

Standardization of Herbal Medicine Through Biotechnology: Ensuring Consistency and Efficacy of Phytopharmaceuticals

Standardisasi Obat Herbal Melalui Bioteknologi: Menjamin Konsistensi dan Efikasi Fitofarmaka

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Abstrak

Latar belakang: Obat herbal masih menghadapi persoalan ketidakkonsistenan mutu antarbatch yang berakibat pada keragaman identitas botani, kondisi tumbuh, waktu panen, dan pengolahan pascapanen, sehingga reproduksibilitas uji klinik dan registrasi fitofarmaka terhambat. **Tujuan:** Ulasan naratif ini bertujuan merangkum kontribusi pendekatan bioteknologi terhadap standarisasi obat herbal pada periode 2020 sampai 2026. **Metode:** Penelusuran pustaka dilakukan pada Scite.ai, PubMed, ScienceDirect, MDPI, Frontiers, dan Google Scholar menggunakan kombinasi kata kunci standarisasi obat herbal, DNA barcoding, sidik jari kromatografi, metabolomik, kultur jaringan tanaman, akar rambut, kemometrik, dan kecerdasan buatan; lima puluh artikel yang terbit antara tahun 2020 sampai 2026 dan memiliki DOI yang dapat ditelusur dimasukkan ke dalam ulasan. **Hasil:** Telaah mengidentifikasi lima pilar bioteknologi yang saling melengkapi, yaitu autentikasi molekuler bahan baku, penyediaan biomassa terkendali melalui kultur in vitro, pengendalian proses melalui elisitasi dan bioreaktor, profil kimia berbasis sidik jari dan metabolomik, serta pemodelan data menggunakan kemometrik dan kecerdasan buatan. Integrasi kelima pilar tersebut memindahkan titik kendali mutu dari pemeriksaan produk akhir menjadi pengendalian sepanjang rantai produksi. **Kesimpulan:** Bioteknologi berpotensi menjamin konsistensi dan efikasi fitofarmaka, tetapi masih terkendala keterbatasan basis data barcode, pergeseran metabolisme sekunder pada sel terdediferensiasi, biaya penskalaan bioreaktor, serta belum adanya kerangka regulasi yang mengakui biomassa hasil kultur in vitro sebagai bahan baku resmi.

Kata kunci: Bioteknologi, DNA Barcoding, Fitofarmaka, Obat Herbal, Standardisasi

Abstract

Background: Herbal medicine still faces batch-to-batch inconsistency arising from variation in botanical identity, growing conditions, harvest time and post-harvest processing, which compromises the reproducibility of clinical trials and delays the registration of phytopharmaceuticals. **Objective:** This narrative review aimed to summarise the contribution of biotechnological approaches to the standardization of herbal medicine during 2020 to 2026. **Methods:** Literature was retrieved from Scite.ai, PubMed, ScienceDirect, MDPI, Frontiers and Google Scholar using combined keywords of herbal standardization, DNA barcoding, chromatographic fingerprint, metabolomics, plant tissue culture, hairy root, chemometrics and artificial intelligence; fifty articles published between 2020 and 2026 with traceable DOIs were included. **Results:** Five complementary biotechnological pillars were identified, namely molecular authentication of raw material, controlled biomass supply through in vitro culture, process control through elicitation and bioreactor cultivation, chemical profiling based on fingerprinting and metabolomics, and data modelling using chemometrics and artificial intelligence. Integration of these pillars shifts the point of quality control from end-product testing to control along the entire production chain. **Conclusion:** Biotechnology can secure the consistency and efficacy of phytopharmaceuticals, but incomplete reference barcode databases, the shift of secondary metabolism in dedifferentiated cells, the cost of bioreactor scale-up and the absence of a regulatory framework recognising in vitro-derived biomass as an official raw material remain to be resolved.

Keywords: Biotechnology, DNA Barcoding, Herbal Medicine, Phytopharmaceutical, Standardization

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1. INTRODUCTION

Herbal preparations remain the first line of treatment for a large part of the world population. Unlike a single-entity synthetic drug, however, a herbal product is a chemically complex matrix whose composition is determined by the genetic identity of the source plant, the environment in which it was grown, the developmental stage at harvest, and the drying, storage and extraction procedures applied afterwards [1,3]. Quality control of herbs therefore has to address identity, purity and content simultaneously, and no single analytical parameter is sufficient on its own [1].

