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Why Chemically Standardized Herbal Medicines Still Produce Variable Exposure: A Translational Review of Matrix Effects, Metabolism, Transport, Microbiota, and Formulation

Patrick O'Connor[1]*, Grace Murphy[1], Niamh Walsh[2]

[1] Department of Herbal Medicine Translation and Bioavailability, School of Pharmacy, University College Cork, Cork, Ireland.
[2] Department of Matrix Effects and Microbiota Metabolism, Faculty of Pharmacy, University of Galway, Galway, Ireland.

***E-mail** ✉ patrick.oconnor@ucc.ie

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ABSTRACT

Chemical standardization is central to the quality control of herbal medicines, yet reproducible constituent content does not necessarily produce reproducible systemic exposure. This translational review examines why that gap persists by integrating evidence on product matrix, co-constituent interactions, dose and administration, host physiology, metabolism, transport, microbiota, formulation, and bioanalytical measurement. The selected literature indicates that exposure is generated downstream of composition through a sequence of conditional processes: liberation from the dosage form, dissolution and stability, intestinal transformation, transporter and enzyme activity, microbial metabolism, first-pass disposition, tissue distribution, and analytical detection of parent compounds and metabolites. Human pharmacokinetic studies show that nominally similar or standardized botanical preparations can yield different exposure profiles, while formulation studies demonstrate that solubilization and delivery systems can modify absorption and distribution. Host-dependent evidence further implicates sex, genotype, physiological state, and microbiome composition or function, although the strength and translational proximity of these findings vary substantially. The review therefore proposes that chemical standardization and exposure standardization should be treated as related but non-equivalent objectives. A product may meet compositional specifications while remaining pharmacokinetically variable across formulations, regimens, or individuals. For development, the implication is not to abandon chemical markers, but to connect them with exposure-relevant testing when mechanistically and clinically justified. Major limitations include heterogeneous products, small human pharmacokinetic datasets, uneven metabolite coverage, species translation, and incomplete causal validation of microbiome and transporter mechanisms.

Keywords: Herbal medicines, Pharmacokinetics, Bioavailability, Microbiota, Formulation, Phytochemicals

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Introduction

Chemical standardization gives herbal medicines a necessary analytical reference point, but it does not define what concentrations of parent constituents or metabolites will ultimately reach systemic circulation or target tissues. Multi-component herbal preparations can undergo gastrointestinal transformation and interact with drug-metabolizing enzymes, transporters, and microbial metabolism before or during absorption [1]. More broadly, oral bioavailability is conditioned by physicochemical properties, dissolution, gastrointestinal physiology, matrix effects, membrane transport, and metabolism [2]. These processes place an exposure-generating layer between the content measured in a finished product and the concentrations observed after administration.

This distinction is increasingly relevant to quality concepts for complex botanical products. Bioavailability-oriented approaches to traditional medicine quality control have argued that chemical characterization should be

linked more directly to what becomes available in vivo rather than relying on marker abundance alone [3]. Such a position does not make conventional standardization obsolete. It instead narrows the claim that standardization can support: it establishes reproducibility for the analytes and attributes specified, but it does not by itself establish pharmacokinetic equivalence. Modern LC-MS methods can characterize highly complex herbal chemical profiles with considerable analytical depth [4], yet chemical detection, annotation, or quantification remains a different evidentiary task from demonstrating absorption, metabolism, and systemic disposition.

This review therefore treats exposure variability as a translational problem connecting product identity to in vivo fate. The central question is not whether a standardized herbal medicine contains its declared constituents, but whether apparently comparable chemical input produces comparable biological availability under different product, formulation, regimen, and host conditions. The synthesis separates product-dependent from host-dependent determinants before considering their interaction through absorption, metabolism, transport, and microbiota. It also distinguishes direct human pharmacokinetic evidence from preclinical mechanism, ex vivo microbial transformation, and analytical inference.

The principal contribution proposed here is a distinction between composition control and exposure control. Composition control concerns reproducible material and analyte specifications at administration. Exposure control concerns the conditional processes that determine the concentration–time profile of absorbed parent compounds and relevant metabolites. These objectives overlap but are not interchangeable. Their separation provides a basis for interpreting when chemical standardization is sufficient for a narrow quality claim, when pharmacokinetic bridging is needed, and where mechanistic uncertainty should prevent stronger translational conclusions.

