



Organ-on-Chip Evidence Should Constrain Natural Product Pharmacology Models Through Dynamic Exposure, Tissue Interfaces, Multicellular Interactions, and Human-Relevant Physiology

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ABSTRACT

Natural-product pharmacology is commonly modeled from nominal concentrations, endpoint responses, simplified barriers, and isolated cell systems, even when the relevant biology depends on changing exposure, transport across tissue interfaces, metabolism, mechanical context, or communication among cell types and organs. Organ-on-chip and related microphysiological systems can reproduce selected features of these conditions, but their value for computational pharmacology is often framed too broadly as increased physiological realism. This methodological framework instead asks what chip measurements can legitimately constrain. Evidence from dynamic absorption, material-associated drug loss, barrier models, airway pharmacology, gut–liver crosstalk, microbiome-dependent metabolism, liver toxicity, and coupled-organ pharmacokinetics supports treating exposure history, permeability, organ-specific transformation, and context-dependent response as separable empirical restrictions on model behavior. We propose a chip-constrained pharmacology framework in which measured chip observables are qualified for provenance and context, transformed only through explicit scaling or computational assumptions, and used to narrow admissible model states rather than replace simpler assays or in-vivo evidence by default. Contradictions among platforms trigger localized model updating and investigation of alternative explanations instead of automatic preference for the more complex system. For natural products, this approach is especially relevant where parent compounds, metabolites, mixtures, and tissue-specific exposure complicate nominal-dose reasoning. Major limitations include sparse direct natural-product chip evidence, material sorption, biological and device variability, uncertain multi-organ scaling, incomplete standardization, and limited prospective validation. The framework is therefore a proposal for disciplined evidence integration, not a validated prediction standard.

Key Words: Organ-on-chip, Natural products, Pharmacokinetics, Dynamic exposure, Microphysiological systems, Computational pharmacology

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INTRODUCTION

Natural-product pharmacology creates a recurring mismatch between what is experimentally applied and

what a model later assumes was biologically experienced. Traditional Chinese medicine and related natural-product research increasingly uses advanced in-vitro approaches to address absorption, distribution, metabolism, excretion,

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and toxicity questions that are difficult to resolve from simple nominal-dose assays alone [1]. Organoid and organ-on-chip approaches have also begun to enter this research space, although direct applications to traditional medicines remain comparatively limited [2]. More broadly, organoids and organ chips are being developed across drug-discovery contexts while questions of qualification, translation, and regulatory use remain unresolved [3].

The problem is therefore not that static wells are intrinsically invalid. They remain efficient systems for isolating cell-autonomous responses and concentration–response relationships. The problem arises when a computational model treats their experimental environment as if it contained every pharmacologically relevant variable. Organ chips can introduce controlled flow, tissue interfaces, multicellular organization, mechanical stimulation, and compartmental communication that are absent or weakly represented in conventional culture [4]. Those additions matter only when they alter a quantity relevant to the modeled claim.

This article proposes that organ-on-chip evidence should be used as a set of experimentally qualified constraints on natural-product pharmacology models. A constraint does not certify a mechanism or guarantee human prediction. It restricts model freedom: an exposure trajectory, permeability assumption, metabolic route, cell-state dependence, or inter-organ relationship becomes less defensible when it conflicts with a well-characterized chip measurement made in a relevant context. Conversely, adding chip complexity without measuring a decision-relevant variable should not increase evidential weight. The framework therefore separates physiological detail from usable constraint, and evidence-supported relationships from the proposed rules used to integrate them. This distinction is especially important for natural products because chemical complexity can create several plausible exposure narratives from the same administered dose. A model that predicts a parent-compound effect may remain numerically accurate for the wrong reason if unmeasured transport or transformation is compensating

elsewhere. Constraint-based integration is intended to expose, rather than conceal, that flexibility.

Dynamic exposure as a missing input in natural product models

Exposure in many natural-product models is represented as a concentration label attached to an endpoint. That representation becomes inadequate when uptake, degradation, protein binding, metabolism, perfusion, or device losses make the cellular concentration-time history diverge from the administered dose. Mathematical and computational modeling of organ-chip systems can help interpret such device-specific dynamics and can inform experimental design before data collection [5]. Flow itself can be engineered as a reproducible experimental variable, as illustrated by recent artery-on-chip work using controlled unidirectional perfusion [6]. Gut microphysiological systems can also measure absorption kinetics over time rather than infer transport from a terminal snapshot [7].

