



Plasma Concentration Is Not Enough for Phytochemical Lead Selection When Tissue Distribution, Unbound Exposure, and Site-of-Action Pharmacokinetics Determine Efficacy

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ABSTRACT

Plasma pharmacokinetics remains the dominant exposure framework in early lead selection, yet plasma concentration may poorly represent the pharmacologically relevant exposure of a phytochemical at its site of action. This perspective examines why total or even unbound plasma exposure can become insufficient when tissue binding, regional partitioning, intracellular access, transporter activity, sequestration, and local concentration–time behavior alter the fraction of compound that reaches the relevant biophase. The analysis distinguishes systemic exposure from site exposure, total from unbound concentration, bulk-tissue accumulation from intracellularly available drug, and measured distribution from mechanistically inferred target access. It further argues that lead ranking should not treat plasma area under the curve or maximum concentration as stand-alone surrogates for efficacy when the intended target resides behind biological barriers or within compartments subject to active transport or binding disequilibrium. The principal contribution is a proposed site-of-action pharmacokinetic perspective for phytochemical lead selection in which plasma data remain necessary but are interpreted alongside evidence for unbound tissue exposure, compartment-specific partitioning, temporal concordance, and measurement or model confidence. This perspective does not assume that tissue measurements always outperform plasma metrics, nor that a single distribution parameter predicts efficacy. Its utility is therefore conditional on target localization, compound chemistry, formulation, biological context, analytical feasibility, and validation of any model used to infer inaccessible compartments. The framework is intended to guide evidence prioritization rather than replace compound-specific pharmacokinetic–pharmacodynamic experiments, and its proposed decision logic requires prospective testing.

Key Words: *Phytochemicals, unbound exposure, Tissue distribution, Site-of-action pharmacokinetics, Intracellular disposition, Lead selection*

eIJPPR 2026; 16(4):89-98

HOW TO CITE THIS ARTICLE: Ali H, Farooq M, Shah U, Khan B, Malik S. Plasma Concentration Is Not Enough for Phytochemical Lead Selection When Tissue Distribution, Unbound Exposure, and Site-of-Action Pharmacokinetics Determine Efficacy. Int J Pharm Phytopharmacol Res. 2026;16(4):89-98. <https://doi.org/10.51847/FAevs6TvKf>

INTRODUCTION

Plasma concentration is convenient, reproducible, and central to pharmacokinetic characterization, but

convenience should not be confused with pharmacological completeness. Total plasma concentration combines free and protein-bound drug and therefore cannot, without additional assumptions, be treated as equivalent to the

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Received: 27 April 2026; **Revised:** 28 July 2026; **Accepted:** 03 August 2026

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concentration available for distribution or target interaction. Contemporary free-drug analysis emphasizes that the pharmacologically relevant fraction depends on the compartment being considered and on whether equilibrium and accessibility assumptions are defensible [1]. For phytochemical lead selection, this creates a practical problem: candidates can appear favorable because they achieve measurable systemic exposure while the relevant unbound concentration in the tissue or cellular compartment containing the target remains unknown.

Spatial structure further weakens any simple plasma-to-effect-site mapping. In airway mucus, spatial pharmacokinetic modeling has shown how diffusion and local transport processes can generate concentration gradients and delays that are not represented by a single systemic concentration [2]. A similar principle applies when a compound must cross a restrictive biological interface. Mechanistic modeling of bedaquiline in tuberculous meningitis, for example, required explicit treatment of central nervous system distribution rather than direct extrapolation from circulating concentrations [3]. Evidence from CNS and pulmonary target-site modeling indicates that unbound or site-specific exposure can diverge from systemic plasma exposure when distribution barriers and local compartment processes intervene [3, 4]. This perspective therefore treats plasma exposure as an upstream descriptor rather than the terminal exposure variable for every lead-selection problem. The argument is not that plasma pharmacokinetics is dispensable. Plasma remains essential for clearance, systemic bioavailability, dose proportionality, safety interpretation, and parameterization of distribution models. The narrower claim advanced here is that lead ranking becomes fragile when plasma exposure is used as a proxy for a pharmacologically distinct compartment without evidence that the proxy is valid. For phytochemicals, whose apparent disposition may be strongly influenced by binding, metabolism, transport, formulation, and heterogeneous tissue affinity, the relevant question is not simply how much compound reaches plasma, but how much pharmacologically available compound reaches the intended site, for how long, and with what uncertainty. A plasma metric can still be decision-relevant when rapid equilibration, limited active transport, and stable binding make systemic exposure a defensible surrogate. The central methodological task is therefore to establish surrogate adequacy rather than reject plasma by default.