Why chemical standardization does not guarantee exposure

The clearest reason chemical standardization cannot guarantee exposure is that the measured product and the measured circulation are separated by both biological processing and analytical choice. Withanolide pharmacokinetic studies illustrate this dual problem: plasma exposure estimates depend on analyte selection, assay sensitivity, and validation, while a crossover comparison of Ashwagandha extracts showed different pharmacokinetic profiles despite administration at the same nominal total-withanolide dose [5, 6]. The observation does not invalidate chemical standardization; rather, it shows that matching one aggregate compositional measure does not necessarily create pharmacokinetic equivalence.

Product-specific human data reinforce this point. After administration of a standardized Ashwagandha root extract, individual withanolide-related analytes displayed distinct concentration–time behavior that required direct UHPLC-MS/MS characterization [7]. Standardization therefore establishes the administered material more securely than it predicts the relative contribution of each measurable circulating species.

Exposure can also change without a change in administered product. In a comparative preclinical study, the same *Gastrodia elata* extract produced different pharmacokinetics and brain distribution in normal and cerebral-ischemic rats [8]. This does not establish an analogous human disease effect, but it demonstrates under controlled conditions that host state can alter the fate of a constant botanical input.

A further boundary concerns what is meant by "quality." Multi-assay evaluation of XueBiJing identified product-quality dimensions not reducible to a narrow marker specification [9]. Such findings do not prove that every detected quality difference changes human pharmacokinetics. They do, however, support a more careful separation of material consistency, analytical comparability, biological activity, and in vivo exposure. Chemical standardization is therefore best interpreted as an upstream control: indispensable for defining what is administered, but insufficient on its own to establish what is absorbed, transformed, distributed, or measured systemically.

Product-dependent sources of exposure variation

Product-dependent variability begins with the fact that an herbal medicine is not merely a set of isolated marker compounds. Co-constituents can change the fate of one another. In a mechanistic study of ginsenosides, schisandra lignans modified absorption of different ginsenoside classes through pathways involving P-glycoprotein and CYP3A4 [10]. The transferable point is not that co-constituents invariably increase bioavailability, but that the matrix can be pharmacokinetically active rather than inert.

Administration conditions are likewise part of the product–exposure relationship. Human pharmacokinetic evaluation of an aqueous *Andrographis paniculata* extract showed that exposure must be interpreted in relation

to the tested dose and repeated-administration regimen [11]. Bioanalytical work on the same botanical further demonstrated that parent compounds alone can provide an incomplete representation when phase-II or other transformed species contribute substantially to circulating signals [12]. Accordingly, an exposure profile is partly defined by which molecular species the assay is designed to capture.

Dose cannot always be treated as a simple scalar multiplier. A high-dose ethanolic *Andrographis* extract displayed nonlinear oral bioavailability under the studied clinical conditions [13]. This makes direct proportional extrapolation from administered amount to systemic exposure unsafe outside the tested context. At the same time, mechanistic plausibility should not be equated with inevitable clinical interaction. A standardized licorice supplement did not produce clinically relevant changes in the tested major CYP probe-substrate pharmacokinetics in female participants [14]. That null result is product-, pathway-, duration-, and population-specific, but it is an important translational counterexample.

Taken together, the evidence supports a product-level interpretation in which constituent interactions, dose, regimen, metabolic conversion, and analytical coverage can each alter the relationship between nominally standardized input and measured exposure. **Table 1** summarizes these product-linked determinants while preserving the evidentiary boundary between a demonstrated exposure effect and a plausible mechanism.

Table 1. Product-linked determinants that can separate chemical standardization from observed exposure

Product-linked determinant	Exposure-relevant consequence	Evidence characteristic	Interpretation boundary
Co-constituent matrix	Altered transporter or enzyme activity during absorption	Mechanistic interaction evidence	Direction and magnitude remain constituent- and context-specific
Dose and regimen	Changed absorption, accumulation, or apparent proportionality	Human pharmacokinetic comparison	Applies to the tested preparation and administration conditions
Parent–metabolite coverage	Different circulating species included in the exposure estimate	Validated bioanalysis	Detection does not establish complete pathway identity
Nonlinear disposition	Exposure does not scale directly with administered amount	Human high-dose pharmacokinetics	Nonlinearity should not be extrapolated beyond the studied range
Interaction liability	Mechanistic potential may or may not become clinically relevant	Human probe-substrate evaluation	A null result for selected pathways does not exclude other interactions