The methodological implication proposed here is a delivered-exposure rule: when the modeled pharmacological claim depends on time above concentration, sequential metabolite formation, transient barrier passage, or delayed cellular response, the model should be constrained by the most directly measured exposure trajectory available rather than by nominal dosing alone. This rule is particularly important for complex natural products because different constituents may partition, transform, and disappear at different rates. It remains conditional: temporal sampling that is too sparse, poorly mass-balanced, or analytically nonspecific may provide a weaker constraint than a simpler but better-characterized assay. The practical target is therefore not maximal temporal complexity, but enough temporal resolution to distinguish the alternative exposure histories that would lead to materially different pharmacological interpretations.

Figure 1 summarizes how dynamic exposure becomes only the first layer of a broader constraint process; later tissue, multicellular, metabolic, and validation information can redirect or qualify the apparent trajectory.

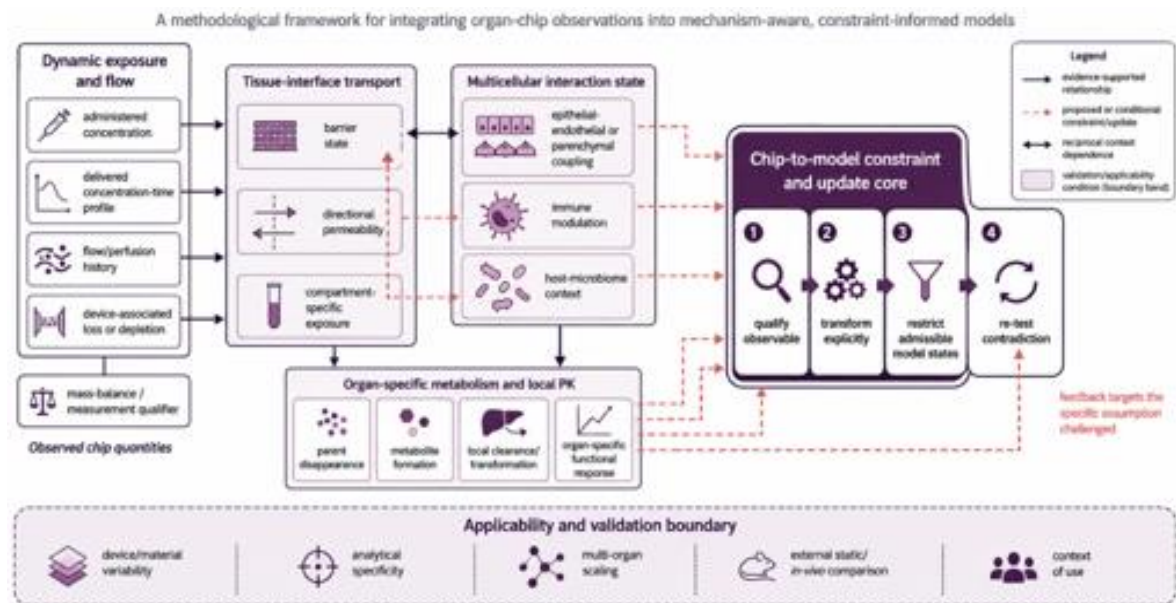


Figure 1. From administered natural product to an admissible chip-constrained pharmacology model

The exposure components that require explicit handling before a chip result can constrain a pharmacology model are organized in **Table 1**.

Table 1. Method components for converting nominal dosing into an interpretable dynamic exposure constraint

Method component	What must be represented	Why it matters for model constraint	Principal boundary
Input dose	Administered amount, concentration, vehicle, schedule	Defines the experimental perturbation, not tissue exposure	Nominal dose may not equal delivered dose
Delivery history	Perfusion, residence time, replenishment, sampling	Determines changing availability to the tissue	Device hydrodynamics are context specific
Material interaction	Sorption, partitioning, tubing or chamber loss	Can distort concentration reaching cells	Compound- and material-dependent
Tissue uptake/transport	Direction, barrier passage, compartment transfer	Converts device exposure into local exposure	Requires qualified barrier state
Transformation	Parent loss and measurable metabolite appearance	Changes the pharmacologically relevant chemical species	Analytical coverage may be incomplete
Temporal response	Time-resolved functional or toxicity readout	Links exposure history to biological state	Sampling density limits interpretation

Note. The table defines proposed modeling components, not universal experimental requirements; the necessary subset depends on the pharmacological question.