Unbound drug as the pharmacologically available fraction

The free-drug concept provides the first correction to plasma-centric ranking, but it must be applied at the correct anatomical level. The unbound brain-to-plasma partition coefficient, $K_{p,uu,brain}$, was developed to distinguish free

brain exposure from total tissue partitioning and has become a useful framework for separating systemic availability from barrier-limited target-site access [5]. Conceptually, $K_{p,uu}$ values near, above, or below unity may indicate different relationships between unbound plasma and unbound tissue exposure, but the coefficient itself is descriptive rather than a direct efficacy measure. Target abundance, turnover, local metabolism, intracellular entry, and temporal behavior remain separate determinants.

Tissue binding introduces another layer of uncertainty because a high total tissue concentration can coexist with a much smaller free concentration. Measurements of fraction unbound in xenografted tumors show that tissue binding must be considered independently when total tissue exposure is used to infer pharmacologically accessible drug [6]. This distinction matters for phytochemicals that are lipophilic, extensively protein-bound, or strongly associated with membranes and intracellular components: apparent accumulation may reflect sequestration rather than productive target access.

Even changes in plasma pharmacokinetics can be mechanistically ambiguous. Analyses of CYP450 probe-drug clearance demonstrate that altered plasma clearance under physiological or pathological conditions does not necessarily identify a single change in enzyme activity because binding, blood flow, and other processes can contribute [7]. Accordingly, unbound plasma exposure is a necessary refinement of total plasma exposure, but it is not automatically the final biophase concentration. Two cautions follow. First, “unbound” should always identify the compartment being measured; unbound plasma, interstitial fluid, cytosol, and organelle-associated pools are not interchangeable labels. Second, a favorable free fraction does not rescue a candidate if the absolute concentration reaching the relevant compartment remains below that required for pharmacological activity.

Tissue partitioning and intracellular distribution

Tissue exposure is not a single scalar property of a molecule. Regional measurements of eletriptan and sumatriptan have demonstrated that unbound partitioning differs across central and peripheral nervous system compartments, supporting the view that anatomical location can materially change the exposure available for pharmacological action [8]. For lead selection, this means that a compound cannot be classified simply as “tissue penetrating” without specifying which tissue region, which binding state, and which pharmacologically relevant compartment are being described.

The problem becomes more pronounced when cellular entry and biological barriers are considered together. Comparative work across drugs with different transport

characteristics has shown that unbound partitioning and cellular distribution can vary across nervous-system barriers and cell-associated compartments [9]. These observations separate at least three quantities that are often conflated during early ranking: concentration in plasma, concentration in bulk tissue or interstitial space, and concentration within the cells that actually contain the target. Measured barrier-distribution data and predictive brain PK modeling both support treating tissue concentration–time behavior as an explicit exposure endpoint rather than an automatic derivative of plasma PK [9, 10].

For phytochemicals, this distinction is especially important when candidate structures differ substantially in lipophilicity, ionization, glycosylation, membrane affinity, or susceptibility to active transport. Those properties can influence total tissue uptake and intracellular exposure in different directions. A lead may therefore show favorable whole-tissue accumulation while remaining poorly available in the cytosol, nucleus, mitochondrion, or another target-containing compartment. Conversely, modest total tissue exposure may still be pharmacologically relevant if the accessible fraction is efficiently delivered to the correct microenvironment. Such interpretations require direct measurement or validated mechanistic inference rather than assumptions based on bulk partitioning alone. Accordingly, tissue partition should be treated as a compound-by-site property with explicit spatial and cellular resolution whenever the mechanism requires it.

Site-of-action pharmacokinetics

Site-of-action pharmacokinetics focuses on the concentration–time profile of the active molecular species in the compartment where its relevant target is located. That definition is deliberately narrower than “tissue exposure.” A bulk organ concentration can combine vascular drug, extracellular drug, intracellular drug, bound drug, sequestered drug, and metabolites, only some of which may contribute to the intended pharmacology. Modeling of an anti-LAG-3 monoclonal antibody illustrates the distinction by linking intratumor exposure to receptor occupancy rather than assuming that systemic concentration alone represents target engagement [11]. Although the molecular scale differs from phytochemicals, the pharmacokinetic principle is transferable: exposure and occupancy are related but nonidentical quantities.

