From Herb to Herbal Drug: Innovation in Quality Control and Standardization of Plant-Based Therapeutics

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Abstract

The global rise in plant-based therapeutics demands a stronger framework for quality control (QC) and standardization to ensure safety and clinical reliability. Standardizing herbal drugs is challenging because they contain many interacting phytochemicals rather than a single active compound, and their composition varies with genetics, environment, cultivation, and processing. These sources of variability, along with risks of adulteration or species substitution, highlight the need for advanced analytical tools.

Modern QC uses high-resolution techniques such as UHPLC-HRMS for detailed chemical fingerprinting and trace-level detection. Molecular authentication methods, including DNA barcoding, further confirm botanical identity. Systems-level approaches, particularly metabolomics and the development of Quality Markers (Q-markers), link chemical features to therapeutic activity and help validate synergistic effects in multi-component formulations. Emerging computational tools, especially Artificial Intelligence (AI) and Machine Learning (ML), are expected to transform QC through predictive modelling, Quality-by-Design workflows, golden-batch analytics, and early prediction of herb–drug interactions.

Together, these innovations support the development of safe, consistent, and globally reliable herbal therapeutics.

Keywords: herbal medicinal products, quality control, standardization, chemical profiling, DNA barcoding, metabolomics, AI-based quality assurance.

Introduction

Plant-derived therapeutics represent the oldest and most widely used form of healthcare, with over 80% of the global population still relying on them for primary medical needs. Their long-standing cultural acceptance, perceived safety, and empirical success have fueled rapid growth in the natural products market. However, this expansion demands a transition from tradition-based practices to rigorous, evidence-based validation to ensure safety, efficacy, and regulatory credibility equivalent to that of conventional pharmaceuticals [1].

A major challenge arises from the intrinsic chemical heterogeneity of botanical extracts. Unlike single-compound synthetic drugs, herbal preparations contain complex matrices of hundreds to thousands of

metabolites. Although this polychemical nature contributes to synergistic therapeutic effects, it complicates dosage accuracy, quality control, and batch-to-batch consistency. Additional variability stems from geographical origin, cultivation practices (GACP), and post-harvest processing.

This review examines key innovations needed to align the biological complexity of phytoconstituents with regulatory expectations for standardized quality assurance [2]. It discusses challenges related to variability and risk, followed by modern authentication tools such as genomic analysis (DNA barcoding) and advanced chemical profiling (e.g., UPLC-MS/MS). Subsequent sections highlight holistic standardization using 'omics' approaches (Herbomics) and the identification of Quality Markers (Q-markers) that link chemical profiles to therapeutic activity. Finally, the review explores computational advances, including AI and machine learning, for predictive modelling and automated process control [3].

The Crucial Need for Standardization and Quality Control in Herbal Drugs

Standardization and quality control (QC) are central to ensuring the therapeutic reliability, safety, and batch-to-batch consistency of herbal medicines. Because herbal drugs derive their activity from complex mixtures of phytochemicals, even subtle compositional shifts can lead to major differences in pharmacological outcomes [4].

Factors Contributing to Chemical Variability

Herbal drug composition is influenced by a wide range of variables. Genetic factors, including species, variety, and chemotype, can significantly alter phytochemical profiles. Environmental conditions such as soil type, climate, altitude, and seasonal changes also impact metabolite production. Additionally, plant age, harvest timing, drying, storage, and extraction procedures contribute to chemical heterogeneity. Such variability necessitates sophisticated standardization techniques to maintain consistent active-compound levels [5,6].

Analytical Approaches for Standardization

Chromatographic fingerprinting and spectroscopic profiling provide comprehensive chemical signatures, while chemometric analysis helps interpret complex datasets. Together, these tools support the development of reproducible profiles, enabling manufacturers to ensure chemical integrity and therapeutic uniformity across production batches [5,6].

