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When Marker Compounds Misrepresent Herbal Quality: A Multi-Attribute Standardization Model Linking Identity, Chemical Consistency, Potency-Relevant Constituents, and Contaminant Risk

Hans Müller[1]*, Anna Schmidt[1], Thomas Weber[2]

[1]Department of Herbal Quality Control and Standardization, Faculty of Pharmaceutical Sciences, University of Bonn, Bonn, Germany.
[2]Department of Potency-Relevant Analytics and Contaminant Risk Assessment, Faculty of Chemistry and Pharmacy, LMU Munich, Munich, Germany.

***E-mail** ✉ hans.mueller@uni-bonn.de
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ABSTRACT

Herbal quality control often relies on one or a few marker compounds because they are measurable, stable, and compatible with routine specifications. Yet a marker can satisfy an assay without establishing that the correct botanical material is present, that the wider chemical profile is consistent, that measured constituents are relevant to biological potency, or that exogenous hazards are adequately controlled. This article develops an original, nonempirical standardization model that treats these questions as analytically related but non-substitutable. The model is built from recent evidence on chromatographic and spectroscopic fingerprinting, DNA-based authentication, metabolomics, multicomponent quantification, spectrum–effect analysis, pharmacokinetic and bioavailability-informed marker selection, process analysis, and contaminant surveillance. Four proposed quality attributes are separated: material identity, chemical consistency, potency-relevant constituent evidence, and contaminant risk. Product state, botanical part, provenance, processing, formulation complexity, and intended use are treated as context modifiers that determine which evidence is observable and which analytical methods are appropriate. The model therefore rejects both a single-marker definition of total quality and the opposite assumption that adding more measurements automatically yields better standardization. Instead, it proposes claim-specific sufficiency, orthogonal evidence where failure modes differ, and explicit validation boundaries. The framework is not a validated scoring system, regulatory standard, or universal assay panel. Its value lies in organizing heterogeneous quality evidence into a testable architecture that can be challenged through product-specific, cross-laboratory, and prospective validation.

Keywords: Herbal medicines, Quality markers, Authentication, Chemical fingerprinting, Potency, Contaminant control

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Introduction

Herbal medicines pose a quality-control problem in which the analytical object is rarely a single molecule. Species identity, plant part, provenance, processing, extraction, storage, and formulation can all influence what is present in the final material, while quality specifications often remain anchored to a small number of analytically convenient constituents. The quality-marker concept was developed in part to connect measurable constituents more closely to the defining properties and therapeutic relevance of traditional medicines, rather than treating abundance or ease of assay as sufficient justification for marker choice [1]. This move is important, but it does not by itself resolve which kinds of evidence are required for a quality claim.

The central difficulty is that different analytical strategies answer different questions. Botanical-forensic work has shown that authentication methods can be vulnerable to deliberate or inadvertent analytical deception; fingerprint

approaches broaden the chemical information captured beyond isolated markers; and multimodal quality-marker strategies integrate more than one evidence source when selecting candidate indicators [2–4]. These developments support a narrower conclusion than "marker testing fails": a marker result can be analytically correct yet insufficient for a broader inference about herbal quality. The failure lies in extending one measurement beyond the construct it can validly represent.

This article develops an original standardization model around that distinction. It proposes that four quality attributes should remain separately interrogable: material identity, chemical consistency, potency-relevant constituents, and contaminant risk. They can interact, but none should automatically substitute for another. A chemically characteristic compound may help confirm compositional consistency without proving species identity; a pharmacologically interesting constituent may be absent from systemic exposure; and a chemically authentic product may still contain unacceptable contaminants. Conversely, a marker can remain entirely appropriate when the claim is narrow—for example, controlling the amount of a defined constituent within a validated manufacturing specification.

The purpose is therefore not to replace marker compounds with maximal analytical complexity. It is to align the breadth of evidence with the breadth of the quality claim. This distinction is important for specification design: an assay can be precise and reproducible yet still have limited construct coverage if the decision being made concerns a different attribute. Conversely, requiring every available technology would add cost and analytical noise without necessarily resolving a relevant uncertainty. The proposed model therefore uses product and process context to determine which attributes are material to a decision, which methods can observe them, and where orthogonal confirmation or independent validation is justified. It is a conceptual integration of established analytical and pharmacognostic evidence, not a prospectively validated scoring system, regulatory standard, or claim of therapeutic effectiveness.

