminants, heavy metals (lead, mercury, arsenic, and cadmium), pesticide residues (organophosphates, organochlorines, and carbamates), mycotoxins, adulterants, residual solvents, and processing by-products. These arise at all production stages—cultivation, harvesting, processing, and storage—and can cause acute toxicity, chronic organ damage, endocrine disruption, carcinogenicity, and reduced therapeutic efficacy. Advanced analytical platforms (GC-MS/MS, LC-MS/MS, ICP-MS, biosensors, DNA barcoding) now offer sensitive multi-residue detection. Adherence to Good Agricultural and Collection Practices (GACP), Good Manufacturing Practices (GMP), and harmonized regulatory frameworks (WHO, USP, Ph. Eur.) is essential.
Conclusions: Comprehensive quality control integrating advanced detection technologies, robust regulatory frameworks, and emerging purification strategies is indispensable for ensuring the safety and efficacy of herbal formulations. Regulatory harmonization across jurisdictions and continued research into AI-assisted contamination prediction represent critical future directions.

Keywords: Herbal formulations, impurities, heavy metals, pesticide residues, mycotoxins, quality control, GMP, GACP, ICP-MS, GC-MS/MS, regulatory guidelines, nanotechnology, adulteration, standardization

Introduction

The global herbal medicine market has witnessed unprecedented growth, valued at approximately USD 130 billion in 2023 and projected to exceed USD 250 billion by 2030, driven by rising consumer preference for natural therapeutic options and increasing awareness of complementary and alternative medicine (CAM).[1, 2] The World Health Organization (WHO) estimates that approximately 80% of the global population depends on traditional medicine, largely herbal-based, as their primary healthcare resource, particularly in low- and middle-income countries.[3, 4] Despite this widespread use, a fundamental paradox exists: herbal products are widely perceived as "safe by virtue of being natural," yet substantial evidence demonstrates that they carry significant contamination risks that can jeopardize consumer health.[5, 6]

Unlike conventional pharmaceutical drugs, which are subject to stringent pre-market regulatory scrutiny, rigorous clinical trials, and standardized manufacturing controls, herbal formulations in many jurisdictions are regulated as food supplements or traditional medicines, with comparatively relaxed oversight.[7, 8] This regulatory disparity creates opportunities for contaminants—including microbial pathogens, toxic heavy metals, pesticide residues, mycotoxins, chemical adulterants, and residual solvents—to enter the final product at multiple points along the supply chain.[9, 10] The consequences can be severe: acute poisoning, chronic organ damage, carcinogenesis, drug–herb interactions, and diminished therapeutic efficacy.[11, 12]

Multiple impurity categories have been documented in herbal products globally. Heavy metal contamination is particularly well-documented in Ayurvedic formulations and Traditional Chinese Medicines (TCM), where lead, mercury, arsenic, and cadmium have been detected at concentrations exceeding WHO permissible limits.[13, 14] Pesticide residue surveys have identified organophosphates, organochlorines, carbamates, and pyrethroids in commercially available herbal products across Asia, Europe, and the Americas.[15, 16] Mycotoxin contamination—particularly aflatoxins from Aspergillus species—represents an underappreciated but clinically significant hazard, especially in products stored under inadequate conditions.[17, 18] Intentional adulteration with undeclared pharmaceuticals (corticosteroids, sildenafil, weight-loss drugs) further complicates the safety landscape.[19, 20]

The scientific and regulatory response to these challenges has accelerated. Advanced analytical platforms—including gas chromatography-tandem mass spectrometry (GC-MS/MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS), inductively coupled plasma mass spectrometry (ICP-MS), DNA barcoding, and emerging nanosensor technologies—now offer sensitive, multi-residue detection capabilities.[21, 22] Simultaneously, international bodies including WHO, the US Pharmacopeia (USP),

European Pharmacopoeia (Ph. Eur.), and national pharmacopoeias have progressively strengthened quality standards.[23, 24] Nevertheless, global harmonization remains incomplete, and significant gaps persist in enforcement, particularly in developing nations.[25, 26]

This review aims to provide a comprehensive, updated synthesis of knowledge on impurities in herbal formulations. Specifically, we (i) classify and characterize the principal impurity categories; (ii) delineate their origins along the production chain; (iii) evaluate their toxicological and clinical consequences; (iv) critically appraise current and emerging analytical methods for their detection; (v) review international regulatory frameworks; and (vi) propose evidence-based strategies for quality control and contamination minimization. By integrating recent high-impact literature with global regulatory perspectives, this review offers a resource for pharmacists, regulatory scientists, herbal medicine manufacturers, and researchers committed to ensuring the safety and efficacy of herbal therapeutics.

Classification and Characterization of Impurities in Herbal Formulations

Impurities in herbal products can be broadly classified as biological (microbial), inorganic (heavy metals), organic chemical (pesticides, solvents, mycotoxins), and intentional (adulterants). A systematic classification is presented in Table 1.