Flow, shear, and time-varying concentration

Microfluidic flow does not automatically make an assay physiological. Its value is that transport and mechanical conditions become explicit and therefore measurable or modelable. A central exposure problem is device sorption. Simulations of PDMS organ chips show that compound–material interactions can produce internal concentrations that differ from the nominally applied concentration [8]. Earlier design analysis likewise demonstrated that polymer-associated drug absorption can be substantial enough to require deliberate mitigation or accounting [9].

For natural-product models, this means that a dose label should not be propagated into a mechanistic or PK model without asking what concentration reached the relevant compartment. Flow rate, chamber geometry, medium composition, tubing, membrane material, and compound physicochemistry may all affect that answer. Shear should also be treated as an organ- and design-specific variable rather than a universal marker of realism. The appropriate computational object is therefore not “flow present” but a time-indexed transport condition with documented device provenance. When direct concentration measurements are unavailable, modeled corrections should remain visibly

assumption-dependent rather than being silently treated as observations.

Tissue interfaces and barrier transport

Many pharmacological questions are determined at interfaces: intestinal absorption, airway deposition and passage, endothelial transfer, or movement between luminal and tissue compartments. Microfluidic intestinal barrier systems demonstrate that barrier organization and function can be constructed and evaluated as explicit experimental properties [10]. Small-airway microphysiological systems likewise permit direct assessment of drug permeability across a differentiated tissue context [11]. These findings support a distinction between concentration in a dosing compartment and concentration available beyond a biologically active interface.

Interface context can also change how activity is interpreted. In a human airway chip, differentiated tissue organization and physiological conditions were used to identify antiviral candidates in a system designed to reproduce features not captured by simpler screens [12]. That result does not establish that a chip should always overrule static assays. It establishes a harder methodological point: disagreement between systems may reflect a changed transport or tissue context rather than experimental noise.

Accordingly, barrier evidence should constrain only the model quantities it actually measures. Permeability in an airway system should not be substituted for intestinal permeability; barrier integrity does not prove transporter mechanism; and an altered downstream response does not identify which interface property caused it. A useful constraint therefore couples permeability or transport measurements with the state and directionality of the relevant interface.

Multicellular crosstalk under drug exposure

Drug response may depend on relationships that isolated monocultures cannot represent. A gut-on-chip incorporating human faecal samples and peristaltic motion showed that microbial and mechanical context can be integrated into a system that distinguishes treatment-response phenotypes in a specific immunotherapy setting [13]. In gut–liver microphysiological systems, coculture altered hepatic CYP activity, supporting the possibility that inter-organ signaling changes metabolic phenotype [14]. A separate gut–liver platform tracked microbiome-associated changes in irinotecan metabolism with LC–MS/MS, demonstrating that connected biological compartments can change the chemical species present during exposure [15]. Taken together, recent gut and gut–liver systems show that

retaining interacting biological compartments can alter measured drug response or metabolism [13–15].

For natural products, this is important because mixtures, conjugates, microbial transformations, and immune-active constituents can create pharmacology that is distributed across cell types rather than localized to one nominal target. Host–microbiome organ-chip scholarship further emphasizes that oxygenation, microbial composition, epithelial state, and environmental control are part of the modeled context [16].

The proposed modeling rule is to represent multicellular state only when it changes a measurable input, intermediate, or response relevant to the model. Crosstalk should not be converted into a causal edge merely because coculture changes an endpoint. Mechanistic attribution requires perturbation or orthogonal evidence. Otherwise, the chip provides a context constraint: the single-cell or monoculture model must explain why it remains valid despite a reproducible multicellular discrepancy.

Organ-specific metabolism and local pharmacokinetics

Pharmacokinetic organs contribute different functions—barrier transport, metabolism, secretion, clearance, or excretion—and current microphysiological systems vary in how completely they reproduce those functions [17]. This matters for natural products because the pharmacologically active species may differ across compartments. The relevant model may need to distinguish parent compound, phase-I or phase-II products, microbial metabolites, deconjugated species, or mixture components rather than assign the administered structure a single systemic concentration.