Why marker-centered standardization can fail

Chromatographic methods remain central to pharmacopoeial quality control because they provide selective identification and quantification of defined constituents [5]. Their strength, however, is also their boundary: a targeted assay can demonstrate conformity for the analytes it measures without representing the full chemical state of a complex botanical preparation. Reviews of multicomponent quantification have therefore emphasized practical strategies for measuring several constituents in complex systems, while also showing that analytical feasibility, selectivity, and calibration remain method-dependent [6]. More analytes are not intrinsically better; the relevant question is whether the measurement set is adequate for the intended claim.

The small-molecule marker paradigm also transfers imperfectly across constituent classes. In *Hericium erinaceus* polysaccharides, enzymatic release followed by capillary electrophoresis–laser induced fluorescence was used to quantify characteristic oligosaccharides, illustrating that macromolecular quality may require indirect structural readouts rather than conventional intact-marker assays [7]. This is a hard case for universal marker logic because analytical observability depends on the chemistry of the material itself.

A second failure mode is conflating chemical conformity with biological-source identity. Complementary DNA metabarcoding and HPTLC applied to commercial Chinese herbal products produced different but informative views of product composition [8]. Reviews of commercial chemical authentication document recurrent quality problems while also showing dependence on the analytical method and reference expectation [9]. HPTLC can expose profile inconsistencies in marketed herbal products [10], whereas DNA barcoding addresses taxonomic identity through sequence evidence and carries distinct limitations when material is highly processed or reference resources are incomplete [11]. Neither modality is a universal gold standard.

A third limitation is semantic rather than instrumental. The terms "marker," "active constituent," "characteristic compound," and "quality indicator" can be treated as though they were interchangeable, although the evidence required for each role differs. A compound may be species-associated yet pharmacologically irrelevant, chemically stable yet insensitive to processing, or biologically active in an assay yet unsuitable for routine quantitative control. The analytical validity of its measurement does not settle those role assignments.

Marker-centered standardization therefore fails chiefly when a valid measurement is asked to support an invalidly broad inference. The proposed model treats this as a claim–evidence mismatch: identity, overall chemical state, biological relevance, and hazard control may overlap, but they should not be collapsed merely because one analytical signal is convenient to specify. This formulation also preserves the legitimate use of narrow marker specifications when the intended claim is correspondingly narrow and analytically validated.

Dimensions of herbal product quality

Material identity is the first proposed attribute because every downstream chemical interpretation presupposes that the material being characterized is the material claimed. DNA barcoding can provide taxonomic evidence, but its limitations in processed products also show why identity is not reducible to one platform [11]. Identity should therefore be treated as an evidential question—supported by botanical, genetic, chemical, or orthogonal authentication as appropriate to the material state—rather than as a conclusion automatically inherited from marker detection.

Chemical consistency is broader than the concentration of one constituent. Plant metabolomics demonstrates how multidimensional chemical profiles can reveal variation associated with medicinal-material quality, while also underscoring that broad profiles require careful interpretation [12]. Consistency is consequently not synonymous with chemical uniformity. A useful profile must distinguish expected variation from deviations relevant to source, processing, degradation, substitution, or manufacturing control.

Some variation reflects context rather than failure. Multiplatform metabolomics has discriminated geographical origins of *Panax ginseng* in studied samples [13], and combined ATR-FTIR/FT-NIR with chemometrics has distinguished plant parts and harvest times in *Dendrobium officinale* [14]. These findings support context sensitivity, not the assumption that every chemical difference denotes inferior quality.

Processing adds another layer because the relevant chemical state can change after harvest. Comparative profiling of *Fritillariae thunbergii* prepared by different processing methods identified processing-dependent chemical differences and candidate quality markers [15]. A specification appropriate to raw material can therefore become less informative after a transformation that predictably changes the analyte profile.

Safety introduces attributes that therapeutic-marker chemistry cannot stand in for. Large analytical studies have directly measured pesticide residues, toxic metals, and fungal or mycotoxin contamination in herbal materials [16–18]. These hazards require dedicated assays and exposure-aware interpretation. Their presence is not inferred from the concentration of a therapeutically relevant marker, and occurrence in a particular surveillance dataset should not be generalized into universal prevalence or patient-level harm.

Potency relevance forms a separate question because chemical representativeness and biological relevance need not coincide. At this stage of the argument, "potency-relevant" is deliberately broader than "active ingredient": it denotes constituent evidence that has a defensible relationship to a relevant biological response or exposure model, without assuming causal mechanism or clinical effectiveness. The evidential requirements for that relationship are developed in the next section.