When the concentration of the active constituents differs between batches, the dose actually administered differs as well, and the outcome of a clinical trial performed with one batch cannot be extrapolated to another. Variability in sourcing, cultivation, extraction and phytochemical composition has produced substantial discrepancies in the content and bioavailability of key bioactives among commercial and research-grade preparations, hampering clinical reproducibility and regulatory approval [25]. Deliberate or accidental adulteration compounds the problem, and chemical analysis alone cannot always reveal it [12,13].

Conventional pharmacopoeial standardization answers these problems from the downstream end, through the assay of one or a few marker compounds in the finished product [3,5]. A marker assay confirms that a specified constituent is present at a specified level, but it neither explains why a batch failed nor prevents the next failure. Fingerprint analysis extends the view to a pattern of constituents and has become the reference tool for holistic quality assessment [4,6], yet it remains an inspection of a material whose history is largely unknown.

Biotechnology offers a different point of intervention. Molecular methods establish the identity of the raw material before any chemistry is performed [8,11]; plant tissue culture replaces field-collected biomass with clonal material produced under defined, season-independent conditions [14,17]; elicitation, precursor feeding and bioreactor cultivation steer the accumulation of the target metabolites rather than merely recording it [16,23]; and metabolomics, chemometrics and machine learning convert the resulting data into quantitative quality models [7,28,34,35]. Together, these tools move the point of control upstream, from the inspection of the finished extract to the design of the process that produces it.

Indonesian research groups have built capacity in the upstream segment of this chain. Callus induction and micropropagation protocols have been established for *Orthosiphon aristatus* [42,43,46], the chemical profile of the in vitro material has been compared with that of the wild-type plant [44,45,47], elicitation has been studied in the same species [48] and the available protocols reviewed [49], and a natural biostimulant has been applied to *Curcuma xanthorrhiza* [50]. These studies show that the technical prerequisites are accessible nationally, but they also expose the gap between a characterised callus line and a raw material accepted by a regulator. The objective of this review is to map the biotechnological approaches reported between 2020 and 2026 that contribute to the standardization of herbal medicine, to show how they connect into a single quality chain, and to identify the technical and regulatory bottlenecks that still prevent that chain from being closed.

2. METHODS

Literature Sources

This work is a narrative literature review. Records were retrieved from Scite.ai, PubMed, ScienceDirect, SpringerLink, MDPI, Frontiers, Wiley Online Library and Google Scholar. Scite.ai served as the primary entry point because it classifies each citation statement as supporting, contrasting or mentioning, which allowed the standing of a claim to be judged before the source was accepted. The Google Scholar profile of the corresponding author was screened separately to ensure that relevant national work on in vitro culture and phytochemical characterisation was represented.

Search Strategy

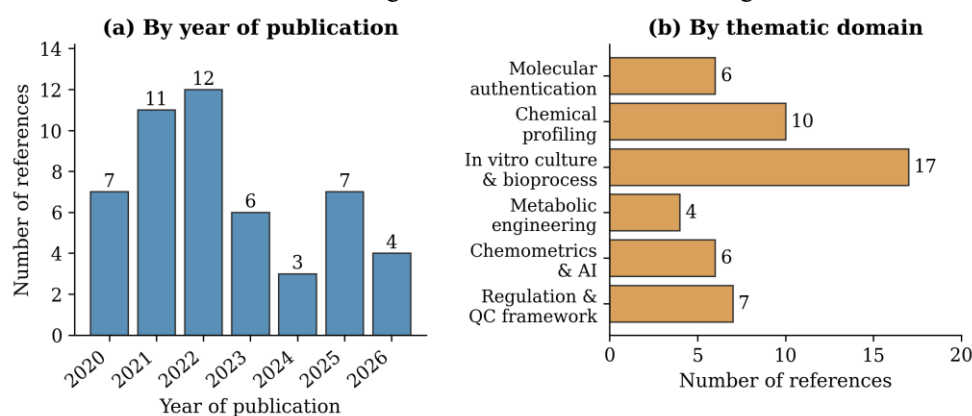
Boolean combinations of the following terms were used: herbal medicine, standardization, quality control, marker compound, chromatographic fingerprint, DNA barcoding, molecular authentication, adulteration,

metabolomics, quantitative NMR, chemometrics, plant tissue culture, micropropagation, callus, cell suspension, hairy root, elicitation, bioreactor, metabolic engineering, CRISPR, artificial intelligence and machine learning. Phrase search and field restriction to title and abstract were applied whenever a query returned more than one thousand records.