Table 1: Classification of impurities in herbal formulations, their origins, and primary health effects

Category	Examples	Source/Origin	Primary Health Effect
Microbial Contaminants	Salmonella, E. coli, Aspergillus spp., yeasts	Soil, water, unhygienic handling, poor storage	Gastroenteritis, mycotoxicosis, systemic infections
Heavy Metals	Lead (Pb), Mercury (Hg), Arsenic (As), Cadmium (Cd)	Contaminated soil, irrigation water, industrial fallout	Nephrotoxicity, neurotoxicity, carcinogenicity
Pesticide Residues	Organophosphates, organochlorines, carbamates, pyrethroids	Agricultural application during cultivation	Neurotoxicity, endocrine disruption, carcinogenicity
Adulterants	Undeclared drugs, synthetic dyes, starch, foreign plant material	Intentional adulteration by manufacturers	Drug interactions, organ toxicity, reduced efficacy
Solvent Residues	Methanol, ethanol, acetone, hexane, chloroform	Extraction and purification processes	Hepatotoxicity, nephrotoxicity, carcinogenicity
Processing By-products	Filter agents, reagent residues, oxidation products	Manufacturing and storage	Variable; dependent on chemical nature
Mycotoxins	Aflatoxins B1, B2, G1, G2; ochratoxin A; fumonisin	Fungal growth during storage under humid conditions	Hepatocarcinogenicity, nephrotoxicity, immunotoxicity

1. Microbial Contamination

Microbial contamination is among the most prevalent quality defects in herbal products, affecting an estimated 5–60% of samples depending on product type, origin, and storage conditions.[27] Herbs, as complex biological matrices with high organic content, readily support microbial proliferation if not correctly dried, processed, and stored.

2.1 Bacteria

Pathogenic bacteria including Salmonella enterica, Escherichia coli (particularly STEC), Staphylococcus aureus, Bacillus cereus, and Clostridium species have been isolated from herbal products. Salmonella contamination of botanical raw materials is particularly well-documented, with outbreaks linked to contaminated dietary supplements. The United States FDA has issued multiple recalls for Salmonella-contaminated herbal products since 2010.[5, 28] Immunocompromised individuals, pregnant women, and the elderly are at elevated risk for serious complications including bacteraemia and sepsis.[27]

2.2 Fungi, Molds, and Mycotoxins

Fungal contamination—predominantly Aspergillus, Fusarium, and Penicillium species—may result in mycotoxin production, representing one of the most serious chemical hazards associated with herbal products. Aflatoxins B1, B2, G1, and G2 are potent hepatocarcinogens classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC). Ochratoxin A, produced by Aspergillus ochraceus and Penicillium verrucosum, is nephrotoxic and potentially carcinogenic (IARC Group 2B).[17, 29] A study of African herbal medicines found aflatoxin B1 exceeding 2 µg/kg (WHO limit) in over 30% of samples.[30] Fumonisins, deoxynivalenol (DON), and zearalenone are additional mycotoxins of concern detected in herbal materials globally.[18]

2.3 Heavy Metal Contamination

Heavy metal contamination in herbal medicines poses significant public health risks due to the potential for bioaccumulation and cumulative toxicity.[31] Luo *et al*. (2021) conducted a systematic review and meta-analysis encompassing 1,773 herbal medicine samples from multiple countries, finding that lead, arsenic, mercury, and cadmium frequently exceeded WHO guideline values.[13] The WHO recommends maximum limits of Pb ≤10 mg/kg, Hg ≤1 mg/kg, As ≤10 mg/kg, and Cd ≤0.3 mg/kg for medicinal plant materials (Table 2).[32]

Table 2: WHO permissible limits for heavy metals in herbal medicines and associated health effects

Heavy Metal	WHO Limit (mg/kg)	Organ/System Targeted	Key Reference Studies
Lead (Pb)	≤ 10.0	CNS, kidneys, bone	Luo *et al*. 2021; Rani & Sisodia 2023
Mercury (Hg)	≤ 1.0	CNS, kidneys, fetal development	Balali-Mood *et al*. 2021; WHO 2007
Arsenic (As)	≤ 10.0	Skin, liver, cardiovascular, carcinogen	Tchounwou *et al*. 2012; Singh *et al*. 2022
Cadmium (Cd)	≤ 0.3	Kidneys, bone (Itai-itai disease)	Keshvari *et al*. 2021; Riyazuddin *et al*. 2021
Copper (Cu)	≤ 150.0	Liver (Wilson's disease risk)	Luo *et al*. 2021
Zinc (Zn)	≤ 50.0	Gastrointestinal tract, immunotoxicity	Singh *et al*. 2022; WHO 2007

In Ayurvedic formulations, deliberate use of rasa shastra (metal- and mineral-containing preparations) including Swarna Bhasma and Tamra Bhasma has historically been defended as therapeutically beneficial. However, toxicological evidence demonstrates that even "purified" (shodhana-processed) heavy metal preparations can exceed safe limits.[33] A study of 42 Ayurvedic preparations from Chandigarh markets reported that 73.8% contained lead, mercury, or arsenic above permissible limits.[14] Similarly, Rani and Sisodia (2023) found that medicinal plants from Maharashtra, Delhi, and Kerala showed the highest rates of exceedance for Pb, Hg, and As contamination in India.[34]

Cadmium toxicity deserves special emphasis given its extended biological half-life (15–30 years in kidney tissue) and its capacity to cause irreversible nephrotoxicity at low chronic exposures.[35] Riyazuddin *et al*. (2021) comprehensively reviewed molecular mechanisms of heavy metal toxicity in plants, highlighting that soil pH, organic matter content, and microbial activity determine phytoavailability and ultimately plant accumulation.[36]

2.4 Pesticide and Herbicide Residues

The increasing commercialization of medicinal plant cultivation has led to widespread use of agrochemicals to maximize yield and prevent pest damage. Pesticide residues in herbal products have been documented globally and represent a complex multi-class contamination challenge.[37, 38] Yang *et al*. (2023) developed a GC-MS/MS method simultaneously detecting 296 pesticide multi-residues in root/rhizome-based herbal medicines, identifying residues in 47 of 47 samples tested from Korea and China.[39]