Role of Quality Control in Safety Assurance

Strong QC practices are also essential for protecting public health. DNA barcoding is increasingly used for species authentication, allowing for the detection of adulterants, substitutions, or misidentified raw materials, issues that may lead to reduced efficacy or toxic reactions [7]. Furthermore, stringent contaminant testing for heavy metals, pesticide residues, microbial toxins, and mycotoxins helps ensure compliance with international safety standards and protects consumers from potential harm [8].
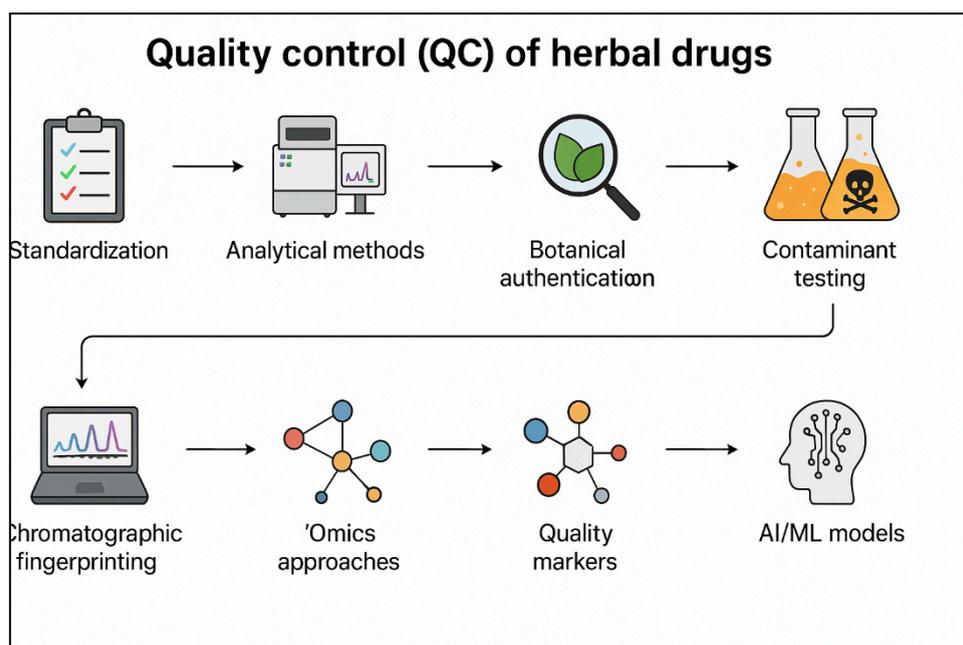
Fig. 1: Workflow of Quality Control (QC) in Herbal Drug Standardization.

Evolution of Herbal Medicine into Modern Therapeutics

1. **Traditional Herbal Medicine (THM):** Grounded in centuries of experience, THM uses complex plant mixtures (*phyto-complexes*) for healing. Documenting these traditional practices helps identify therapeutic plants and supports the discovery of bioactive natural compounds [9].

2. **Early Scientific Inquiry:** The isolation of compounds like morphine and digoxin revealed that specific molecules drive therapeutic effects, establishing the "one compound, one target" model that guided early pharmacology [10].
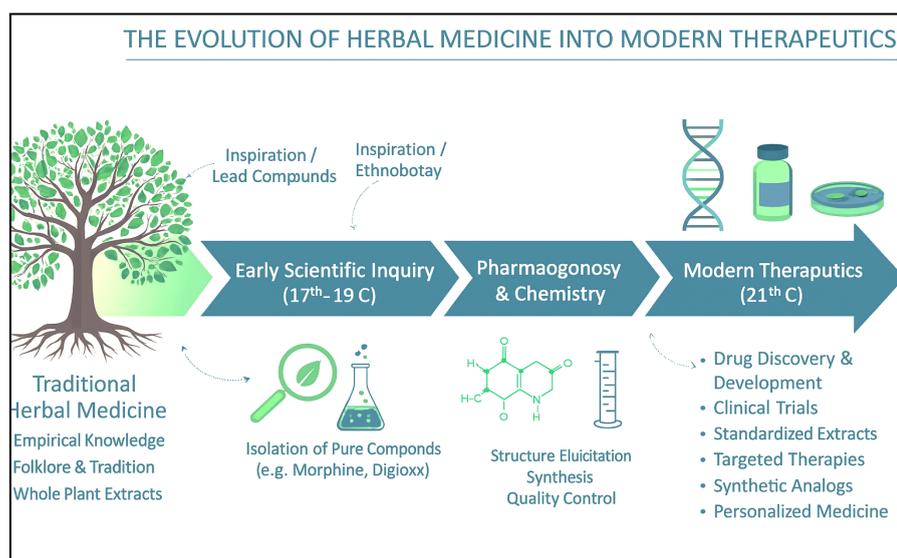

Fig. 2: *The figure presents a chronological overview of how herbal medicine transitioned into modern pharmacotherapy, from empirical traditional practices and whole-plant extracts, to the isolation of pure bioactive compounds, advances in structural elucidation and synthetic chemistry, and contemporary therapeutic approaches such as standardized extracts, clinical trials, and targeted or personalized medicines.*

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3. **Pharmacognosy & Chemistry:**

Scientific standardization strengthened herbal research.

   o Pharmacognosy ensures correct plant identification and material quality.

   o Analytical chemistry allows precise structure determination of bioactive compounds [11].

   o Medicinal chemistry refines these molecules into safer, more potent analogs, such as aspirin derived from salicin [12].