Taken together, the evidence supports distinguishing what is being claimed before deciding what should be measured. The four attributes are not proposed as equally weighted dimensions or as components of an additive score. They are separate evidential obligations whose importance depends on the product, intended use, and decision context. **Table 1** formalizes this proposed classification and the principal boundary that prevents one attribute from substituting for another.

Table 1. Proposed classification of non-substitutable herbal-quality attributes

Quality attribute	Primary question	Appropriate evidence role	Boundary against overinterpretation
Material identity	Is the declared botanical material represented?	Taxonomic, morphological, or orthogonal authentication	Identity does not establish chemical consistency or potency
Chemical consistency	Does the material show the expected compositional state?	Targeted quantification, fingerprinting, metabolomics	Similar profiles do not prove botanical identity or efficacy
Potency-relevant constituents	Are measured constituents plausibly linked to relevant activity or exposure?	Bioactivity, spectrum–effect, pharmacokinetic, or bioavailability evidence	Association or exposure does not establish clinical effectiveness
Contaminant risk	Are independent exogenous hazards adequately controlled?	Dedicated residue, elemental, microbial, or toxin assays	Marker conformity cannot substitute for hazard testing

Note: The classification is proposed here as an analytical organizing model. Attribute importance, assay selection, and decision thresholds remain product- and context-specific.

Evidence for multi-attribute quality assessment

Evidence for multi-attribute assessment is strongest where different measurements contribute nonredundant information rather than simply multiplying variables. A trinity fingerprint system combining chromatographic, ultraviolet, and terahertz information in licorice showed that distinct analytical layers could contribute complementary quality information in the studied material [19]. An electrochemical fingerprint strategy combined with multicomponent assay likewise demonstrated that profile-level information and quantitative constituent measurements can coexist within one quality-control design [20]. These studies support analytical complementarity, but not a universal requirement to deploy every available platform.

Potency relevance requires a different evidential step. Spectrum–effect analysis of *Zanthoxylum nitidum* used chromatographic–mass-spectrometric data with statistical filtering to prioritize peaks associated with measured bioactivity [21]. Such associations can help distinguish constituents that merely characterize a sample from those plausibly related to a biological response, but they remain vulnerable to collinearity, assay dependence, and confounding. They should therefore be described as activity-associated candidates rather than causal effectors.

Exposure can further qualify that interpretation. In Danlou tablet, a strategy integrating drug metabolism and pharmacokinetics, network pharmacology, and bioactivity evaluation was used to nominate candidate quality markers [22]. The important inference for standardization is not that these candidates are clinically validated, but that nominal abundance and pharmacologically plausible exposure are different properties. Constituents that are analytically prominent may not be the constituents most relevant to a systemic biological claim.

Quality evidence can also extend beyond finished-product testing. Miniature mass spectrometry has been used to monitor active-ingredient extraction online in a Chinese-medicine process, demonstrating the feasibility of acquiring time-resolved chemical information during manufacture [23]. At the data-integration level, machine-learning studies of medicinal plants show opportunities for combining multisource information while also exposing problems of data quality, model transfer, and external validation [24]. These developments favor an architecture in which analytical layers are selected for the specific uncertainty they resolve.

The collective pattern is therefore one of complementarity rather than convergence on a single best assay. Identity methods, profile measurements, effect-linked analyses, exposure evidence, process measurements, and contaminant tests become valuable when they reduce different uncertainties. Their outputs should not be numerically combined merely because they can be measured. The proposed model instead asks whether each quality claim has sufficient and appropriately validated evidence, then allows context to determine which evidence streams are necessary.

Figure 1 synthesizes this logic by separating marker-centered failure, quality attributes, evidence modalities, context-dependent application, analytical consequences, and the implementation boundary rather than compressing them into