Organophosphates (e.g., chlorpyrifos, malathion, dimethoate) are the most commonly detected class, acting as irreversible acetylcholinesterase inhibitors causing neuromuscular dysfunction at acute exposures and potential cognitive impairment with chronic low-level exposure.[40] Organochlorine compounds (e.g., DDT, hexachlorocyclohexane, endosulfan) persist in the environment and bioaccumulate in lipid-rich tissues. Though banned in most countries, residues continue to appear in herbal products, particularly those imported from regions with less rigorous agricultural controls.[41] Carbamates and pyrethroids complete the major residue classes; pyrethroids are generally considered less acutely toxic but are associated with endocrine-disrupting effects and allergic sensitization at elevated exposures.[15]

2.5 Mycotoxins

Mycotoxins warrant distinct consideration given their potent carcinogenicity at trace concentrations. Post-harvest contamination under high humidity and elevated temperature conditions is the predominant route of exposure. Aflatoxin B1, the most toxic naturally occurring carcinogen known, has WHO limits set at 2 µg/kg for medicinal plant materials. Aflatoxin-related hepatocellular carcinoma is recognized as a significant burden in sub-Saharan Africa and parts of Asia, regions where unregulated herbal products are widely consumed.[17, 30] Ochratoxin A co-contamination with aflatoxins creates synergistic toxicological risks that are incompletely characterized.[29]

2.6 Adulterants

Adulteration of herbal products ranges from economic adulteration (substituting cheaper plant species or adding bulking agents) to deliberately adding pharmacologically active substances. Newmaster *et al*. (2013) used DNA barcoding to authenticate commercial herbal products from 12 North American companies, finding that 59% contained plant species not listed on the label and one-third contained fillers (e.g., rice, soybean) not disclosed.[42] Undeclared pharmaceuticals detected in herbal preparations include sildenafil and analogues in sexual enhancement products, corticosteroids in anti-inflammatory herbal formulations, hypoglycaemic agents in anti-diabetic herbs, and stimulants in weight-loss preparations.[19, 43] These adulterations expose consumers to pharmacologically active substances without medical supervision, creating substantial risks for drug interactions and adverse effects.

2.7 Residual Solvents

Extraction processes routinely employ organic solvents including methanol, ethanol, acetone, hexane, dichloromethane, and chloroform. Incomplete removal leads to solvent residues in finished products. ICH Q3C classifies residual solvents into three classes based on toxicological risk: Class 1 (carcinogenic and environmentally hazardous; to be avoided), Class 2 (non-genotoxic, limit-based), and Class 3 (low toxic potential).[44] Methanol residues at high concentrations cause optic nerve damage and metabolic acidosis; chlorinated solvents are recognized carcinogens. Supercritical CO2 extraction has emerged as a green alternative minimizing solvent residue concerns while maintaining extraction efficiency.[45]

Sources of Impurities Along the Production Chain

Impurities can be introduced at every stage of the herbal product life cycle, from cultivation to the consumer's hands (Figure 1). Understanding the production-chain origin of specific impurities is essential for targeted contamination control.

3.1 Cultivation and Harvesting Phase

Soil contamination with industrial heavy metals, proximity to mining operations or smelters, and use of heavy metal-containing fertilizers or agrochemicals represent primary sources of inorganic impurities in medicinal plants.[34, 36] Pesticide drift from neighbouring agricultural fields, use of contaminated irrigation water, and application of banned pesticides are key routes of pesticide residue introduction.[37] Airborne deposition of pollutants in peri-urban and industrial areas further compounds contamination at the cultivation stage. Harvesting under poor hygienic conditions—including contact with contaminated soil, use of unsterilized equipment, and exposure to infected plant material—introduces microbial contaminants.[28]

3.2 Processing and Manufacturing Phase

Inadequate drying after harvest creates conditions favouring fungal growth and mycotoxin elaboration. High-temperature drying may degrade thermolabile bioactive compounds while failing to eliminate heat-stable mycotoxins. During extraction, inadequate solvent recovery leaves residual solvents in concentrates; metal contamination can be introduced through use of substandard equipment without food-grade coatings.[46] GMP-non-compliant facilities may lack segregation controls, leading to cross-contamination between different herbal batches or between herbal and pharmaceutical products.[7]