Direct verification is therefore important when models are used to bridge from plasma to inaccessible sites. Physiologically based models of tyrosine kinase inhibitors have incorporated positron emission tomography to test predicted target-site penetration, demonstrating how imaging can provide an orthogonal check on tissue-distribution assumptions [12]. Whole-body dynamic PET

modeling of glyburide similarly shows that organ-specific concentration–time behavior can be extracted in ways that conventional plasma sampling cannot spatially resolve [13]. These methods do not automatically measure unbound intracellular concentration, and their signals remain constrained by tracer design, quantification, metabolism, and model structure.

For phytochemical development, site-of-action pharmacokinetics should therefore be framed as an evidence problem rather than a demand that every candidate undergo invasive tissue sampling. The relevant question is whether the intended mechanism depends on a compartment whose exposure is plausibly discordant with plasma. Where that risk is low, plasma may remain an adequate surrogate. Where barriers, heterogeneous tissue distribution, intracellular targets, or local metabolism are central, the lead-selection decision should explicitly state what is known, inferred, or still unmeasured about the actual biophase. This shifts evidence priority toward sites where surrogate failure is plausible, consequential, and experimentally or computationally testable.

Transporters, binding, and sequestration

A concentration gradient does not determine distribution by itself. Membrane transport can change how much unbound compound enters, leaves, or remains within a target-containing compartment. Comparative analysis of oxycodone uptake across brain endothelial and parenchymal cells illustrates how transporter-mediated processes can differentiate exposure on opposite sides of a biological barrier and within its cellular components [14]. For phytochemical candidates, the implication is conditional rather than class-wide: transporter involvement should be investigated when chemistry, disposition data, or discordant tissue penetration makes it plausible, not assumed merely because a molecule is plant-derived.

Binding and sequestration can produce the opposite interpretive error: abundant measured drug may be mistaken for abundant pharmacologically available drug. A physiologically based pharmacokinetic analysis of pyronaridine incorporated lysosomal trapping and infection-related physiology as determinants of compartmental disposition [15]. More direct multimodal imaging of PARP inhibitors identified lysosomal drug reservoirs associated with heterogeneous intracellular distribution [16]. Neither finding means that lysosomal accumulation is intrinsically unfavorable. A reservoir could alter persistence, redistribution, or toxicity, while its pharmacological significance depends on whether the intended target is accessible from that pool.

Lead evaluation should therefore ask sequentially what measured concentration represents. Total plasma exposure should first be separated from unbound plasma exposure;

tissue entry should then be distinguished from tissue binding; cellular entry should be separated from sequestration; and only then should measured or modeled concentration be interpreted as evidence of target-site

availability. This manuscript-derived sequence is summarized in **Table 1**. It is proposed as an analytic workflow, not as a validated scoring system.

Table 1. Exposure-interpretation workflow before a phytochemical distribution signal is treated as site-relevant

Workflow stage	Question resolved	Misinterpretation avoided	Decision consequence
Systemic availability	What fraction of circulating parent or active species is unbound?	Treating total plasma as accessible drug	Retain plasma as upstream exposure descriptor
Tissue access	Does unbound drug cross the relevant anatomical barrier?	Equating plasma exposure with organ penetration	Escalate to tissue measurement or mechanistic modeling when discordance is plausible
Tissue disposition	Is measured accumulation free, bound, extracellular, or mixed?	Reading bulk tissue concentration as a single biophase	Qualify the compartment represented by the assay
Cellular access	Does drug reach the target-containing cell and intracellular space?	Equating organ entry with intracellular availability	Prioritize cellular exposure when the target is intracellular
Sequestration check	Is drug trapped in a compartment that is pharmacologically non-equivalent to the target site?	Treating storage as productive exposure	Separate reservoir formation from target-accessible concentration
Site inference	Are exposure, target location, and time course sufficiently aligned?	Converting distribution evidence directly into efficacy	Use site exposure as one evidence layer in lead ranking

Note: The workflow is a proposed synthesis of the manuscript argument. Its steps are qualitative and do not define universal thresholds.