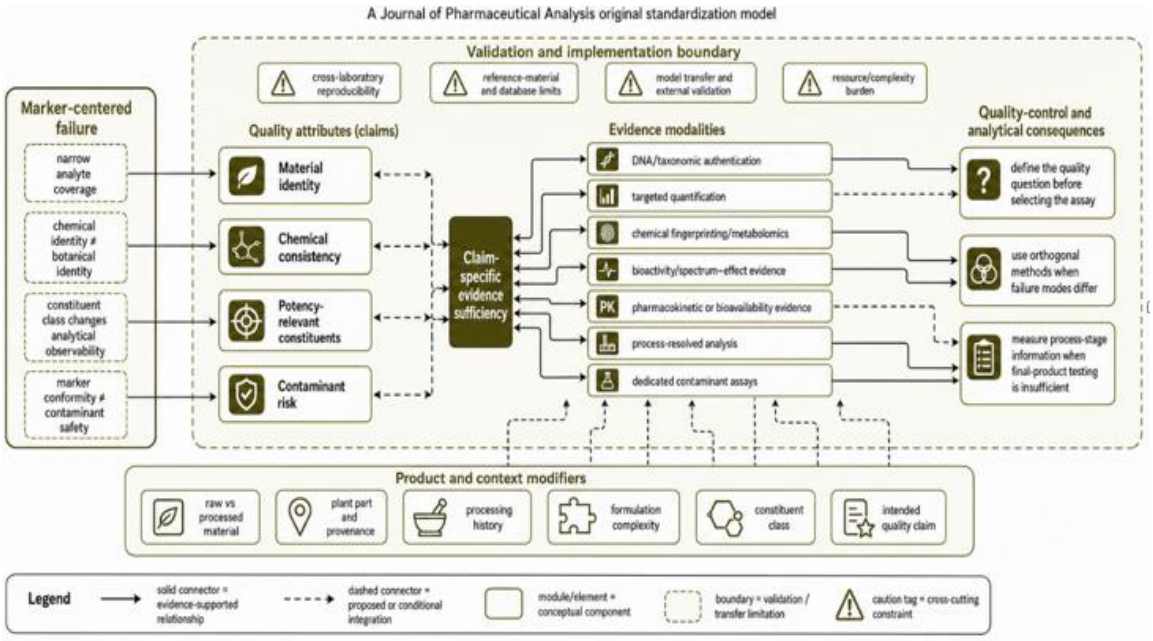

Figure 1. From marker sufficiency to context-conditioned multi-attribute herbal quality assessment

Caption. Evidence-supported analytical relationships are shown as solid connectors; dashed connectors denote the article's proposed integration. Marker-centered failure modes remain separate from four quality attributes, which are interrogated by nonidentical evidence modalities and conditioned by material state, provenance, processing, and formulation. Quality-control consequences sit downstream, while validation, transferability, analytical uncertainty, and implementation burden form an explicit outer boundary.

Alt text**.** Layered framework read from left to right with cross-links: marker-centered failure modes feed four separate quality-attribute lanes; identity, chemical consistency, potency relevance, and contaminant risk connect to appropriate analytical evidence. Context modifiers alter method suitability before quality-control decisions. An enclosing boundary marks validation, transferability, uncertainty, and implementation limits.

The proposed standardization model

The proposed model begins with a constraint: a quality claim should not be broader than the evidence used to support it. Earlier Q-marker work argued that marker selection can incorporate drug properties and effect characteristics rather than depend only on chemical convenience [25]. Biological-activity-oriented quality markers extended this reasoning by treating measured activity as relevant to marker selection [26]. These approaches support separating analytical presence from potency relevance, but they do not establish a universal hierarchy among quality attributes.

For products in which systemic exposure is relevant, pharmacokinetic information can further qualify marker selection because constituents that enter circulation, or relevant metabolites derived from them, may be more plausible indicators of systemic pharmacological contribution than abundant but poorly exposed compounds [27]. This criterion is conditional: locally acting gastrointestinal constituents, transformation products, and other non-systemic mechanisms can remain important even when circulating parent concentrations are low. Exposure is therefore proposed as a context-dependent qualifier, not a mandatory gate.

The model also treats production history as part of quality interpretation. Quality-transitivity concepts link markers across stages of herbal-product production and emphasize traceability rather than evaluating the finished product in isolation [28]. Bioavailability-oriented screening likewise shows that constituent priority can change when intestinal absorption and downstream biological relevance are considered [29]. Together, these studies support a shift from "Which marker is present?" to "Which evidence is required for the particular quality claim at this product stage?"

The central proposal is a four-attribute, claim-specific architecture. Material identity asks whether the declared source is represented; chemical consistency asks whether the expected compositional state is present; potency-relevant evidence asks whether selected constituents have defensible activity or exposure relevance; and contaminant risk asks whether independent hazards are controlled. Product state and intended use determine which attributes require testing and which analytical modalities can observe them. Candidate markers remain useful within this architecture, but their interpretive role must be declared: identity-supporting, consistency-monitoring, potency-relevant, process-monitoring, or another product-specific function.