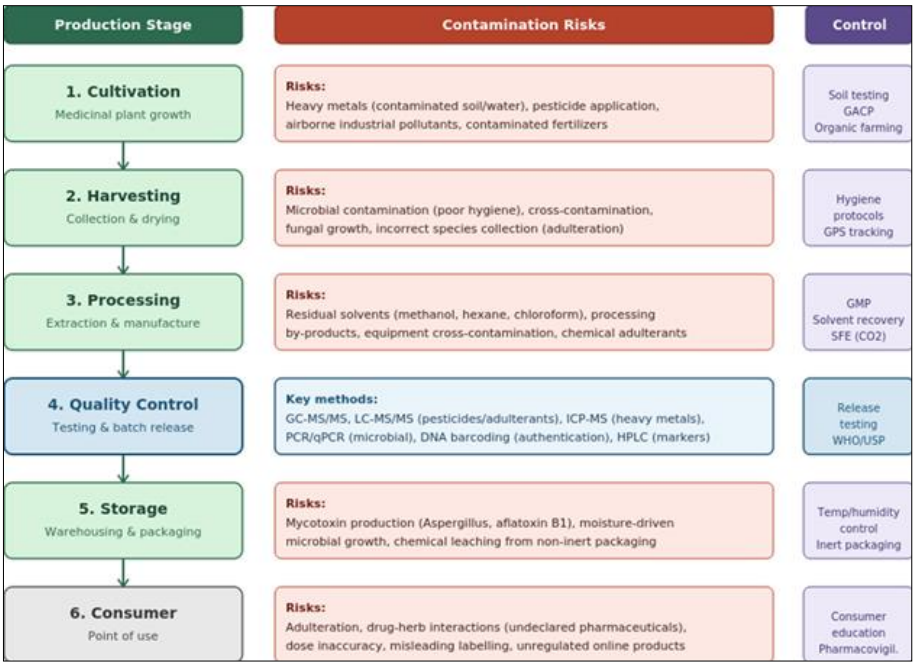

Fig 1: Schematic representation of impurity introduction pathways along the herbal formulation production chain (Cultivation → Harvesting → Processing → Storage → Distribution → Consumer). Each stage identifies the principal contamination risks and corresponding control strategies

3.3 Storage and Distribution Phase

Temperature and humidity fluctuations during storage are the primary drivers of post-manufacturing microbial and mycotoxin contamination. Products stored in high-humidity environments (>65% RH) are particularly susceptible to Aspergillus growth and aflatoxin elaboration. Packaging materials may leach plasticizers, UV stabilizers, or heavy metals into the product, particularly for lipophilic formulations.[47] Extended or improper storage may also catalyze chemical degradation of active constituents, generating new chemical impurities.

3.4 Intentional Adulteration

Economic motivations drive intentional adulteration at multiple points in the supply chain. Replacement of expensive plant species with cheaper alternatives, addition of synthetic dyes to improve visual appeal, and underdeclared pharmaceutical addition to "demonstrate" efficacy are all documented practices.[42, 43] Supply chain complexity—often spanning multiple continents from cultivation to retail—creates numerous opportunities for adulteration and reduces traceability.

Toxicological and Clinical Consequences of Impurities

The health consequences of herbal product impurities span a broad spectrum from acute life-threatening toxicity to insidious chronic disease.

4.1 Acute Toxicity

Acute heavy metal poisoning from herbal products has been documented in multiple case series. Saper *et al*. reported lead poisoning with blood lead levels up to 480 µg/dL in patients using Ayurvedic preparations; manifestations included abdominal colic, anaemia, and encephalopathy.[48] Acute arsenic poisoning presents as gastrointestinal haemorrhage, cardiovascular collapse, and multi-organ failure. Mercury vapour inhalation from cinnabar-containing TCM formulations has caused acute respiratory distress.[31]

4.2 Chronic Toxicity and Carcinogenicity

Chronic exposure to sub-toxic heavy metal concentrations leads to progressive nephrotoxicity (cadmium, lead), neurotoxicity (lead, mercury, arsenic), cardiovascular disease (arsenic), and osteotoxicity (cadmium).[35] Carcinogenic impurities of highest concern include aflatoxin B1 (hepatocellular carcinoma), arsenic (bladder, lung, skin cancer), and certain organochlorine pesticides. Tchounwou *et al*. (2012) provided a landmark review of heavy metal toxicity mechanisms, documenting that lead interferes with haem synthesis, calcium signalling, and DNA repair pathways.[49]

4.3 Endocrine Disruption

Organochlorine pesticides (DDT, endosulfan, lindane), certain phthalates from packaging, and heavy metals including cadmium and arsenic are classified as endocrine-disrupting chemicals (EDCs). EDC exposure through contaminated herbal products may contribute to thyroid dysfunction, reproductive toxicity, and developmental effects in children, even at concentrations below acutely toxic thresholds.[15, 50]

4.4 Microbial and Mycotoxin-Related Illness

Salmonellosis, E. coli-related haemolytic uraemic syndrome (HUS), and aflatoxin-related hepatocellular carcinoma are the most clinically significant microbial and mycotoxin hazards from herbal products. In immunocompromised patients (those with HIV/AIDS, post-transplant, or receiving chemotherapy), opportunistic infections from Aspergillus, Candida, or Mucor in herbal products can be fatal.[27, 28, 30]

4.5 Drug–Herb Interactions Mediated by Adulterants

Undeclared pharmaceuticals in herbal products are an underappreciated cause of adverse drug–herb interactions. Sildenafil-adulterated "herbal" sexual enhancement products taken concurrently with nitrate medications can cause potentially fatal hypotension. Undeclared warfarin analogues in herbal anti-diabetic preparations may cause uncontrolled anticoagulation.[19]

4.6 Impact on Therapeutic Efficacy

Beyond direct toxicity, impurities can diminish therapeutic efficacy by competing with or degrading active constituents. Adulterant-mediated dilution of bioactive compounds reduces standardized extract potency. Microbial protease activity can degrade protein-based bioactive fractions. Heavy metals may chelate polyphenolic active compounds, altering their bioavailability.[46]

Analytical Methods for Detection and Quantification of Impurities

The detection of impurities in complex herbal matrices requires a range of complementary analytical strategies (Table 3). Selection of method depends on the impurity class, required sensitivity, regulatory acceptance, and laboratory infrastructure.