Host-dependent sources of exposure variation

Even when product and administration are held constant, exposure can differ because the recipient is not a fixed biological environment. Sex-related pharmacokinetic differences have been reported for several *Codonopsis pilosula* constituents in a controlled study system [15]. Natural-product pharmacogenetic evidence also supports a role for variation in metabolic enzymes and transporters, although predictive utility is uneven across compounds and populations [16]. These findings justify host biology as a source of variance without implying that sex or genotype alone can forecast exposure for a standardized herbal product.

The intestinal microbiome adds another host layer because it can transform phytochemicals before or alongside host metabolism. In a disease-model study, gut microbiota mediated pharmacokinetic differences for constituents of Zhi-zi-chi decoction [17]. Human- and mouse-derived fecal communities also showed interspecies and individualized differences in transformation of selected saponins [18]. Human evidence on plant phenolics more broadly indicates substantial interindividual variability in metabolite formation and bioavailability, with multiple demographic, physiological, lifestyle, and microbiome-associated determinants [19].

Mechanistically, microbial variability is plausible at several levels. Gut microbes possess diverse chemistries capable of transforming xenobiotics, and experimental mapping shows that this capacity varies across bacterial taxa, genes, and individual donor communities [20-22]. Microbial effects on luminal availability need not require chemical transformation: bacterial bioaccumulation can sequester some xenobiotics and thereby create an additional interaction route [23]. For a plant-specific example, metabolism of the ginger constituent [6]-shogaol differed among human fecal microbiota donors [24].

Host variables may also influence one another. Age- and sex-associated trajectories in adult gut-microbiota composition have been observed across populations [25], creating a plausible link between demographic context and microbial metabolic capacity. However, microbiome composition is not equivalent to metabolic function, and neither automatically establishes altered systemic herbal exposure. The strongest interpretation is therefore conditional: host physiology, genotype, disease state, and microbiota can modify the exposure-generating environment, but the responsible factor and its quantitative contribution remain product- and study-specific.

Formulation and administration context

Formulation is not a cosmetic layer added after botanical standardization; it can change the physicochemical conditions under which standardized constituents become available for absorption. In healthy volunteers, a micellar *Boswellia serrata* preparation produced a pharmacokinetic profile distinct from that of a native dry extract [26]. The study is especially informative because it places formulation directly between characterized botanical material and human exposure. It does not, however, establish that higher or altered exposure necessarily improves therapeutic outcomes.

Preclinical comparisons provide mechanistic support for this formulation dependence. Solubilizing agents and a bioenhancer changed andrographolide exposure from *Andrographis* formulations in beagle dogs [27]. Such findings support dissolution and solubilization as upstream exposure determinants, while the species and excipient context prevents direct quantitative extrapolation to humans.

Human *Centella* data further show why formulation and measurement must be considered together. A phase-1 study of a standardized water-extract product in healthy older adults required validated multi-analyte bioanalysis to characterize triterpenoid-related pharmacokinetics [28]. Thus, a standardized product may still need population-specific and analyte-specific exposure characterization. The broader lipid-delivery literature reinforces the opportunity but also the evidentiary asymmetry: a scoping review found that most studies of lipid-based formulations for medicinal herbal compounds were preclinical rather than clinical [29].

The formulation effect can also interact with biotransformation. In healthy volunteers receiving a modified standardized *Centella* preparation, parent glycosides and aglycone-related species displayed different disposition patterns [30]. In beagle dogs, increasing extract water solubility altered triterpenoid-glycoside exposure [31]. These studies cannot be pooled across species or formulations, but together they support a recurring principle: the administered chemical inventory is filtered through formulation-conditioned dissolution, transformation, and absorption. Engineered delivery may additionally redirect distribution; transporter-targeted silybin liposomes altered pharmacokinetics and liver targeting in a preclinical system [32]. That example extends the exposure problem beyond plasma concentration while remaining distinct from evidence for whole-herb clinical performance.

Formulation comparison is therefore most informative when it preserves three separate questions: what changed in the dosage form, what changed in measured exposure, and whether that exposure difference has demonstrated biological or clinical relevance. **Table 2** compares the principal formulation strategies and the evidentiary boundary attached to each.