No additive quality score or fixed weighting is proposed. A serious identity failure should not be "compensated" by excellent chemical similarity, and absence of a contaminant signal should not rescue a compositionally nonconforming product. Conversely, minor profile variation may be acceptable when identity is secure and the variation is explained by validated provenance or processing effects. Analytical strategies for Q-marker discovery and validation emphasize that marker nomination and marker validation are separate stages [30]. The same separation applies to the present model: its architecture organizes evidence, but its decision rules require product-specific validation before standard-setting use.

Table 2 compares the analytical role, evidential strength, and principal interpretive boundary of each proposed attribute so that integration does not erase non-substitutability.

Table 2. Comparative analytical logic of the proposed multi-attribute standardization model

Attribute	Typical analytical objective	Evidence considered sufficient in principle	What it cannot substitute for
Material identity	Establish declared biological source or detect substitution	Appropriate botanical, genetic, chemical, or orthogonal authentication validated for the material state	Whole-profile consistency, potency, or contaminant control

Chemical consistency	Demonstrate conformity of the expected compositional state	Validated targeted assays, fingerprints, or broader profiling suited to the product	Taxonomic proof, causal activity, or safety from unrelated hazards
Potency-relevant constituents	Support relevance of selected constituents to a defined biological or exposure claim	Reproducible activity association, exposure, bioavailability, or stronger mechanistic evidence appropriate to the intended claim	Clinical effectiveness or complete product identity
Contaminant risk	Detect and control independent exogenous hazards	Validated hazard-specific testing against justified specifications	Therapeutic quality, authenticity, or pharmacological potency

Note: "Sufficient in principle" denotes the type of evidence that could support the stated claim after product-specific analytical validation; it does not imply universal methods or thresholds.

Figure 2 presents the proposed model as a decision architecture in which quality attributes remain separate, context conditions evidence selection, and validation determines whether an attribute-level conclusion can support a product-

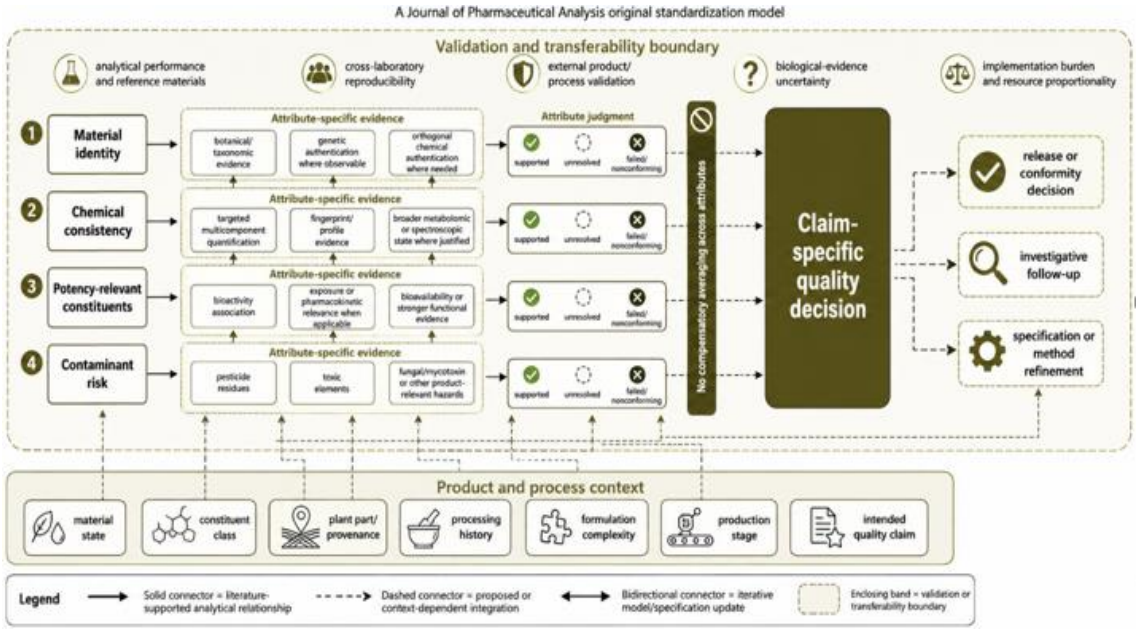

Figure 2. Proposed claim-specific architecture for non-substitutable herbal-quality evidence

Caption. Original conceptual synthesis. Four quality attributes remain parallel rather than additive. Product and process context conditions which attributes are material and which evidence modalities are suitable. Attribute-level conclusions converge only at a proposed claim-specific decision layer, surrounded by validation and transferability constraints. Dashed connectors denote proposed integration; solid connectors denote relationships grounded in the reviewed analytical evidence.