Table 3: Comparative overview of analytical methods used for detection of impurities in herbal formulations

Method	Impurity Type	Sensitivity / LOD	Advantages	Limitations
HPLC-UV/DAD	Pesticides, adulterants, active compounds	µg/kg range	Versatile, reproducible, widely available	Less sensitive than MS-based methods
GC-MS / GC-MS/MS	Volatile pesticides, solvent residues	ng/kg range	High specificity, multi-residue capability	Non-volatile analytes excluded
LC-MS/MS	Polar pesticides, mycotoxins, adulterants	ng/kg range	Broad analyte coverage, no derivatization	Complex matrix effects
ICP-MS	Heavy metals (trace level)	pg/kg – ng/kg	Multi-element, extremely low LOD	Expensive equipment
AAS (FAAS / GFAAS)	Heavy metals	µg/L range	Cost-effective, simple operation	Single element per run
PCR / qPCR	Microbial DNA, species authentication	Highly specific (DNA-level)	Rapid, highly specific	Requires DNA extraction expertise
ELISA / Immunoassay	Mycotoxins, microbial antigens	µg/kg range	High throughput, field-deployable	Cross-reactivity risks
Nanosensor / Biosensor	Multiple contaminant classes	Ultra-trace (ppt level)	Real-time, miniaturizable	Largely experimental; limited regulatory acceptance

5.1 Chromatographic Methods for Chemical Impurities

High-Performance Liquid Chromatography (HPLC) coupled with UV/DAD or fluorescence detection remains a workhorse analytical technique for quantification of adulterants, active markers, and some pesticide classes.[51] For multi-residue pesticide analysis, GC-MS/MS and LC-MS/MS have become the gold standard, enabling simultaneous determination of hundreds of pesticides in a single analytical run. Lee *et al*. (2023) validated a GC-MS/MS method for 296 pesticide residues in root/rhizome herbs using modified QuEChERS extraction, demonstrating LOQs of 0.002–0.05 mg/kg for the majority of target compounds.[39] Song *et al*. (2023) developed a GC-MS/MS method for 147 pesticides in TCMs achieving recoveries of 70–120% with RSDs below 20%, suitable for routine regulatory monitoring.[52]

LC-MS/MS has particular advantages for polar pesticides, mycotoxins, and pharmaceutical adulterants that are not amenable to GC analysis. Multiple Reaction Monitoring (MRM) mode provides superior selectivity by requiring ion-pair confirmation before positive identification, drastically reducing false positives in complex matrices.[38, 53] Kim *et al*. (2023) demonstrated simultaneous 320-pesticide analysis in Korean herbal decoctions by combining LC-MS/MS and GC-MS/MS, achieving excellent method performance across all pesticide classes.[54]

5.2 Elemental Analysis for Heavy Metals

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is the premier technique for trace heavy metal analysis, offering sub-ng/kg detection limits and simultaneous multi-element quantification.[13, 32] For routine industrial QC, Atomic Absorption Spectrometry (AAS)—both Flame AAS (FAAS) and Graphite Furnace AAS (GFAAS)—offers cost-effective alternatives with acceptable sensitivity for regulatory compliance testing (LODs typically 0.1–10 µg/L).[34] X-ray fluorescence (XRF) spectrometry provides rapid, non-destructive screening but with higher detection limits than ICP-MS.[55]

5.3 Microbiological Methods

Traditional culture-based methods (ISO 21149, USP <61> and <62>) remain regulatory standards for total aerobic microbial count (TAMC), total combined yeasts/moulds count (TYMC), and specified pathogens (Salmonella, E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans).[27] PCR-based molecular methods, including quantitative real-time PCR (qPCR), provide faster identification with higher specificity, enabling detection of viable but non-culturable (VBNC) organisms that evade culture detection.[28]

5.4 Authentication and Anti-Adulteration Methods

DNA barcoding, using standardized markers (rbcL, matK, ITS2), has emerged as a powerful tool for botanical species authentication and detection of substitution or admixture adulteration.[42] Newmaster *et al*. (2013) demonstrated that DNA barcoding could detect contamination and substitution in North American herbal products with greater sensitivity than traditional morphological identification.[42] Near-infrared (NIR) spectroscopy and Raman spectroscopy offer rapid, non-destructive fingerprinting for routine material authentication without sample preparation.[56]

5.5 Emerging Technologies

Nanotechnology-based sensors offer transformative potential for herbal product QC. Gold nanoparticle (AuNP)-based colorimetric sensors have achieved detection of heavy metals at picomolar concentrations in aqueous matrices. Electrochemical biosensors combining molecularly imprinted polymers (MIPs) with nanostructured electrodes have demonstrated simultaneous detection of multiple mycotoxins.[22] Hyperspectral imaging combined with machine learning algorithms enables rapid, non-contact detection of surface contamination and adulteration in bulk herbal materials, promising real-time quality monitoring in production lines.[57] Blockchain-enabled supply chain traceability systems are being integrated with analytical QC data to provide immutable provenance records from farm to pharmacy.[58]