4. **Modern Therapeutics:**

Natural compounds remain key to modern drug discovery, as shown by artemisinin's ethnobotanical origins [13,14].

   ● Standardized Extracts & Synergy: Multiple plant components can work synergistically to boost efficacy and minimize side effects [15].

   ● Targeted & Personalized Medicine: AI tools now streamline natural-product screening and enable personalized therapies based on genetic profiles [16].

Modern Innovations in Plant Identification & Authentication

DNA Barcoding

DNA barcoding enables precise species identification by analysing short, standardized genomic regions that serve as unique molecular signatures, remaining effective even for highly processed or degraded herbal materials [17]. Using validated markers such as the ITS2 region, it achieves high species-level resolution across diverse medicinal plants [18]. By comparing a sample's barcode sequence with curated reference databases, DNA barcoding rapidly detects both unintentional and deliberate adulteration, including substitution with inert or toxic species. When integrated with chemical profiling, it represents the gold standard for verifying the identity and quality of herbal raw materials [19].
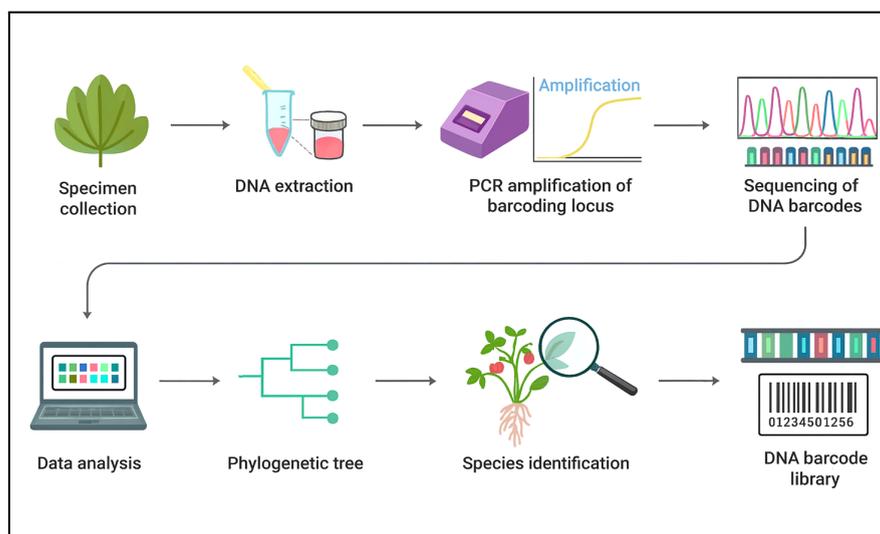

Fig. 3: DNA Barcoding and Its Applications (Adapted from Maurya et al., 2024.)

Chemotaxonomy

Chemotaxonomy works hand in hand with genetic testing by confirming a plant's identity through its unique chemical profile. Because a plant's chemistry is closely tied to its healing properties, this approach helps ensure

that the herb being used is both authentic and therapeutically reliable. With tools like LC-MS and NMR, researchers can create highly detailed "chemical fingerprints" that indicate whether each batch contains the correct amounts of key active or marker compounds. Maintaining this consistency is essential not only for guaranteeing quality but also for understanding how different plant compounds work together synergistically. This reliable chemical profiling strengthens clinical research outcomes and helps meet regulatory expectations for standardized herbal products [20].

Advanced Green Extraction and Purification Technologies

Traditional extraction techniques often rely on large volumes of harsh, petroleum-based solvents that require significant energy and produce toxic waste. Green Extraction Technologies were developed to address these concerns by focusing on safer, cleaner, and more sustainable methods. These modern approaches reduce solvent use, lower energy consumption, and prioritize environmentally friendly materials. They also make use of non-toxic solvents, such as supercritical CO_2 or other eco-friendly alternatives, ensuring that extraction is both efficient and gentle on the environment [21].