Direct natural-product chip evidence remains sparse but is not absent. An immune–liver microphysiological system has been used to evaluate hepatotoxicity induced by *Polygonum multiflorum* extract [18]. That study is important as an existence proof that complex botanical exposure can be investigated in a multicellular liver context; it does not validate the approach for unrelated extracts or establish general predictive performance.

More mature liver-chip evidence illustrates how stronger calibration can look. Human and cross-species Liver-Chip systems reproduced selected drug-toxicity patterns [19], and subsequent performance assessment evaluated a human Liver-Chip against a defined predictive-toxicology context [20]. Recommendations for ADME microphysiological systems similarly emphasize characterization according to intended use [21]. The proposed framework therefore treats organ-specific measurements as conditional constraints whose weight depends on chemical coverage, tissue function, analytical specificity, and prior qualification. Local PK should be modeled as a property of a defined organ–device–

compound system, not as a generic attribute transferred from any chip bearing the organ's name. For mixtures, the unit of analysis may also need to change during the experiment: the relevant model entity at dosing may be a formulation or extract, whereas the relevant downstream entities may be individually resolved parents, metabolites, or composite chemical fractions. The framework permits that change only when analytical evidence supports it.

What organ-on-chip systems can constrain in computational models

A chip cannot constrain a model through physiological resemblance alone. It must provide an observable that maps to a model quantity or to a falsifiable consequence of that quantity. Recent reviews of organ-chip pharmacological analysis show that analytical modality determines which aspects of exposure and response are actually observable [22]. Artificial-intelligence methods may help analyze high-dimensional outputs, images, or multi-parameter chip data, but they do not remove uncertainty in the experimental system or establish mechanism from correlation [23].

The strongest examples of direct computational coupling use measured time-dependent quantities. Fluidically coupled vascularized organ chips have been combined with quantitative modeling to predict human pharmacokinetic responses for selected drugs [24].

Reviews of organ-chip applications to human PK nevertheless emphasize scaling, validation, and context-of-use limitations when translating chip measurements to systemic behavior [25]. The lesson is not that chip PK replaces conventional PK modeling. It is that chip data can restrict parameter ranges or trajectory shapes when the transformation from device measurement to model variable is explicit.

In this framework, five questions determine whether a chip result is constraint-ready: What was measured? At what biological and temporal level? What transformation is required before entering the model? Which assumptions dominate that transformation? Against what independent evidence can the updated model be checked? These questions separate constraint generation from model fitting. A flexible model may reproduce a chip endpoint while violating the measured concentration history or assigning an effect to the wrong compartment. Fit alone is therefore insufficient; admissibility requires consistency with the specific observables that motivated the update. **Table 2** converts those questions into an operational workflow.

Figure 2 shows the resulting methodological architecture: biological evidence remains separate from the computational operation that qualifies, transforms, and applies it.