The same reasoning is represented visually in **Figure 1**: plasma exposure becomes informative for site action only

after the evidence branches that can modify its meaning have been interrogated.

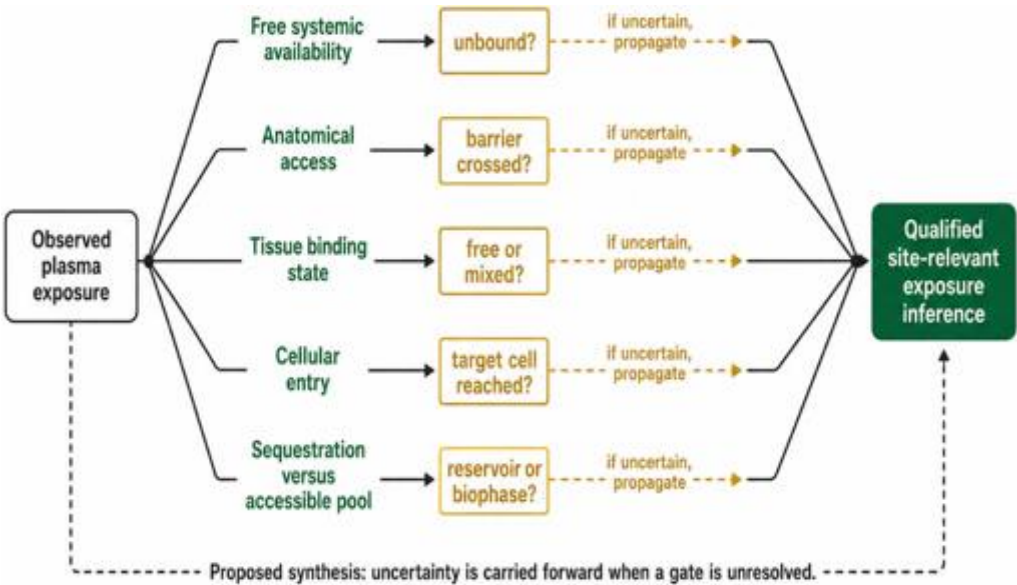


Figure 1. Evidence gates converting systemic exposure into a site-relevant pharmacokinetic inference

Temporal mismatch between plasma and tissue exposure
Even when plasma and tissue concentrations are directionally related, their trajectories can differ. This is not an argument that tissue kinetics must always be discordant. In patients resuscitated after cardiac arrest, paired plasma and soft-tissue microdialysis data for penicillin/beta-lactamase inhibitor combinations provide

an important boundary case: target-site behavior did not justify a universal assumption of large plasma–tissue divergence [17]. Lead-selection logic should therefore test temporal surrogate adequacy rather than presuppose failure. Mismatch becomes more consequential when local distribution is delayed, nonlinear, or sustained. Long-term

microdialysis of voriconazole demonstrated target-site exposure under nonlinear pharmacokinetics that could not be reduced safely to an isolated plasma snapshot [18]. Cross-species PBPK analysis of bedaquiline likewise represents lung microcompartments as distinct kinetic spaces whose concentration-time profiles depend on local distribution processes [19]. These examples support a temporal question that is often missing from phytochemical ranking: not only whether a compound reaches a tissue, but whether relevant local exposure overlaps with the biological window in which the target can be modulated.

Accordingly, a site-to-plasma relationship should be considered dynamic. A candidate can have an attractive plasma maximum yet delayed target access, or declining plasma levels while a tissue reservoir sustains local exposure. The reverse can also occur. Ranking based on a single time point or systemic area under the curve may therefore obscure differences in onset, persistence, and fluctuation at the biophase. The appropriate remedy is proportional to risk: richer plasma sampling may suffice when equilibration is credible, whereas microdialysis, imaging, tissue sampling, or mechanistic modeling becomes more informative when slow distribution, trapping, or barrier transport is plausible.

Integrating tissue exposure into lead ranking

The purpose of adding tissue PK to lead selection is not to maximize tissue accumulation. It is to improve correspondence between the exposure metric being ranked

and the biology the lead is expected to influence. Concentration-dependent intracellular $K_{p,uu}$ has been used to correct exposure-related discrepancies between biochemical and cellular potency for KAT6A inhibitors, showing that nominal potency comparisons can change meaning when intracellular availability differs [20]. In cynomolgus monkeys, brain microdialysis across drugs with diverse blood–brain barrier transport characteristics further demonstrates that candidate molecules can differ substantially in unbound intracerebral distribution [21].