Alt text**.** Layered decision framework with four parallel lanes for identity, chemical consistency, potency-relevant constituents, and contaminant risk. A context band modifies method selection beneath the lanes. Evidence modules feed attribute-specific judgments, which converge through dashed links at a claim-specific decision core. An outer boundary represents validation, transferability, and implementation limits.

Product- and context-specific application

A multi-attribute model becomes useful only if it changes with the material being assessed. DNA-based biomonitoring of complex traditional herbal products has demonstrated that sequencing can reveal botanical signals in multi-ingredient preparations, while studies of Ayurvedic and *Hypericum* products show both label-fidelity problems and the nonidentical information produced by genetic and chemical authentication [31–33]. These studies justify orthogonality where method failure modes differ, not universal deployment of DNA analysis for every product.

Material state determines observability. DNA evidence can be strong for taxonomic identity when recoverable sequence material and adequate reference databases are available, yet processing may degrade DNA or remove it from highly refined extracts [11]. Conversely, chemical profiles can remain measurable after processing but cannot automatically prove that every declared biological source is present. Comparative *Hypericum* authentication illustrates why genetic and chemical evidence should be interpreted as complementary rather than forced into a single authenticity surrogate [33].

Constituent class and formulation complexity add further contingencies. Polysaccharide-rich products may require structural-fragment or other class-appropriate analytical strategies rather than conventional small-molecule marker assays [7]. Multi-herbal formulas create another problem: a chemically prominent constituent may be easy to monitor yet weakly linked to the biological claim, whereas integrated exposure and bioactivity evidence can prioritize a different subset [22]. The appropriate standardization package therefore depends on what the product contains, what transformations it has undergone, and what decision the quality system must support.

Provenance and processing should also change interpretation before they change acceptance criteria. Origin-associated metabolomic differences and processing-dependent shifts can be genuine characteristics of acceptable materials rather than defects [13]. Processing studies similarly show that marker relevance may change when expected chemical transformations occur [15]. The proposed rule is therefore context-conditioned equivalence: compare a product against an appropriate material-, process-, and use-specific expectation rather than an undifferentiated universal profile.

Table 3 translates this principle into a product-context decision workflow without prescribing a universal assay panel.

Table 3. Context-conditioned workflow for selecting herbal-quality evidence

Decision point	Question	Analytical response	Main caution
Material state	Raw, powdered, extracted, highly processed, or formulated?	Select identity and chemistry methods that remain observable in that state	Method failure can reflect processing, not substitution
Constituent class	Small molecules, macromolecules, or mixed chemistry?	Match quantitative strategy to chemical class	One marker paradigm does not fit all constituent types
Provenance/processing	Is variation expected from origin, harvest, or processing?	Define an appropriate comparison state before judging deviation	Legitimate variation must not be mislabeled as failure
Intended quality claim	Identity, consistency, potency relevance, hazard, or several?	Add only evidence streams that address the claim	More measurements do not automatically improve inference
Decision consequence	Screening, release, investigation, or specification setting?	Increase orthogonality and validation as consequence increases	The proposed workflow is not a validated regulatory decision rule

Quality-control and analytical implications

The practical implication is to define the quality question before selecting the analytical platform. Multicomponent quantification can strengthen compositional control when several constituents matter, but it cannot answer a taxonomic question merely by increasing analyte count [6]. DNA-based approaches provide a different evidential route to identity [11], while pesticide testing addresses a hazard class that neither chemistry fingerprints nor genetic authentication can infer [16]. Analytical design should therefore begin with the construct being decided, not with the instrument that happens to be available.

Orthogonality is most valuable when methods fail differently. Complementary DNA and chromatographic authentication can expose discrepancies that either modality may miss alone [8]. Multilevel fingerprint systems likewise show that nonredundant analytical layers can contribute different information about a material [19]. The proposed criterion is not “use more methods,” but “add a method when it resolves a material uncertainty that the existing method cannot.” That distinction limits unnecessary complexity while preserving independent checks for high-consequence claims.