Supercritical Fluid Extraction (SFE)

Supercritical Fluid Extraction (SFE) is an advanced technique that uses fluids brought above their critical temperature and pressure, producing a gas–liquid hybrid state ideal for efficient extraction. Supercritical CO_2 ($scCO_2$) is the most widely used solvent because it is non-toxic, non-flammable, cost-effective, and leaves no residue once it returns to its gaseous state during depressurization [22]. Its density and solvating power can be finely tuned by adjusting temperature and pressure, allowing selective extraction of non-polar to moderately polar compounds such as essential oils and carotenoids [23]. As a result, SFE delivers rapid, highly selective extraction and produces clean, high-purity extracts without solvent contamination.
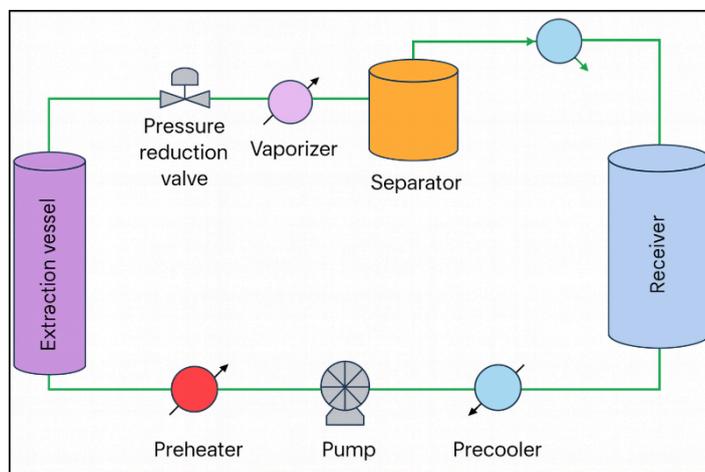
Fig.4: Supercritical Fluid Extraction (SFE) system (Adapted from ScienceDirect (2023))

Ultrasound-Assisted Extraction (UAE)

Ultrasound-Assisted Extraction (UAE) employs high-frequency sound waves (20–100 kHz) to enhance extraction efficiency. These waves generate microscopic bubbles that collapse violently, a phenomenon known as cavitation, creating localized heat and pressure that rupture plant cell walls and release intracellular compounds. By increasing surface area and reducing diffusion distance, UAE dramatically accelerates extraction compared with conventional techniques [24]. It also shortens processing time, operates at lower temperatures to preserve heat-sensitive constituents, and reduces solvent consumption.
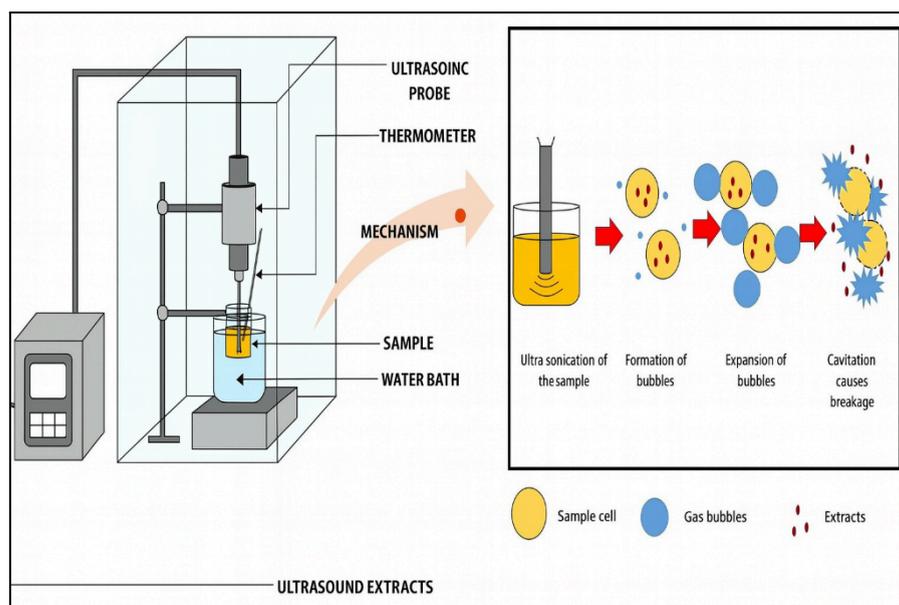
Fig.5: Ultrasound-Assisted Extraction (UAE) (Adapted from Patra et al., 2021)

Microwave-Assisted Extraction (MAE):

Microwave-Assisted Extraction uses electromagnetic energy to rapidly and uniformly heat both the solvent and the moisture within plant tissues.

- **Mechanism:** Microwave radiation excites polar molecules (e.g., water, polar solvents), causing rapid rotation and frictional heating. The resulting internal vapor pressure ruptures plant cell walls, enhancing compound release [25].
- **Scientific Principle:** Fast, simultaneous heating and pressure buildup accelerate the diffusion of both volatile and non-volatile constituents into the solvent, making MAE an efficient extraction method [25].