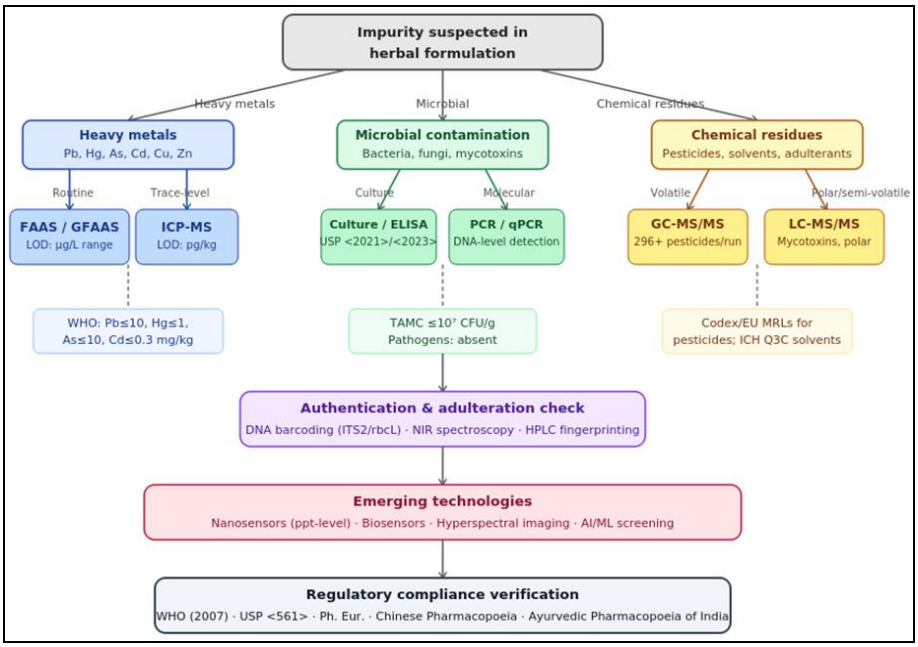

Fig 2: Decision tree for selection of analytical method based on impurity class, required sensitivity (LOD/LOQ), and regulatory framework context. (HPLC = high-performance liquid chromatography; GC = gas chromatography; MS = mass spectrometry; ICP = inductively coupled plasma; AAS = atomic absorption spectrometry; PCR = polymerase chain reaction; NIR = near-infrared spectroscopy).

International Regulatory Frameworks

The regulatory landscape for herbal product quality and safety is fragmented globally (Table 4), creating challenges for manufacturers seeking multi-jurisdictional market access and for regulators seeking to protect consumers from contaminated imports. [23, 25]

Table 4: International regulatory frameworks governing impurity limits in herbal formulations

Regulatory Body / Pharmacopoeia	Heavy Metal Limits	Microbial Limits (CFU/g)	Pesticide Approach	Mycotoxin Limits	Scope
WHO (2007, 2018)	Pb ≤10; Hg ≤1; As ≤10; Cd ≤0.3 mg/kg	TAMC ≤ 10^7; Pathogens absent	MRL aligned with Codex	Aflatoxin B1 ≤ 2 µg/kg	Global guidance
European Pharmacopoeia (Ph. Eur.)	ICH Q3D-based PDEs	Stringent limits by product type	EC 396/2005 MRLs	Strict aflatoxin limits	EU nations
USFDA / USP	ICH Q3D limits	USP <2021> / <2023>	Zero tolerance for banned pesticides	Aflatoxin total ≤ 20 ppb	USA
Chinese Pharmacopoeia (ChP 2020)	Pb ≤5; Cd ≤0.3; As ≤2; Hg ≤0.2 mg/kg	Per product monograph	MRLs for 33 pesticides in TCMs	Aflatoxin B1 ≤ 5 µg/kg	China
Ayurvedic Pharmacopoeia of India (API)	Pb ≤10; Hg ≤1; As ≤10; Cd ≤0.3 mg/kg	Per product monograph	Reference to FSSAI guidelines	Not fully harmonized	India

6.1 WHO Framework

The WHO has been central to developing international quality standards for herbal medicines. The WHO Traditional Medicine Strategy 2014–2023 identifies quality assurance as a core pillar for the safe integration of traditional medicine into health systems.[3] Key technical documents include WHO Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues (2007), WHO Guidelines on GACP for Medicinal Plants (2003), and the WHO Expert Committee for the International Herbal Pharmacopoeia.[32, 59]

6.2 Regional Pharmacopoeial Standards

The European Pharmacopoeia (Ph. Eur.) applies ICH Q3D Elemental Impurities guidelines to herbal medicines and maintains specific monographs for hundreds of medicinal plant materials, including limits for heavy metals, pesticides, and microbial contamination. The European Commission Regulation (EC) No. 1881/2006 sets maximum levels for aflatoxins in foodstuffs, applicable to many herbal teas.[24] The USP-NF provides general chapters <561> Articles of Botanical Origin, <2021> Microbial Enumeration Tests, and <2023> Identification of Specified Microorganisms for herbal products.[44] Comparison of arsenic and heavy metal limits across pharmacopoeias of nine countries by Suyama *et al*. (2023) revealed significant discordance that complicates international trade and regulatory harmonization.[60]

6.3 Challenges in Regulatory Harmonization

Key barriers to global harmonization include: (i) inconsistent classification of herbal products (food supplement vs. traditional medicine vs. drug) across jurisdictions; (ii) varying scientific thresholds for acceptable daily exposure (ADE) to contaminants; (iii) inadequate laboratory infrastructure for compliance testing in many developing countries; (iv) trade pressures creating disincentives for enforcement; and (v) insufficient post-market surveillance capacity.[25, 26]

Quality Control and Contamination Minimization Strategies

A comprehensive quality management approach spanning the entire supply chain is essential for producing safe herbal formulations (Table 5, Figure 3).