Selection Criteria and Data Extraction

Records were included when they were published between January 2020 and June 2026, were written in English or Indonesian, carried a resolvable Digital Object Identifier, and addressed at least one biotechnological or analytical element of herbal quality assurance. Records reporting pharmacological screening without any quality or production component, records whose full text could not be retrieved, and preprints duplicating a peer-reviewed article were excluded. Fifty records met these criteria. For each record the plant species, the technique and the quality attribute addressed were extracted into a matrix and organised thematically; their distribution by year and by thematic domain is shown in Figure 1. Three recent articles published in Jurnal Farmasimed on extract quality parameters and on the microbial quality of jamu were additionally consulted to relate the review to national quality-control practice [51–53].

Figure 1. Distribution of the Fifty References Included in This Review: (a) by Year of Publication; (b) by Thematic Domain. A reference addressing more than one domain was assigned to its dominant theme.



3. RESULTS

Sources of Variability and the Limits of Conventional Standardization

The variability of herbal material arises at four successive points. The first is botanical identity, since closely related species and even varieties of the same species differ in their metabolite profile. The second is the growing environment; NMR-based metabolomic comparison of *Adhatoda vasica* leaves collected from different regions discriminated the samples by geographical origin, demonstrating that provenance alone leaves a measurable chemical signature [30]. The third is developmental stage and harvest time, and the fourth is post-harvest processing, extraction solvent and storage [1,26].

Conventional quality control addresses these sources through macroscopic and microscopic examination, ash and extractive values, moisture content, heavy metal and microbial limits, and the assay of one or more marker compounds [1–3,5]. National studies illustrate this practice: specific quality parameters of *Stachytarpheta jamaicensis* leaf extract have been established as a reference for standardized herbal medicine [51], while microbial testing of jamu has shown that compliance with BPOM limits depends on hygiene during production rather than on the plant material itself [52,53]. The limitation of the marker approach is conceptual: a single constituent rarely accounts for the whole pharmacological effect of a multi-component extract, so compliance with a marker specification does not guarantee therapeutic equivalence.

Fingerprint analysis was developed in response to this limitation and evaluates the chromatographic or spectroscopic pattern as a whole rather than a single peak [4]. Recent refinements fuse the information from several detection wavelengths into a single composite fingerprint, which improves the discriminating power of

the method for complex herbal matrices [6]. In traditional Chinese medicine the concept has been formalised as the quality marker, which attempts to establish a demonstrable correlation between the multi-component content of a formula and its clinical efficacy rather than relying on a pharmacopoeial constituent chosen for analytical convenience [35].

Molecular Authentication of the Raw Material

DNA-based identification addresses the first source of variability directly, because the genome of the source plant is unaffected by season, processing or extraction. Two decades of work on DNA barcoding in herbal medicine have established standard loci such as ITS2, *rbcL*, *matK* and *psbA-trnH*, and have extended the approach from raw crude drugs to processed products through mini-barcodes and next-generation sequencing [8]. Strategies for molecular authentication now cover the whole workflow from experimental design to data analysis, including reference database construction and the statistical treatment of mixed samples [11].

The method is nonetheless not self-sufficient. Barcoding in the Lamiaceae, a family of major medicinal importance, illustrates the recurrent difficulties: incomplete reference libraries, recent radiations in which the standard loci lack resolution, hybridisation between species, and degradation of DNA in heavily processed material [10]. For this reason the current consensus is orthogonal rather than exclusive, combining DNA barcoding with chemical and macroscopic evidence so that the weaknesses of each technique are covered by the others [9]. Chemical authentication of botanical ingredients in commercial herbal products has shown how frequently declared and actual composition diverge [12], and a national survey of Brazilian medicinal plants and herbal products reached a similar conclusion, recommending the systematic combination of botanical, chemical and molecular evidence [13].