Table 2. Formulation and administration approaches as modifiers of herbal constituent exposure

Approach	Exposure process principally affected	Evidence level represented	Translational interpretation
Micellar delivery	Solubilization and intestinal availability	Direct human comparative pharmacokinetics	Exposure change is product-specific; efficacy is not inferred
Solubilizers or bioenhancers	Dissolution, absorption, possible metabolic modulation	Comparative animal pharmacokinetics	Human magnitude requires direct bridging
Standardized water-extract dosing	Product-specific parent and metabolite disposition	Phase-1 human pharmacokinetics	Standardization does not remove population or assay dependence
Lipid-based delivery	Solubilization, dispersion, absorption, sometimes lymphatic transport	Predominantly preclinical evidence base	Platform effects should not be generalized across compounds
Targeted carrier systems	Systemic disposition and tissue distribution	Preclinical formulation evidence	Organ targeting is distinct from whole-product clinical benefit

Interdependence of absorption, metabolism, transport, and microbiota

Absorption, metabolism, transport, and microbial transformation are analytically separable, but in vivo they can operate as a coupled exposure system. An integrated preclinical study of specnuezhenide linked microbiota-dependent processes with pharmacokinetics, pharmacodynamics, and a carboxylesterase-related mechanism [33]. The value of this evidence is not that it supplies a universal pathway for herbal medicines, but that it demonstrates experimentally why a sequence of independent boxes can misrepresent multi-level disposition.

Microbiota introduces particularly strong reciprocity. Polyphenol-focused mechanistic and metabolomic evidence indicates that microbes can transform ingested compounds while polyphenols and their metabolites can, under some conditions, alter microbial ecology [34]. Reviews of herbal medicines in metabolic-disease contexts similarly describe bidirectional herb–microbiota relationships across heterogeneous experimental systems [35]. Reciprocity should therefore be shown as conditional rather than assumed for every constituent or patient.

The resulting metabolites can connect compartments that are often studied separately. In a preclinical Xiaoyao Pills model, gut-microbiota-derived metabolites were linked to a distal brain mechanism involving fatty acid amide hydrolase [36]. Such evidence supports a cross-compartment route from luminal transformation toward systemic or tissue-level biology, but it does not establish the same pathway or exposure magnitude in humans.

Human data provide a narrower but important translational anchor. In healthy volunteers given red ginseng, gut-microbiota characteristics were associated with the pharmacokinetics of several protopanaxadiol ginsenoside-related analytes [37]. This supports microbiota as one contributor to human constituent disposition without establishing it as the sole source of interindividual variation.

The synthesis proposed here therefore treats exposure as an emergent property of a product–formulation–host system. Product composition and administration define the chemical input; formulation changes liberation and accessibility; host enzymes, transporters, physiology, and microbiota condition transformation and transfer; and bioanalysis determines which resulting species are observed. Feedback can occur, particularly at the microbiota interface, while tissue distribution adds a downstream branch rather than a guaranteed consequence of plasma exposure. **Figure 1** represents this architecture while separating evidence-supported processes from proposed integration and making analytical, causal, and transferability limits visible.