Cellular pharmacology provides the same warning at another scale. Combining intracellular drug exposure with growth-rate inhibition can distinguish nominal dosing from the concentration actually achieved inside cells [22]. These studies do not establish a universally superior ranking formula, but they support incorporating exposure at the most mechanism-relevant level that can be measured or credibly inferred.

The proposed ranking logic is therefore comparative and confidence-aware. Potency should remain one axis, while systemic PK, site-relevant unbound exposure, temporal concordance, and confidence in measurement or prediction provide separate evidence dimensions. A lead should not receive automatic preference merely because one dimension is high. Instead, the decisive question is whether the observed exposure profile is adequate for the intended target and whether uncertainty could plausibly reverse the ranking. **Table 2** defines the applicability domains that follow from this argument.

Table 2. Applicability domains for deciding how strongly tissue exposure should influence phytochemical lead ranking

Pharmacokinetic situation	Plasma as surrogate	Additional evidence priority	Ranking interpretation
Rapid, credible equilibration with accessible target	Potentially adequate	Confirm unbound exposure and temporal concordance	Plasma can retain substantial decision weight
Restrictive anatomical barrier	Uncertain	Unbound site penetration or validated barrier model	Penalize confidence, not the compound, until site access is resolved
High bulk-tissue accumulation with uncertain binding	Potentially misleading	Tissue free fraction and compartment identity	Do not reward accumulation alone
Intracellular target with variable cellular uptake	Incomplete	Intracellular unbound exposure	Compare candidates at the target-relevant cellular level
Evidence of trapping or persistent reservoir	Time dependent	Compartment identity and release kinetics	Separate persistence from productive exposure
Site exposure estimated mainly by model	Conditional on credibility	Fit-for-purpose verification and uncertainty analysis	Carry prediction confidence into the ranking

Note: This applicability-domain matrix is proposed. It does not prescribe quantitative cut-offs or a validated composite score.

The site-of-action pharmacokinetic perspective

Target-site pharmacokinetics is already supported by several population and mechanistic modeling strategies, reflecting differences in what can be sampled directly and what must be inferred [23]. Pulmonary PBPK work

likewise shows that target-site concentrations may require explicit permeability, extracellular, and intracellular processes rather than a simple scaling of plasma concentrations [24]. The contribution proposed here is not another universal compartment model. It is a decision

perspective for determining when the location and state of exposure are sufficiently important to alter phytochemical lead interpretation.

The proposed perspective begins with target localization rather than with the available PK assay. It then moves outward: identify the active molecular species, determine the relevant extracellular or intracellular biophase, evaluate barriers and transport, distinguish free from bound or sequestered pools, compare local and plasma time courses, and assign confidence to each measured or modeled link. Plasma remains the common systemic anchor, but its inferential distance from the target determines how much additional evidence is warranted. A surface-accessible target in a well-perfused compartment may require little escalation; an intracellular target behind an active barrier may require several independent lines of evidence.

Evidence sufficiency should also be separated from candidate quality. A candidate should not be downgraded

merely because its site exposure has not yet been measured; instead, uncertainty should lower confidence in the ranking when that missing information could plausibly change the decision. Conversely, a richly characterized candidate should not be preferred solely because it has more data. This distinction is particularly important in natural-product programs, where compound availability, analytical standards, and formulation maturity can differ across leads. The proposed perspective therefore treats additional tissue PK as decision-relevant when it resolves a material uncertainty, rather than as a mandatory data package for every molecule.

This is intentionally threshold-free. The same $K_{p,uu}$, tissue concentration, or model error need not carry identical meaning across targets, doses, formulations, or therapeutic contexts. **Figure 2** expresses the perspective as progressively more site-specific terraces while preserving uncertainty rather than converting it into an arbitrary numerical gate.