Biotechnological Control of the Raw Material Supply

In vitro culture removes the environmental component of variability by producing biomass under defined conditions. Micropropagation generates clonal plantlets that are genetically identical to a selected mother plant and has been developed for a wide range of medicinal species, including endangered ones [14]. Because the resulting clones are true to type, the chemical variability attributable to genotype is eliminated at the outset, and the same protocol simultaneously serves conservation by relieving collection pressure on wild populations [15]. Undifferentiated cultures go further by producing the metabolite in the vessel rather than in the field. Cell suspension culture is generally preferred because it combines homogeneity of yield and quality with the most favourable scale-up characteristics [23]. For *Panax ginseng*, adventitious root, cell suspension and hairy root systems have been scaled in bioreactors, yielding product of regulated quality that is free from pesticide contamination and independent of geography and season [17], and *Rhodiola rosea* callus, suspension and root cultures have been characterised as a defined source of flavonoids and ecdysteroids [20].

Hairy root cultures obtained by *Rhizobium rhizogenes* transformation occupy a particular position in a standardization context because of their genetic and biosynthetic stability, which offers the possibility of establishing standards for the parameters that affect biomass accumulation and metabolite production [19]. They grow without exogenous plant growth regulators and reproduce the metabolite profile of the source organ, often at higher concentration [22]. Root cultures in general show greater constancy in metabolite production than suspension cultures, which is attributed to the instability and non-uniformity of undifferentiated cells in liquid medium [18].

The yield of an unstimulated culture is usually insufficient, and elicitation, precursor feeding and the choice of culture system are the standard remedies [16]. In submerged adventitious root cultures of *Stevia rebaudiana*, 3.0 mg/L melatonin combined with 0.5 mg/L naphthalene acetic acid gave the maximum dry biomass of 28.64 g/L and the highest stevioside content of 91.45 mg/g dry weight [21]. Work from the present authors on purple *Orthosiphon aristatus* similarly showed that elicitation and precursor supply modulate the accumulation of the main secondary metabolites in culture [48].

Scale-up is where most of these systems fail. Plant cells form aggregates up to half a centimetre in diameter that limit substrate and oxygen transfer and depress growth and product formation, so the bioreactor configuration must reconcile the properties of the cell line with the transport phenomena imposed by the operating conditions [23]. Low yield, cell line instability and inconsistent product quality remain the principal barriers to industrial adoption [24]. For hairy roots of *Gentiana dinarica*, simple temporary immersion and bubble column bioreactors gave higher dry matter and xanthone content than flasks and were proposed as the basis for commercial production [19]. The main platforms are summarised in Table 1.

Table 1. Biotechnological Platforms for Controlled Raw Material Supply and Their Contribution to Standardization.

Platform	Standardization gain	Main limitation
Micropropagation	Clonal, true-to-type plantlets; genotype variability removed; supports conservation [14,15]	Field growth still exposes plantlets to environmental variation
Callus and cell suspension	Season- and geography-independent biomass; homogeneous yield; best scale-up profile [17,23]	Metabolite profile may shift on dedifferentiation; line instability [20]
Hairy root culture	Genetic and biosynthetic stability; hormone-autotrophic; profile matches source organ [19,22]	Shear sensitivity and clumping; specific reactor geometry required [19]
Elicitation and precursor feeding	Raises marker content to a defined target level at low cost [16,21,48]	Response depends on elicitor dose, exposure and culture age
Bioreactor cultivation	Documented, controllable process parameters compatible with GMP reasoning [19,23]	Aggregate formation limits mass transfer; capital cost

Chemical Profiling and Metabolomics as Standardization Tools

Whatever the origin of the biomass, its chemical identity has to be documented. Metabolomics extends fingerprinting from a target set of constituents to the widest accessible portion of the metabolome, and its role in the standardization of herbal medicine, together with the sustainability implications of large-scale profiling, has recently been reviewed [7]. Nuclear magnetic resonance spectroscopy is particularly suited to this purpose because it is intrinsically quantitative, requires minimal sample preparation and is highly reproducible between laboratories; the combination of quantitative NMR data with chemometric exploration has been established as a general framework for the quality assessment of medicinal plants [28], and its application in nutraceutical research has been surveyed in detail [29].