Quality control should also consider where in the product lifecycle information is most observable. Online miniature mass spectrometry demonstrates that process-stage constituent changes can be measured directly rather than reconstructed only from a final product [23]. Quality-transitivity reasoning similarly encourages continuity

across production stages [28]. For some products, final-release testing may remain sufficient; for others, transformations during extraction, processing, or formulation may justify in-process evidence because the relevant intermediate state disappears by the time the finished product is tested.

These implications change validation priorities. A fit-for-purpose system should establish analytical performance within each evidence stream, then evaluate whether combining streams actually improves decision accuracy, robustness, or failure detection. A redundant second assay adds little if it shares the same blind spot. Conversely, an orthogonal assay may be valuable even when it measures a different construct, provided the additional construct is material to the quality decision. The proposed model therefore favors minimum sufficient, nonredundant evidence over maximal analytical accumulation.

Implementation challenges

Broader quality characterization creates practical costs. Fingerprint methods differ in preprocessing, similarity assessment, platform performance, and chemometric dependence [3], while multicomponent assays remain constrained by selectivity, standards, calibration, and matrix behavior [6]. Marker discovery itself does not remove the need for validation [30]. A multi-attribute system must therefore justify each added analytical layer by the uncertainty it resolves and must demonstrate reproducibility before transfer between laboratories or product classes.

Potency-linked evidence introduces another tier of uncertainty. Spectrum–effect relationships can identify activity-associated peaks, but correlation among constituents and assay-specific effects complicate causal interpretation [21]. Integrated pharmacokinetic, network, and bioactivity strategies can strengthen biological plausibility yet still combine measured and predicted evidence with different error structures [22]. Machine-learning integration adds risks of biased source data, overfitting, and domain shift when models are transferred to new medicinal-plant datasets [24]. These evidence types should therefore carry explicit status labels rather than being flattened into one confidence category.

Authentication has analogous limits. DNA barcoding depends on recoverable DNA, appropriate loci, and adequate reference information [11]. Sequencing of complex products can reveal taxonomic signals, but read abundance is not a direct measure of ingredient quantity and non-detection can have technical explanations [31]. Market authentication findings also remain bound to their sampled products and cannot be treated as global prevalence estimates [32]. The model consequently requires an “unresolved” state when evidence is insufficient or discordant rather than forcing every product into pass/fail classification.

Prospective validation is the major remaining requirement. Product-specific studies should predefine quality claims, analytical methods, and decision rules; challenge the system with authentic variation, substitution, adulteration, processing differences, degradation, and contaminant scenarios; and evaluate repeatability across laboratories. The contribution of each attribute should be tested rather than assumed, including whether removing an evidence stream materially changes correct classification. Where biological relevance is claimed, independent replication and appropriate exposure or functional validation are necessary. Analytical-strategy literature supports staged discovery and validation of candidate markers [30], but no approved evidence establishes that the present integrated architecture is ready for regulatory or routine universal implementation.

Conclusion

Marker compounds remain useful analytical tools, but their meaning depends on the claim they are asked to support. A precise assay of a characteristic compound can establish conformity for that constituent while leaving botanical identity, wider chemical consistency, biological relevance, or contaminant safety unresolved. The central contribution of this article is therefore not a rejection of markers, but a proposed redefinition of their place within herbal standardization.

The model separates four non-substitutable quality attributes: material identity, chemical consistency, potency-relevant constituent evidence, and contaminant risk. Product state, constituent class, provenance, processing, formulation complexity, and intended use determine which attributes are material and which analytical evidence is observable. Integration occurs at the level of the quality claim, not through an additive score in which strength in one domain compensates for failure in another.

This architecture also imposes limits. Chemical similarity does not prove taxonomic identity; activity association does not prove mechanism or clinical effectiveness; systemic exposure is not required for every relevant biological

effect; and contaminant surveillance does not by itself establish patient-level harm. More analytical measurements are not automatically better, and orthogonal methods are justified only when they resolve distinct uncertainties. The model remains a conceptual standardization framework rather than a validated regulatory system. Its value should ultimately be judged by prospective, product-specific and cross-laboratory testing: whether it detects meaningful quality failures more reliably, preserves legitimate variation, and clarifies rather than obscures uncertainty. Until that validation exists, the framework should be used as an organizing logic for designing evidence, specifications, and analytical studies, not as a universal quality score.

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