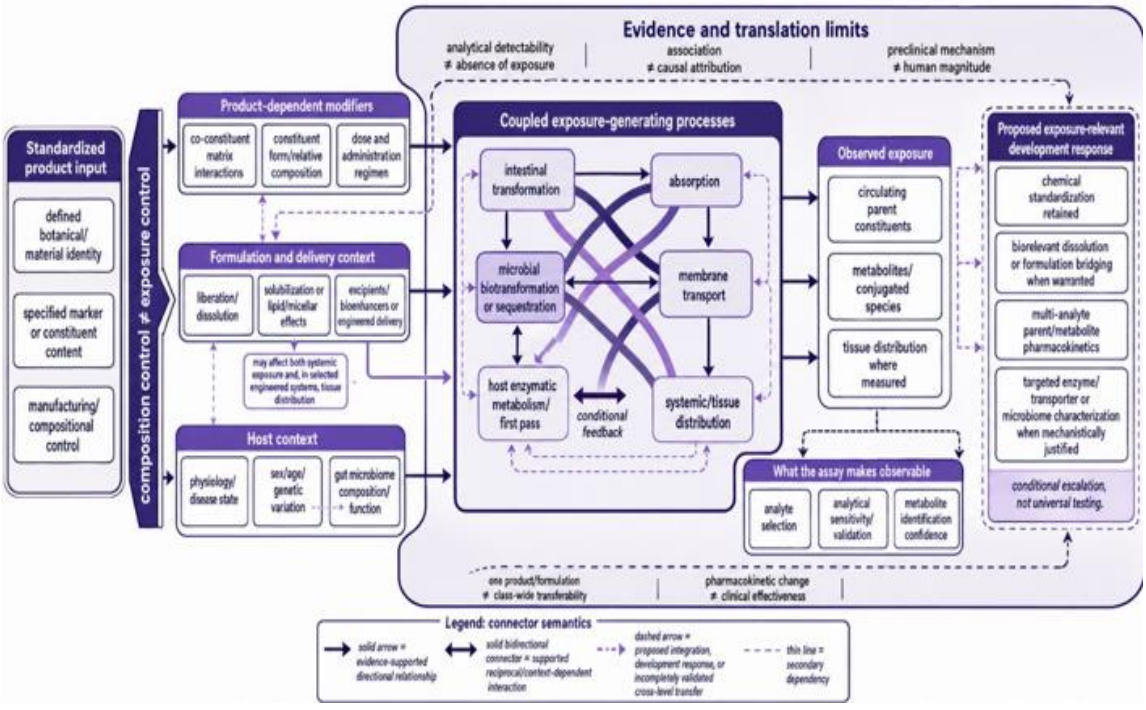

Figure 1. From standardized composition to conditional exposure: an evidence-bounded product–formulation–host framework for herbal medicines

Translational interpretation of exposure variability

The translational problem is not simply whether a mechanism exists, but how close the evidence lies to the exposure claim being made. Analytical reviews of withanolide pharmacokinetics show that apparent exposure can

depend on assay coverage and sensitivity [5]. Direct human formulation comparisons can establish that two tested products yield different pharmacokinetic profiles [26]. Phase-1 product-specific studies can characterize exposure in a defined population [28]. Human microbiota–pharmacokinetic associations can identify a plausible host contributor [37]. These forms of evidence answer different questions and should not be collapsed into a single category of "bioavailability evidence."

This review therefore proposes an evidence-proximity interpretation rather than a formal certainty grading system. Direct comparative human pharmacokinetics is closest to claims of product or formulation exposure difference. Human mechanistic associations are informative about possible modifiers but may not establish causation. Controlled animal studies can resolve mechanisms or distribution under experimentally tractable conditions, whereas ex vivo microbial systems identify metabolic capacity without reproducing absorption, first-pass metabolism, or whole-host physiology. Reviews can establish consistency, heterogeneity, and conceptual structure but cannot upgrade the designs they summarize.

A further implication is that apparent discordance between studies should first be decomposed rather than averaged away. An undetected constituent may reflect inadequate analytical sensitivity or an analyte panel that omits relevant metabolites, as the withanolide literature illustrates [5]. Conversely, validated parent–metabolite profiling can reveal that exposure has shifted molecular form rather than simply disappeared [12]. Host-associated signals require a different test: the relevant question is whether the covariate explains exposure after product, dose, formulation, sampling, and analytical conditions have been controlled. Human microbiota–ginsenoside associations provide a reason to perform that analysis, but not a license to assign causality from correlation [37]. Translational interpretation is therefore strongest when analytical validity, product comparability, and biological mechanism converge on the same exposure difference.

Counterexamples are essential to this interpretation. A human licorice study found no clinically relevant change in the tested CYP probe pharmacokinetics [14]. By contrast, microbiota-mediated pharmacokinetic effects have been demonstrated in a disease-model system [17]. An integrated preclinical natural-product study has linked microbiota, pharmacokinetics, and downstream mechanism within one experimental architecture [33]. These findings are not contradictory: they show that mechanistic plausibility, experimental causation, and human interaction magnitude occupy different evidentiary levels.

The same discipline applies to product bridging. Matched nominal withanolide dose did not guarantee comparable Ashwagandha exposure [6]. A human *Boswellia* formulation comparison directly demonstrated formulation-dependent pharmacokinetics [26]. A modified *Centella* preparation generated a product-specific parent/metabolite disposition profile [30]. Consequently, compositional similarity should not be used as a surrogate for pharmacokinetic equivalence when a formulation or matrix change could reasonably affect exposure.