The discriminating power of this combination is well documented. NMR metabolomics differentiated *Actaea* species that are routinely confused in commerce [32], discriminated *Adhatoda vasica* leaves by geographical origin [30], and authenticated spices when coupled with multivariate statistics [31]. Applied to traditional Chinese medicine, holistic 1H-NMR profiling combined with discriminant analysis was able to classify materials according to their traditional medicinal properties, which is a direct attempt to link a chemical pattern to a therapeutic category [33]. Chemical characterisation in our own laboratory has followed the same logic on a smaller scale, comparing the thin-layer and high-performance liquid chromatographic profiles of in vitro and wild-type material of *O. aristatus* and quantifying the marker compounds sinensetin and rosmarinic acid [44,45,47].

Table 2. Analytical Approaches Applied to Herbal Standardization and the Quality Attribute They Address.

Approach	Quality attribute	Representative evidence
Pharmacopoeial parameters	Purity, moisture, ash, contaminants	Reviews of quality control parameters for herbal drugs [1,3]
Marker compound assay	Content of a defined constituent	Flavonoid markers in routine quality control [5]; sinensetin and rosmarinic acid quantification [47]

Approach	Quality attribute	Representative evidence
Chromatographic fingerprint	Holistic pattern of constituents	Fingerprint analysis for standardization [4]; wavelength fusion fingerprints [6]
DNA barcoding	Species identity and adulteration	Retrospective and prospective account of barcoding [8]; orthogonal authentication [9]
NMR and LC-MS metabolomics	Global chemical profile; origin	qNMR with chemometrics [28]; geographical discrimination [30]; species differentiation [32]
Chemometrics and AI	Classification, grading, prediction	Intelligent sensory systems for TCM [34]; quality marker mining [35]; image-based authentication [36]

Chemometrics and Artificial Intelligence

The data generated by fingerprinting and metabolomics are high-dimensional, heterogeneous and frequently non-linear, which exceeds the capacity of univariate specification limits. Artificial intelligence has entered herbal quality evaluation along two routes. The first is the interpretation of instrumental sensory data: electronic nose, electronic tongue and machine vision platforms generate datasets containing redundancy and noise, and machine learning and deep learning have become the essential analytical tools for linking these patterns to quality attributes such as origin, authenticity, degree of processing and pharmacological property [34]. The second is image-based authentication, illustrated by a deep learning system that distinguished *Zizyphus jujuba* from the visually similar and therapeutically unverified *Zizyphus mauritiana* with 98.36 per cent accuracy, using explainable AI to show that the model attended to the same features as an expert evaluator [36].

A more ambitious application is the derivation of quality markers themselves. Conventional marker selection inevitably involves human judgement; machine learning offers a route to a quantifiable, multi-component efficacy-quality correlation in which the marker set is derived from data rather than chosen a priori [35]. The recurrent obstacles reported across this literature are data standardization between laboratories, sensor drift, model robustness on unseen batches, and interpretability [34].

Metabolic Engineering and the Omics Toolkit

Beyond controlling the conditions of production, biotechnology can alter the biosynthetic capacity of the producing organism. Metabolic engineering through CRISPR/Cas and related tools allows key enzymes and transcription factors to be raised or suppressed, so that the metabolite profile itself becomes a design parameter [37–39], and functional genomics, pathway engineering and scalable culture are now presented as a unified framework for producing medicinal plant metabolites [40]. The reconstruction of the thirty-step vinblastine pathway in engineered yeast shows that precursors of an essential anticancer drug can be produced independently of crop factors [41]. Such an engineered chassis represents the theoretical endpoint of consistency, although titres remain far below commercial requirements [41] and off-target effects, complex genomes and low transformation efficiency limit most medicinal species [38].