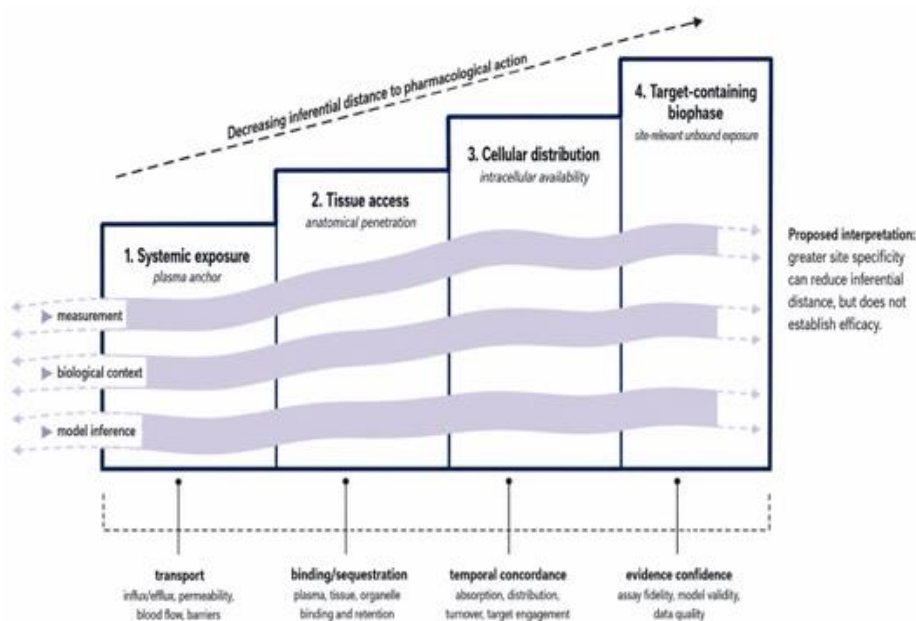


Figure 2. A threshold-free site-of-action pharmacokinetic landscape for phytochemical lead interpretation

Implications for efficacy and toxicity interpretation

An exposure-aware perspective changes both efficacy and toxicity interpretation because neither outcome is necessarily governed by the compartment that is easiest to sample. This is particularly relevant to phytochemicals whose formulation can substantially change apparent disposition. Evidence synthesized for intravenous curcumin nanodelivery shows that delivery systems can alter pharmacokinetic and pharmacodynamic behavior, meaning that “curcumin exposure” cannot be interpreted independently of formulation, route, and the species actually reaching relevant tissues [25]. A favorable plasma profile generated by a formulation may therefore reflect

improved systemic delivery without establishing that the intended target compartment receives proportionately improved free exposure.

The converse problem is high local accumulation with low available concentration. Experimental work on intracellular drug bioavailability demonstrates that neutral lipids and phospholipids can contribute to intracellular binding, separating total cellular drug from the unbound pool available for interaction [26]. This distinction prevents a common interpretive shortcut: tissue enrichment is not necessarily target enrichment. For efficacy, the relevant question is whether the active species occupies the correct biophase at a sufficient time and concentration to

support the proposed mechanism; for toxicity, it is whether vulnerable cells or organ compartments experience an exposure capable of contributing to harm.

Organ-specific modeling can make this asymmetry explicit. PBPK analysis of bosentan separately predicts systemic and liver exposure, illustrating why an organ associated with metabolism or toxicity may require its own concentration-time representation [27]. The same principle should be applied cautiously to phytochemical leads. A candidate with modest plasma exposure could still generate substantial local exposure through uptake or sequestration, whereas a candidate with high plasma exposure may fail to reach a protected target. Neither observation alone proves efficacy or toxicity. Site exposure is one causal prerequisite among others, and biological sensitivity, target engagement, active metabolites, off-target pharmacology, and adaptive responses may still determine outcome.

The practical implication is symmetrical: efficacy should not be dismissed solely because plasma exposure appears modest, and safety should not be assumed because plasma concentrations appear low. Both interpretations should ask which molecular species reaches which site, in what free state, for what duration, and how securely that exposure is known.

Measurement and modeling boundaries

No single analytical modality resolves every element of site-of-action exposure. Mass spectrometry imaging can localize drugs and metabolites within tissue architecture and thereby reveal spatial patterns hidden by bulk homogenates, but its signal does not automatically correspond to unbound, target-accessible concentration [28]. Microdialysis samples selected extracellular spaces rather than every intracellular compartment; PET provides dynamic organ or tissue information but depends on tracer behavior and quantification assumptions; tissue homogenization can improve sensitivity while destroying spatial and cellular resolution. Method selection should therefore follow the exposure question rather than the reverse.