AI-Driven Quality Control and Digital Standardization

The growing chemical complexity of herbal medicines and the vast datasets generated from modern analytical platforms, such as liquid chromatography–mass spectrometry (LC-MS), nuclear magnetic resonance (NMR), and DNA sequencing, have accelerated the adoption of artificial intelligence (AI) and machine learning (ML) in quality control workflows. These technologies enable high-throughput, data-driven decision-making that surpasses the limitations of conventional manual interpretation. AI- and ML-based models can process thousands of chromatographic peaks, spectral features, and barcode sequences simultaneously, creating predictive systems capable of real-time evaluation and automated QC [26].

By training on large libraries of chromatographic and spectral fingerprints, ML algorithms can accurately classify herbal samples, detect adulteration, identify substitution, and even predict geographic origin or cultivation conditions, tasks that would be time-consuming or impossible using classical methods alone [27]. Beyond authentication, advanced AI-driven ADMET (absorption, distribution, metabolism, excretion, and toxicity) models provide early predictions of toxicity, pharmacokinetics, herb–drug interactions, and potential biological targets before laboratory experimentation. AI–robotic platforms further enhance QC by automating sample handling, extraction, and chromatographic runs, allowing continuous monitoring for contamination,

equipment deviations, or irregular peak profiles in real time [28,29]. Collectively, these digital technologies markedly increase the accuracy, reproducibility, and efficiency of herbal drug standardization.

Safety, Toxicity, and Contaminant Evaluation

Safety remains a core focus in pharmacognosy due to the risk of contaminants or intrinsic plant toxins. Heavy metals such as Pb, Cd, As, and Hg are quantified at trace levels with ICP-MS [30], while pesticides and aflatoxins are screened using GC-MS/LC-MS because of their potent toxicity [31]. Intrinsic toxic constituents, such as aristolochic acids and pyrrolizidine alkaloids, require detailed evaluation through predictive AI-based toxicity modelling and confirmatory in vitro/in vivo assays, which define cytotoxicity, mutagenicity, and safe dosage ranges [32]. Ensuring safety is a fundamental requirement in pharmacognosy due to the potential presence of external contaminants, environmental pollutants, or intrinsic plant toxins. Heavy metals such as lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) pose serious health hazards even at trace concentrations; therefore, high-sensitivity quantification using inductively coupled plasma mass spectrometry (ICP-MS) is essential for regulatory compliance [30]. Pesticide residues and aflatoxins, both highly toxic and carcinogenic, are routinely screened using gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS), which offer the sensitivity required for detecting contaminants at parts-per-billion (ppb) levels [31].

In addition to environmental contaminants, several medicinal plants naturally produce hazardous secondary metabolites. Compounds such as aristolochic acids and pyrrolizidine alkaloids are well-known for their nephrotoxic, genotoxic, and carcinogenic potential. Their evaluation requires an integrated strategy combining AI-based predictive toxicity modeling with confirmatory in vitro assays (cytotoxicity, mutagenicity, hepatotoxicity) and in vivo studies when necessary. These approaches help define safe dosage ranges, establish acceptable daily intake (ADI) limits, and guide regulatory recommendations for herbal medicines [32].

Future Directions: Next-Generation Herbal Therapeutics

The future of herbal medicine is rapidly shifting toward technologically integrated, evidence-based therapeutics. Omics platforms, particularly metabolomics, proteomics, and transcriptomics, enable holistic profiling of biological responses to herbal extracts, offering insights into synergistic interactions and multi-target pharmacology. These systems-level analyses validate the multi-component mechanisms that underlie the efficacy of herbal formulations, bridging traditional knowledge with modern biomedical science.

Nanotechnology has also emerged as a transformative tool in herbal drug delivery. Nanoformulations such as nanoemulsions, liposomes, phytosomes, and polymeric nanoparticles significantly enhance the solubility, stability, and bioavailability of phytochemicals with poor absorption or rapid metabolism. Moreover, targeted nano-delivery systems can concentrate herbal actives at specific tissues or pathological sites, supporting personalized, more precise therapeutic interventions. Together, these advancements are shaping the next generation of standardized, high-performance herbal medicines.

Conclusion

Transforming traditional herbs into reliable, standardized medicinal products requires a comprehensive and multi-layered approach. Rigorous authentication methods—such as DNA barcoding—ensure botanical accuracy, while chemotaxonomy and advanced analytical profiling establish detailed chemical signatures. Green and optimized extraction technologies support efficient recovery of bioactive compounds with minimal environmental impact. In parallel, thorough contaminant testing and toxicity assessments protect patient safety.

Integrating AI-driven quality control, predictive toxicity modelling, and nanotechnology-based formulations further enhances precision, consistency, and therapeutic efficacy. Collectively, these innovations form the foundation for developing evidence-based, next-generation herbal therapeutics that meet global standards of quality and safety

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