An Integrated Standardization Chain

The techniques reviewed above are frequently reported in isolation, but their value in quality assurance is cumulative. Molecular authentication guarantees that the correct species entered the process; controlled culture guarantees documented production conditions; elicitation and bioreactor control set the marker content at a target level; chemical profiling records what was obtained; and chemometric modelling converts that record into a release decision. Figure 2 presents this sequence as an operational chain with a feedback path through which an out-of-specification batch returns to process re-optimisation, and Figure 3 shows that consistency and efficacy are obtained only where genomic, metabolomic and bioprocess control intersect.

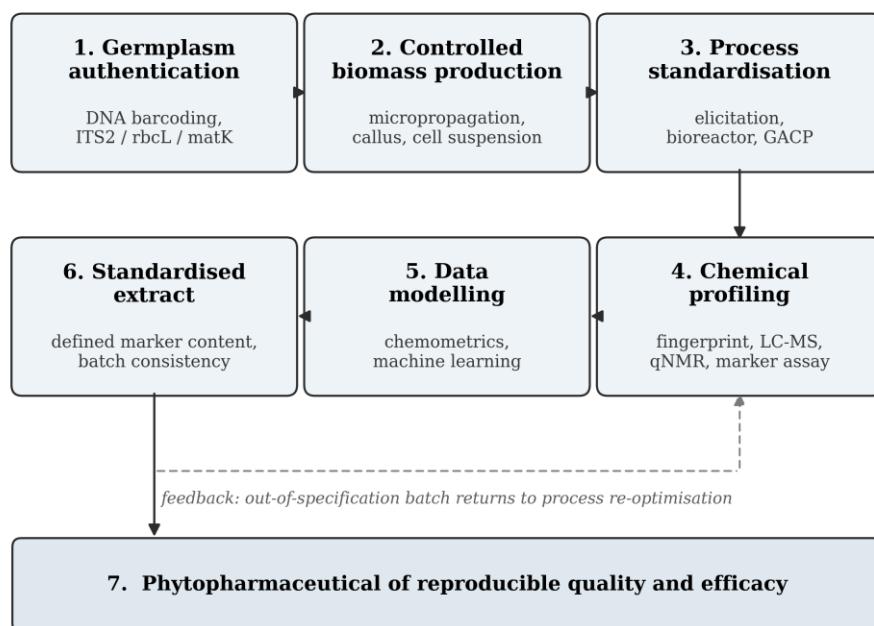


Figure 2. Integrated Biotechnology-Based Standardization Chain for Phytopharmaceutical Production, from Germplasm Authentication to the Release of a Standardized Extract, with the Feedback Path for Out-of-Specification Batches.

4. DISCUSSION

The material reviewed indicates that the standardization of herbal medicine has shifted in emphasis between 2020 and 2026, from the refinement of end-product testing towards the control of the process that generates the product. The analytical literature has become progressively more holistic, moving from single markers to fingerprints [4] and then to fused multi-wavelength patterns [6]. Targeted assays have likewise given way to untargeted metabolomics coupled with multivariate statistics [7,28]. In parallel, the biotechnological literature has moved from demonstrating that a metabolite can be produced in vitro towards demonstrating that it can be produced reproducibly and at scale [19,23]. These two trajectories converge on the same conclusion: quality is a property of the process, not of the final assay.

A tension nevertheless runs through the in vitro literature. Dedifferentiated plant cells are not miniature plants, and the metabolite profile of a culture may diverge systematically from that of the source organ. Root and organ cultures give more constant metabolite production than suspension cultures because undifferentiated cells in liquid medium are unstable and non-uniform [18], and hairy roots are valued for a genetic and biosynthetic stability that makes standards possible at all [19]. A culture-derived raw material therefore requires its own specification, benchmarked against the whole plant rather than assumed equivalent to it, and the age of the cell line should be documented alongside medium composition and elicitor dose.

The pillars also differ in maturity. Molecular authentication and chemical profiling are technically mature and embedded in pharmacopoeial thinking, although barcode reference databases remain incomplete for many tropical taxa [10]. In vitro production is mature at laboratory scale but commercial only for a few high-value metabolites [17]. Artificial intelligence is the least mature: reported accuracies are high [36], but most studies classify samples without a mechanistically interpretable link between pattern and therapeutic property [34], and a model that cannot explain its decision is difficult to defend in a regulatory dossier.