A practical consequence is that analytical and modeling methods should be combined according to the uncertainty they resolve. Tissue homogenates can establish that a compound reaches an organ, spatial imaging can refine where it localizes, microdialysis can inform extracellular unbound kinetics, and mechanistic models can connect sparse observations across time or compartments. These outputs are complementary rather than interchangeable. Agreement among them increases confidence only when each method has been interpreted within its own measurement domain; apparent disagreement may instead

reveal that the methods are observing different molecular pools or spatial scales.

Modeling is indispensable when direct sampling is infeasible, but mechanistic detail does not itself establish predictive credibility. Evaluation of a published PBPK model-building strategy across five compounds showed the importance of preclinical verification for first-in-human prediction [29]. Model-informed and machine-learning-assisted PK predictions remain conditioned on empirical verification, data suitability, and model interpretability [29, 30]. For site-of-action applications, the validation target must also match the claim: a model that reproduces plasma profiles may still have weakly identified tissue permeability, binding, transporter, or intracellular parameters.

This creates a hierarchy of uncertainty rather than a hierarchy of technologies. Direct site measurements can be limited by invasiveness, recovery, spatial averaging, temporal sparsity, assay sensitivity, or inability to distinguish free from bound drug. Models can integrate mechanisms and extrapolate across conditions, yet they inherit uncertainty from parameterization, structural assumptions, and chemical-space transfer. Orthogonal methods can reduce—but not eliminate—these weaknesses when they interrogate genuinely different aspects of the distribution process.

For phytochemical leads, additional analytical complications may arise from extensive metabolism, conjugation, instability, stereochemical complexity, or formulation-associated species. Consequently, the measured analyte must be matched to the pharmacologically relevant species. Model inputs should distinguish measured properties from predictions, and uncertainty should accompany the resulting site-exposure estimate into any lead-ranking decision. The appropriate standard is not maximal methodological sophistication, but sufficient evidence to support the specific inference being made.

Limitations

This perspective integrates evidence drawn from multiple drug classes, organs, analytical platforms, and modeling traditions. That breadth supports general pharmacokinetic distinctions but prevents direct quantitative transfer to every phytochemical. Many cited examples concern antimicrobials, CNS drugs, anticancer agents, or biologics rather than plant-derived compounds. Their mechanistic lessons should therefore be treated as testable distribution principles, not as compound-specific estimates.

Model-derived site exposure is also only as credible as its purpose, parameter support, verification, and uncertainty analysis. Established PBPK confidence principles emphasize that qualification is fit-for-purpose rather than

conferred simply by model complexity [31]. Moreover, even measurements intended to estimate unbound intracellular exposure are method dependent: comparative hepatic $K_{p,uu}$ approaches demonstrate distinct experimental strengths and limitations [32].

The proposed perspective consequently does not establish a universal lead-ranking algorithm, a minimum acceptable $K_{p,uu}$, or a rule that tissue measurements must always supersede plasma PK. It also does not resolve pharmacodynamic sensitivity, target engagement, active-metabolite contributions, disease-dependent distribution, or interindividual variability by itself. Prospective evaluation should test whether adding site-relevant exposure information materially changes candidate ordering and improves prediction of appropriately selected pharmacodynamic outcomes across chemically diverse phytochemical series.

CONCLUSION

Plasma pharmacokinetics is necessary for phytochemical development, but it is not automatically the pharmacologically decisive exposure compartment. The relevant exposure may instead reside in unbound tissue fluid, a target-containing cell, or a more restricted intracellular biophase whose concentration-time profile is shaped by barriers, transport, binding, sequestration, metabolism, and formulation.

This perspective therefore proposes that lead selection treat plasma concentration as an anchor from which inferential distance to the site of action is assessed. Greater distance creates a stronger rationale for site-specific measurement or validated mechanistic modeling; credible equilibration allows plasma to retain greater decision weight. The aim is not to maximize tissue accumulation or to replace potency with pharmacokinetics, but to align the exposure metric used for ranking with the biology the candidate is expected to influence.

The proposed approach remains conditional and requires prospective evaluation. Site measurements can be incomplete, models uncertain, and exposure itself cannot establish target engagement, efficacy, or safety. Its principal value is methodological: making the location, free state, timing, and evidential confidence of exposure explicit before a phytochemical is advanced because its plasma profile appears favorable.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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