Table 5: Key requirements and impurity-reduction impact of GACP, GMP, quality control, and distribution practices for herbal formulations

Practice	Key Requirements	Impact on Impurity Reduction
GACP (Pre-harvest)	Selection of uncontaminated sites; restricted pesticide use; soil and water testing; trained harvesters; documentation of collection procedures	Reduces heavy metal accumulation, pesticide residues, and microbial load at source
GMP (Manufacturing)	Validated cleaning procedures; controlled environment (temperature, humidity); calibrated equipment; batch records; personnel hygiene; solvent recovery protocols	Minimizes cross-contamination, microbial growth, solvent residues, and processing by-products
Quality Control (QC)	In-process testing; finished product release testing; reference standards; validated analytical methods; stability testing per ICH Q1A	Ensures impurity levels are within regulatory limits before market release
Storage & Distribution	Controlled temperature/humidity storage; light-protected packaging; inert container materials; shelf-life labelling; cold chain for sensitive products	Prevents post-manufacturing contamination and chemical degradation

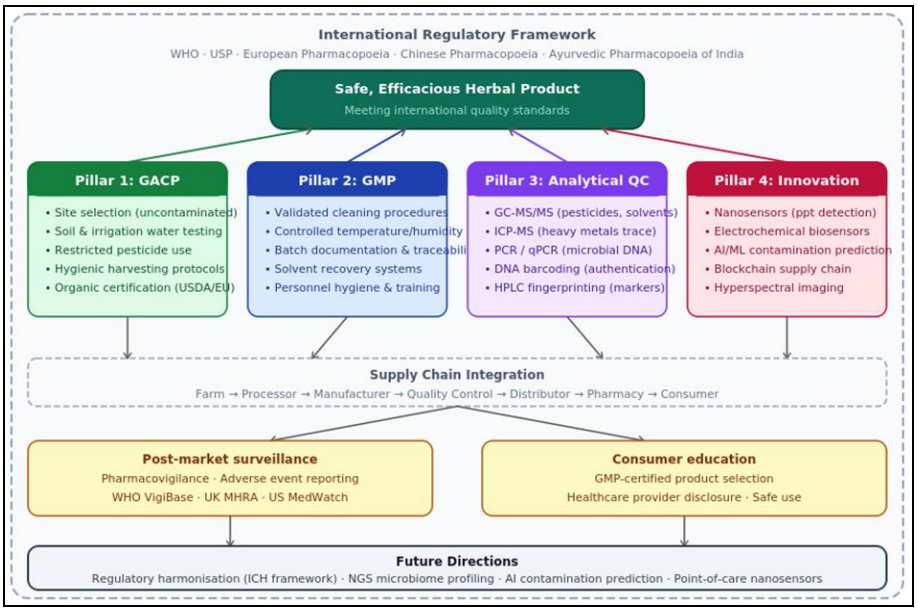

Fig 3: Integrated quality management framework for herbal formulations showing the interconnection of GACP, GMP, analytical QC, regulatory compliance, and emerging technologies in ensuring product safety and efficacy

7.1 Good Agricultural and Collection Practices (GACP)

GACP implementation is foundational to controlling impurity introduction at the source. WHO GACP guidelines (2003) address site selection, soil testing, water quality monitoring, restricted and documented use of pesticides, hygiene during harvesting, proper drying, and post-harvest handling.[59] Site selection criteria must exclude areas with historical heavy metal contamination, proximity to industrial facilities, and documented soil or water pollution. Soil testing protocols should include baseline heavy metal profiling and ongoing monitoring of pesticide degradation. Organic certification systems (e.g., USDA Organic, EU Organic) provide third-party verification of pesticide restriction compliance and represent a market signal for quality commitment.[61]

Wild-crafting (collection from natural populations) presents particular challenges for GACP compliance given the inability to control soil and environmental conditions. GPS-tagged collection records, standardized botanical authentication by trained personnel, and testing of wild-collected materials for environmental contaminants are essential controls.[62]

7.2 Good Manufacturing Practices (GMP)

Pharmaceutical-grade GMP applied to herbal formulation manufacturing encompasses validated cleaning procedures to prevent cross-contamination; controlled environmental conditions (temperature, humidity, particulates); equipment qualification and calibration; solvent recovery systems with validated residual solvent testing; personnel hygiene and training programs; and comprehensive batch documentation enabling full traceability.[7, 63] WHO GMP guidelines specifically address herbal medicine manufacturing, recognizing the unique challenges of botanical raw material variability compared to chemically defined pharmaceutical actives.[3]

7.3 Advanced Purification Technologies

Supercritical fluid extraction (SFE) using CO2 as solvent offers an environmentally benign extraction approach that avoids toxic solvent residues while providing selective extraction of target bioactive compounds.[45] Molecular distillation, membrane filtration (nanofiltration, ultrafiltration), and preparative chromatography can effectively reduce heavy metals, pesticide residues, and other contaminants from herbal extracts while preserving bioactive content. Activated carbon treatment effectively reduces mycotoxin levels but may also remove beneficial phenolic compounds; optimized treatment conditions require careful balancing.[64]

7.4 Standardization and Biomarker Profiling

Standardization of herbal formulations—ensuring consistent content of marker compounds across production batches—is

a prerequisite for both therapeutic reliability and quality control.[51] Chemical fingerprinting by HPLC-DAD, HPLC-MS, or NMR spectroscopy generates comprehensive chemical profiles that simultaneously confirm botanical authenticity and detect chemical adulterants. Combined marker-compound standardization with impurity testing represents best practice for batch release.[56]

7.5 Post-Market Surveillance

Active pharmacovigilance programs that solicit and analyze adverse event reports attributable to herbal products are essential for identifying contamination patterns not detected in pre-market testing. The WHO Programme for International Drug Monitoring (VigiBase) includes herbal products, and several national pharmacovigilance centers (e.g., UK MHRA, US MedWatch) actively track herbal adverse events. [6, 65] Coordinated post-market sampling and testing programs for imported herbal products are especially important given the documented higher contamination rates in imports from regions with lower regulatory enforcement.

Future Research Directions and Perspectives

Several critical research and policy gaps require prioritization to advance the safety of herbal formulations.