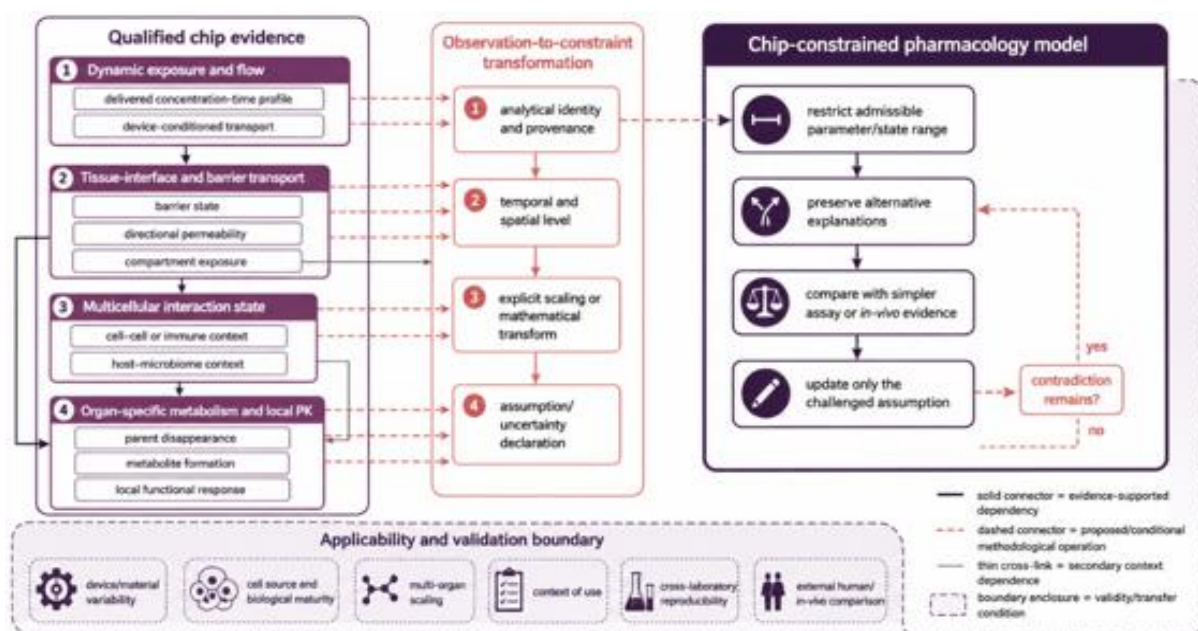


Figure 2. Methodological architecture for qualifying organ-chip evidence as a pharmacology-model constraint

Table 2. Workflow for deciding whether a chip observation can constrain a computational pharmacology model

Workflow step	Decision question	Acceptable output	Reason to stop or qualify
Define observable	What quantity was actually measured?	Concentration, permeability, metabolite, functional state	Proxy is too remote from modeled claim

Establish context	Where and when was it measured?	Tissue, compartment, flow condition, time window	Context differs materially from prediction target
Check provenance	Is device and analytical behavior characterized?	Traceable material, assay, sampling information	Sorption, instability, or nonspecific readout unresolved
Transform explicitly	Is scaling or mathematical conversion required?	Declared mapping with assumptions	Transformation dominates evidence
Apply constraint	Which model state becomes less admissible?	Narrowed parameter, trajectory, or hypothesis set	Observation cannot distinguish alternatives
External check	Does the constrained model remain compatible elsewhere?	Qualified agreement or explainable disagreement	Contradiction remains unexplained

Note. The workflow is proposed as a decision discipline; it is not a validated scoring system.

A chip-to-model constraint framework

The proposed Chip-to-Model Constraint Framework treats organ-chip evidence as neither decoration for a computational model nor a replacement for existing evidence. Its unit of integration is a qualified constraint: an observation linked to a defined tissue context, time scale, analytical method, and transformation rule. Recent work coupling a digital twin with a three-organ microphysiological system demonstrates that computational and experimental models can be operated together rather than as isolated stages [26]. A human duodenum-chip study similarly translated measured permeability through regression and PBPK modeling and compared resulting exposure predictions with observed plasma profiles for three model compounds [27]. These studies establish feasibility in specific settings, not a universal workflow.

The framework has four proposed operations. First, qualify the observable: establish what the chip actually measures and which uncontrolled variables could generate the same result. Second, transform explicitly: if a chip concentration, permeability coefficient, or metabolic rate must be scaled before entering a model, retain the transformation and its uncertainty as part of the evidence. Third, constrain rather than overwrite: reduce the admissible range of parameters, trajectories, or mechanistic explanations only to the extent justified by the observation. Fourth, challenge externally: test whether the constrained model remains compatible with independent static, in-vivo, clinical, or orthogonal mechanistic evidence.

Standardization is essential because a constraint that cannot be reproduced or traced across systems has limited transfer value [28]. Assessment should also follow intended use rather than a universal notion of platform quality [29]. Thus, the framework does not ask whether a chip is “human-like” in aggregate. It asks whether a specific chip-derived observation is sufficiently characterized to exclude a particular model behavior. Constraint strength can therefore differ within the same experiment: a well-resolved concentration-time profile

may strongly restrict exposure assumptions while a correlated cytokine change remains insufficient to identify a causal pathway. This asymmetry is intentional. The framework does not assign one credibility score to an entire device or study; it evaluates each observation according to what it can exclude. A single experiment may consequently provide a strong PK constraint, a moderate contextual constraint, and no mechanistic constraint at all.