Table 3 converts this evidence-proximity approach into an evidence-synthesis and gap framework. It is proposed as an interpretive aid, not as a validated grading instrument or regulatory standard.

Table 3. Proposed evidence-proximity framework for interpreting variable exposure from standardized herbal medicines

Evidence position	Question it can answer most securely	Principal residual uncertainty	Development use proposed here
Direct comparative human PK	Do tested products, doses, or formulations yield different exposure?	Population, duration, product transferability	Empirical bridging after material or formulation changes
Product-specific human PK	What parent/metabolite exposure occurs under defined use?	External generalization and unmeasured covariates	Exposure fingerprint and analyte selection
Human mechanistic association	Which host factor may track with exposure?	Confounding and causal direction	Targeted covariate validation
Controlled animal evidence	Can a mechanism or distribution difference occur in vivo?	Species translation	Mechanism prioritization before human testing
Ex vivo/in vitro transformation	Does a matrix, enzyme, transporter, or microbiome have relevant capacity?	Whole-host contribution	Hypothesis generation and assay selection
Integrated synthesis	Where do evidence gaps recur across levels?	No prospective predictive validation	Proposed study-design and quality-control priorities

Implications for herbal product development

For development, the appropriate response to exposure variability is not to replace chemical standardization with pharmacokinetics. Chemical specifications remain necessary to define identity, strength, and manufacturing consistency. The more defensible extension is to determine when composition alone is insufficient for the intended translational claim. Bioavailability-oriented quality-control scholarship already argues for linking chemical characterization more closely to in vivo availability [3]. Multi-assay evaluation of an herbal product likewise shows that quality can have dimensions beyond a narrow marker panel [9]. Building on these observations, this review proposes an exposure-relevant quality package that is activated by risk rather than imposed uniformly.

The first trigger is plausible transformation between administered and circulating species. Validated clinical analysis of *Andrographis* identified parent compounds together with presumptive phase-II metabolic products [12]. A standardized *Centella* phase-1 study similarly depended on validated multi-analyte measurement [28]. Where substantial conversion is expected, development should therefore predefine which parent compounds and metabolites are analytically relevant, justify their inclusion, and avoid interpreting a narrow analyte panel as the complete exposure state.

A second trigger is formulation change. Human *Boswellia* evidence shows that formulation can alter pharmacokinetics [26]. Yet the broader lipid-formulation literature remains dominated by preclinical studies [29]. Accordingly, formulation improvement should be separated into demonstration of physicochemical performance, demonstration of changed exposure, and demonstration—if clinically necessary—of changed pharmacodynamic or therapeutic consequence. None should be inferred automatically from the preceding step.

A third trigger is credible host dependence. Integrated preclinical evidence can identify microbiota-linked PK–PD mechanisms [33], while human red-ginseng data support a microbiota–pharmacokinetic association for defined ginsenoside species [37]. These findings justify targeted microbiome assessment when the chemistry, metabolism, or prior evidence makes microbial involvement plausible; they do not justify routine microbiome profiling for every herbal medicine.

Conditional escalation also requires stopping rules. Not every compositional difference merits a clinical pharmacokinetic study, and not every in vitro interaction warrants a mechanistic development program. The clinical licorice study demonstrates why an experimentally plausible interaction can prove negligible for the tested pathways and regimen [14]. Conversely, the Ashwagandha crossover shows that nominal marker matching can fail to secure comparable exposure when products differ in ways not captured by the aggregate specification [6]. Direct *Boswellia* evidence further shows that a deliberate formulation change can produce a measurable human pharmacokinetic difference [26]. A development program should therefore escalate when the suspected modifier is credible, exposure-relevant, and consequential for interpretation; it should de-escalate when well-designed bridging demonstrates that the difference is negligible for the intended claim.

The proposed development principle is therefore conditional escalation. Begin with rigorous compositional control, then add biorelevant dissolution, formulation bridging, multi-analyte pharmacokinetics, enzyme/transporter phenotyping, or microbiome characterization when a specific exposure uncertainty could change interpretation. Such escalation should be hypothesis-driven and product-specific, with prespecified analytical endpoints and explicit separation between exposure, pharmacological response, and clinical effectiveness.