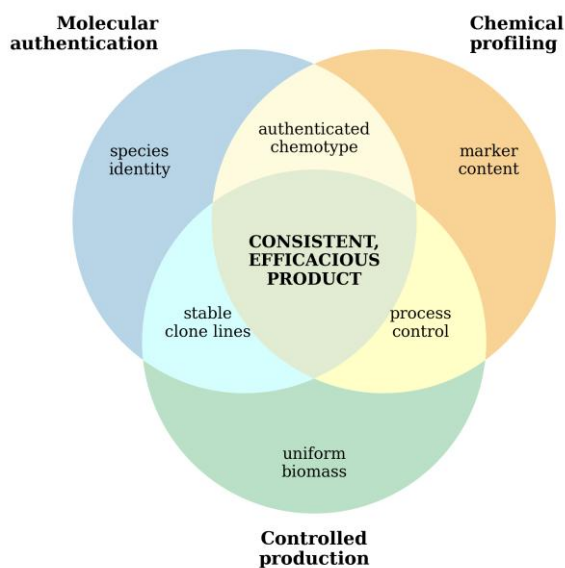


Figure 3. Venn Representation of the Three Biotechnological Domains Contributing to Herbal Standardization; Consistency and Efficacy Are Achieved Only in the Central Intersection Where All Three Are Applied Together.

The regulatory dimension is in fact the least developed part of the chain. Pharmacopoeial monographs are written for material of defined botanical origin collected under good agricultural and collection practice; they do not generally provide for biomass generated by cell suspension or hairy root culture, however well characterised. The literature reviewed here shows repeatedly that the technical obstacle to commercialisation is no longer whether a compound can be produced in vitro but the duration and cost of certifying the resulting product [27]. Closing this gap will require specifications written for culture-derived material, including identity criteria for the cell line, stability data across subcultures, and acceptance limits benchmarked against the traditional raw material.

For research groups in Indonesia, the analysis suggests a pragmatic sequence. The establishment and phytochemical characterisation of in vitro lines for local species, achieved for *O. aristatus* [42,43,46] and recently extended to *C. xanthorrhiza* [50], is the prerequisite but not yet a standardization technology. The next step is the quantitative validation of marker content in culture-derived biomass against wild-type material [44,45,47]; elicitation can then bring that content to a defined specification [48], and a molecular identity check can be added to existing macroscopic, chromatographic and microbial testing [51–53] at low cost relative to its regulatory weight.

Three research priorities follow. The first is the systematic pairing of in vitro production with orthogonal authentication and full chemical profiling in the same study, which is currently rare; most papers report either the culture or the analysis. The second is the reporting of bioreactor work in engineering terms, with explicit description of aggregate size distribution, oxygen transfer and shear, so that results become transferable between laboratories [23]. The third is the development of interpretable machine learning models validated on independent batches rather than on random splits of a single dataset [34]. The principal limitation of the present review is that it is narrative rather than systematic, and that the heterogeneity of the units in which yields and accuracies are reported precluded any quantitative synthesis.

5. CONCLUSION

Biotechnology contributes to the standardization of herbal medicine through five complementary pillars: molecular authentication of the raw material, controlled biomass production by in vitro culture, process control by elicitation and bioreactor cultivation, chemical profiling by fingerprinting and metabolomics, and data modelling by chemometrics and artificial intelligence. Applied together, these pillars move quality control from

the inspection of the finished extract to the design and documentation of the process that produces it, which is the condition for batch-to-batch consistency and therefore for reproducible clinical efficacy. Molecular authentication and chemical profiling are technically mature, in vitro production is mature at laboratory scale, and artificial intelligence remains at the stage of correlative classification. The principal remaining obstacles are incomplete barcode libraries for tropical taxa, the metabolic shift that accompanies dedifferentiation, mass transfer limitations and cost in bioreactor scale-up, the limited interpretability of machine learning models, and the absence of pharmacopoeial specifications for culture-derived raw material, which future work should address in dialogue with regulators.

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