8.1 Artificial Intelligence and Machine Learning Applications

Machine learning algorithms applied to large-scale analytical datasets (GC-MS, HPLC, ICP-MS profiles) can identify contamination patterns, predict high-risk products or sources, and optimize extraction processes to minimize impurity retention.[57] Natural language processing (NLP) applied to pharmacovigilance databases and scientific literature can enable real-time signal detection for emerging contamination events.

8.2 Regulatory Harmonization Initiatives

Global convergence of pharmacopoeial standards for herbal medicines—akin to the ICH framework for conventional pharmaceuticals—would significantly reduce regulatory complexity for manufacturers and strengthen consumer protection internationally. WHO, USP, EDQM, and national pharmacopoeial commissions need structured collaboration mechanisms to accelerate harmonization.[60] Implementation of mutual recognition agreements (MRAs) for herbal GMP inspections between major regulatory authorities would reduce duplication and resource demands.

8.3 Nanotechnology-Enhanced Detection

The translation of nano-enabled biosensors from laboratory to field-deployable, cost-effective instruments is a priority research area. Point-of-care sensors capable of simultaneously detecting multiple contaminant classes would transform quality monitoring in resource-limited settings, particularly in developing countries where most medicinal plant cultivation occurs. [22, 57]

8.4 Genomic and Metabolomic Approaches

Next-generation sequencing (NGS) for comprehensive microbiome profiling of herbal products offers advantages over culture-based methods for total microbial risk characterization. Untargeted metabolomics integrating LC-HRMS (high-resolution MS) can simultaneously characterize bioactive compounds and detect novel or unexpected chemical contaminants, providing a comprehensive chemical safety assessment in a single analysis.

8.5 Consumer Education and Health Literacy

Evidence-based consumer education programs targeting herbal medicine users are essential components of the public health response to herbal product contamination. Education should address: selection of products from GMP-certified manufacturers; risks of unregulated online purchases; importance of disclosing herbal medicine use to healthcare providers; recognition of adverse event signs; and the regulatory distinction between herbal medicines and dietary supplements.[65]

Conclusion

Impurities in herbal formulations constitute a complex, multidimensional public health challenge that demands an integrated scientific, regulatory, and educational response. This review has documented that microbial contamination, heavy metals, pesticide residues, mycotoxins, adulterants, and solvent residues—arising at multiple stages of the production chain—pose risks ranging from acute poisoning to chronic carcinogenesis and endocrine disruption. The global burden of impurity-related illness from herbal products is poorly characterized but likely substantial, particularly in low- and middle-income countries where regulatory infrastructure is less developed and herbal medicine reliance is highest.

Significant advances in analytical capability—including multi-residue GC-MS/MS and LC-MS/MS methods detecting hundreds of pesticides simultaneously, ICP-MS for trace metal profiling, DNA barcoding for botanical authentication, and emerging nanosensor platforms—provide the technical tools necessary for comprehensive impurity control. The challenge lies in translating these analytical capabilities into routine industrial practice through regulatory mandates, capacity building, and cost-effective implementation.

The path forward requires: (i) universal implementation of GACP and pharmaceutical GMP throughout the herbal medicine supply chain; (ii) accelerated global regulatory harmonization of impurity limits and testing requirements; (iii) investment in post-market surveillance infrastructure; (iv) integration of emerging technologies (AI, blockchain, nanosensors) into quality management systems; and (v) sustained consumer education promoting safe herbal medicine use. Only through this comprehensive approach can herbal medicine fulfill its potential as a safe, effective, and evidence-based component of global healthcare.

Abbreviations

AAS: Atomic Absorption Spectrometry ADI: Acceptable Daily Intake

AI: Artificial Intelligence As: Arsenic

CAM: Complementary and Alternative Medicine Cd: Cadmium

CFU: Colony-Forming Units ChP: Chinese Pharmacopoeia

DNA: Deoxyribonucleic Acid EDC: Endocrine-Disrupting Chemical

ELISA: Enzyme-Linked Immunosorbent Assay FAAS: Flame Atomic Absorption Spectrometry

FDA: Food and Drug Administration GACP: Good Agricultural and Collection Practices

GC-MS: Gas Chromatography-Mass Spectrometry **GFAAS:** Graphite Furnace Atomic Absorption Spectrometry
GMP: Good Manufacturing Practices Hg: Mercury
HPLC: High-Performance Liquid Chromatography
IARC: International Agency for Research on Cancer
ICH: International Council for Harmonisation ICP-MS: Inductively Coupled Plasma Mass Spectrometry
LC-MS: Liquid Chromatography-Mass Spectrometry
LOD: Limit of Detection
LOQ: Limit of Quantification MIP: Molecularly Imprinted Polymer
MRL: Maximum Residue Level MRM: Multiple Reaction Monitoring
NGS: Next-Generation Sequencing NIR: Near-Infrared Spectroscopy
NMR: Nuclear Magnetic Resonance Pb: Lead
PCR: Polymerase Chain Reaction Ph. Eur.: European Pharmacopoeia
QC: Quality Control QuEChERS: Quick, Easy, Cheap, Effective, Rugged and Safe
RSD: Relative Standard Deviation SFE: Supercritical Fluid Extraction
SPE: Solid-Phase Extraction STEC: Shiga Toxin-Producing Escherichia coli
TAMC: Total Aerobic Microbial Count TCM: Traditional Chinese Medicine
TYMC: Total Yeast and Mould Count USP: United States Pharmacopeia
WHO: World Health Organization XRF: X-ray Fluorescence

Declaration of Interests
The authors declare no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions
M.D.G.: supervision, writing—review and editing, correspondence.
R.S.G.: writing—review and editing, data curation.
S.N.K.: conceptualization, writing—original draft, literature search.

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