Evidence gaps

The largest gap is not the absence of plausible mechanisms but the difficulty of connecting them into validated human exposure explanations. Microbiome metabolomics illustrates this problem: mass-spectrometry workflows can provide extensive molecular information, yet metabolite annotation, coverage, integration, and causal assignment remain substantial methodological limitations [38]. An unidentified or tentatively annotated feature should therefore not be treated as a structurally proven mediator of herbal disposition.

Human variability also remains incompletely partitioned. Systematic evidence on plant phenolics identifies substantial interindividual differences in metabolism and bioavailability, but the relative contribution of demographics, physiology, lifestyle, microbiota, and other covariates varies across compounds and studies [19]. Future work should prioritize variance decomposition within well-characterized products rather than assuming one dominant host determinant.

Personalized microbial metabolism is another unresolved bridge. Donor-specific ex vivo microbiome mapping demonstrates heterogeneous xenobiotic-metabolic capacity [22], but prospective studies are needed to determine whether such profiles predict systemic parent/metabolite exposure after standardized administration. Designs should integrate controlled dosing, dense pharmacokinetic sampling, targeted and untargeted metabolomics, microbiome functional measurements, and relevant host enzyme or transporter phenotypes.

Study design should also make negative and discordant results informative. Reporting should preserve exact extract identity, marker definition, manufacturing or formulation state, dose, fed or fasted context where relevant, sampling schedule, analyte panel, assay performance, and prespecified host covariates. Without these details, an apparent replication failure may represent a different exposure experiment rather than biological inconsistency. Metabolomics studies additionally require transparent annotation confidence and orthogonal confirmation for metabolites assigned mechanistic importance [38]. Human variability analyses should report the dispersion and covariate structure needed to distinguish stable between-person differences from sampling noise [19]. Product-specific phase-1 pharmacokinetic designs provide a useful starting architecture, but broader replication across demographic and formulation contexts is required before an exposure signature can be treated as transferable [28].

External validity requires equal attention. Age and sex are associated with population-level microbiome trajectories [25]. Product-specific human PK studies also show that exposure is characterized within defined demographic and formulation contexts [28]. Multicenter or replicated studies should therefore test product × formulation × host interactions directly rather than transferring findings across populations by assumption. Additional priorities include matched-marker crossover comparisons, biorelevant dissolution linked prospectively to human PK, replicate assessment of manufacturing lots, and explicit testing of whether observed exposure differences are large enough to alter downstream pharmacology. Until such validation exists, the proposed framework should be used to organize uncertainty and study design, not to predict individual exposure.

Conclusion

Chemical standardization and exposure standardization address different stages of the herbal-medicine translation problem. The first establishes what is administered according to defined chemical and material specifications; the second concerns what becomes biologically available after formulation-dependent liberation, gastrointestinal transformation, transport, host and microbial metabolism, first-pass processing, and distribution. Evidence across human pharmacokinetic, preclinical, ex vivo, analytical, and review studies supports the existence of these modifiers, but their importance is neither uniform nor interchangeable across products.

The central contribution of this review is therefore an evidence-bounded, proposed product–formulation–host interpretation of exposure. It explains how two products that appear comparable by a marker specification can diverge pharmacokinetically, while also accommodating the opposite case in which a plausible interaction fails to become clinically relevant. This framing prevents chemical quality, mechanistic plausibility, systemic exposure, tissue distribution, pharmacodynamic response, and clinical effectiveness from being treated as equivalent endpoints.

This distinction also preserves a critical translational boundary: reproducibility of exposure is valuable for interpretation, but it cannot substitute for independent evidence of efficacy, safety, or patient benefit.

For herbal product development, the practical implication is conditional rather than universal escalation. Chemical characterization remains foundational. Additional dissolution, parent–metabolite pharmacokinetics, formulation bridging, enzyme/transporter evaluation, or microbiome analysis becomes justified when a defined uncertainty could materially alter exposure interpretation. The principal unresolved task is prospective validation: identifying which product and host attributes reproducibly explain human exposure differences, which are merely associated, and which are analytically apparent but biologically minor. Until that evidence matures, standardized composition should be treated as a necessary starting condition for reproducible herbal medicines, not as proof of reproducible exposure.

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