Learning from temporal rather than endpoint measurements

Temporal evidence is particularly valuable when the same endpoint can arise through different histories. Modeling and gut-MPS studies support treating delivered exposure as a device- and time-dependent quantity rather than assuming that the nominal medium concentration alone characterizes tissue exposure [5, 7]. A transient peak, slow accumulation, metabolite lag, or delayed barrier failure may produce similar terminal values but imply different pharmacological mechanisms and different extrapolation risks.

The proposed temporal-state rule is therefore to constrain trajectories before endpoints whenever the prediction target is history-dependent. Time-resolved parent and metabolite measurements can distinguish disappearance from transformation; sequential permeability measurements can separate barrier adaptation from constitutive permeability; and repeated functional readouts can reveal recovery or delayed injury. This does not make dense sampling intrinsically superior. Sampling can perturb small-volume systems, analytical sensitivity may fail at relevant times, and interpolation can create false precision. Temporal data should narrow the model only at resolutions supported by direct measurement, while unsampled intervals remain uncertain rather than silently reconstructed as fact.

Incorporating human-relevant physiological boundary conditions

“Human relevance” should not be a single platform label. It is better represented as a set of boundary conditions tied to the question being modeled: flow and mechanical

regime, tissue-interface state, cellular composition, metabolic competence, oxygenation, microbial context, and the spatial scale at which concentrations are measured. A permeability model may require a differentiated barrier but not immune cells; a hepatotoxicity model may require metabolic competence and immune interaction but not a coupled kidney module. Adding every available feature can increase variance and obscure interpretation.

We therefore propose a minimum-sufficient-context principle. A chip-derived constraint should include the physiological dimensions necessary to make the modeled claim credible, but additional complexity should earn its place by changing an observable or excluding a plausible alternative. Qualification evidence from liver and ADME systems shows why function, reproducibility, and intended use matter more than organ labels alone. The resulting boundary conditions are not claims of whole-human equivalence. They define the experimental domain within which a measured relation is allowed to restrict model behavior and outside which transfer requires new evidence.

Model updating when chip evidence contradicts simpler assays

Contradiction is often the most informative use of an organ chip. If a static assay predicts activity but a qualified chip does not, the correct response is not to declare the static assay wrong. Differences may arise from delivered exposure, barrier access, metabolism, cell state, assay sensitivity, or device artifacts. Conversely, an apparent chip-specific effect may disappear after correcting for sorption or analytical bias. The airway and liver-chip literature shows that cross-model disagreement can expose context dependence, but its meaning remains compound- and system-specific.

The proposed update rule is localized: revise only assumptions that the chip measurement directly challenges. A measured fall in delivered concentration should first update exposure, not target potency. A permeability discrepancy should update transport before mechanism. A metabolite-dependent response should prompt chemical-species revision before invoking a new target. If several explanations remain compatible, the model should retain them rather than force a single mechanistic story.

Table 3 contrasts this constraint-oriented response with common but less defensible ways of handling disagreement.

Table 3. How the proposed constraint approach differs when experimental systems disagree

Situation	Static-assay-only response	Chip-overrides-all response	Proposed constraint response
Lower activity on chip	Reduce expected potency	Reject static result	Test exposure, access, metabolism, and state before updating potency
Different permeability	Ignore if endpoint is active	Adopt chip value directly	Update tissue-specific transport only after barrier qualification
New metabolite appears	Treat as secondary detail	Attribute response to metabolite	Reframe chemical species, then test causal contribution
Multicellular response changes	Average across models	Prefer complex system	Preserve context dependence and seek discriminating perturbation
Chip and in-vivo data disagree	Retain original model	Assume in-vivo data are flawed	Examine scaling, device, sampling, and biological-domain mismatch
Mechanism remains ambiguous	Select best-fitting narrative	Select chip-associated pathway	Keep competing explanations until independently resolved

Note. “Proposed constraint response” is an original methodological recommendation, not a validated superiority claim.

Multi-organ coupling and systemic interpretation

Systemic pharmacology introduces another level of inference because local organ observations must be connected through transport and scaling. Automated fluidic platforms have demonstrated controlled coupling of multiple vascularized organ chips [30]. More recent work has extended this engineering ambition to an eighteen-organ microphysiological system incorporating vascular and excretory connections [31]. Such systems show that increasingly complex inter-organ communication can be

modeled experimentally; they do not establish that the resulting network is a miniature human body.

For natural products, multi-organ coupling is attractive where intestinal transformation, hepatic metabolism, circulating conjugates, renal handling, or tissue reactivation jointly determine which species reaches a target. Yet every added compartment creates scaling questions about fluid volume, organ mass, residence time, protein binding, flow partition, and metabolite exchange. Current multi-organ PK scholarship therefore treats scaling as an unresolved methodological issue rather than a solved

translation step [32]. Qualification and regulatory activity around microphysiological systems is expanding, but acceptance remains context- and jurisdiction-dependent [33].

The proposed framework accordingly treats multi-organ evidence as a higher-order constraint only when organ-specific measurements remain identifiable after coupling. If a systemic output changes but the contributing compartment cannot be resolved, the system may generate a valuable phenotype while providing a weak mechanistic constraint. Cross-organ complexity should be used to test distributed hypotheses, not to hide unmeasured transformations inside a more elaborate device.

Device variability, scaling problems, and validation limits

Organ-chip evidence inherits uncertainty from both biology and engineering. Field-wide analyses identify persistent barriers involving reproducibility, usability, materials, manufacturing, standardization, and deployment [34]. Compound loss to polymers is distinct from biological clearance, and scaling uncertainty in coupled

systems is distinct from assay noise; combining them into one generic “model error” obscures where a pharmacology model should be revised.

A constraint should therefore carry provenance: device material and geometry, cell source and maturation state, medium, flow conditions, sampling schedule, analytical method, and the transformation used to connect chip measurement to model quantity. Transfer across laboratories or platforms should be conditional rather than assumed. Standardization, context-of-use qualification, and reproducibility remain necessary before MPS outputs can be treated as transferable constraints across laboratories or decision settings [28, 29, 34].

Table 4 summarizes the assessment criteria that determine whether an apparently human-relevant observation should narrow a model strongly, weakly, or not at all. Importantly, a weak constraint is not a failed experiment: it may still reveal which measurement, comparator, or scaling assumption must be improved before the evidence can travel beyond its originating device.

Table 4. Assessment criteria for the evidential weight of a chip-derived model constraint

Criterion	Stronger basis for constraint	Warning condition	Consequence for interpretation
Exposure provenance	Measured or mass-balanced delivered exposure	Nominal dose only	Keep exposure assumptions broad
Biological qualification	Relevant tissue function documented	Immature or poorly characterized phenotype	Limit transfer to target physiology
Analytical specificity	Chemical species and compartment resolved	Composite or nonspecific signal	Do not assign mechanism
Device characterization	Material and flow behavior documented	Sorption or hydrodynamics uncertain	Down-weight concentration inference
Scaling transparency	Transformation to model quantity explicit	Hidden or dominant scaling assumptions	Treat systemic prediction as conditional
Reproducibility	Replication across runs or settings	Strong device-to-device dependence	Restrict generalization
External comparison	Independent assay, in-vivo, or human evidence considered	No external challenge	Treat validity as internal only

Note. These criteria organize evidential judgment qualitatively; they do not define numerical weights or acceptance thresholds.

CONCLUSION

Organ-on-chip evidence is most useful to natural-product pharmacology when it reduces unjustified freedom in a model rather than when it is used as a generic badge of physiological realism. Dynamic exposure can constrain what concentration history is plausible; tissue interfaces can constrain access; multicellular systems can constrain context independence; organ-specific models can constrain metabolism and local pharmacokinetics; and coupled systems can test whether those local constraints remain coherent across compartments.

The proposed framework keeps those contributions conditional. A chip observation becomes model-relevant only after its analytical identity, biological context, device provenance, temporal scale, and required computational transformation are made explicit. Contradiction with a simpler assay should trigger localized revision and examination of alternative explanations, not automatic replacement. More physiological complexity also does not compensate for weak measurement, poor scaling, or limited reproducibility.

For natural products, where mixtures, metabolites, tissue transformation, and exposure heterogeneity often complicate parent-compound reasoning, this constraint-

based approach offers a disciplined path for integrating human-relevant dynamic evidence. Its value now requires prospective testing across chemically diverse compounds, platforms, laboratories, and independently observed pharmacokinetic or pharmacological outcomes.

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