



The Active Molecule Is Not the Phytochemical You Swallow: Reframing Pharmacology Around Metabolites and Exposure

Kenji Tanaka^{1*}, Yui Kobayashi¹, Takeshi Nakamura²

¹Department of Pharmacokinetics and Metabolite Pharmacology, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.

²Department of Biotransformation and Systemic Exposure Modeling, Graduate School of Pharmacy, Kyoto University, Kyoto, Japan.

ABSTRACT

Natural-product pharmacology conventionally begins with the isolated, formulated, or ingested phytochemical and carries that molecular identity forward into screening, target prediction, docking, and mechanistic interpretation. For orally administered compounds, however, the molecule entering an assay or computational model may not be the species that reaches systemic circulation or the relevant biological site. Intestinal transformation, microbial metabolism, phase I and phase II reactions, transporter-dependent disposition, conjugation, and local deconjugation generate multiple molecular entities with distinct exposure profiles and potentially distinct pharmacology. This mechanistic perspective argues that natural-product pharmacology should distinguish oral identity from exposure identity and, ultimately, from the molecular identity implicated at the proposed site of action. Evidence from human metabolomics, pharmacokinetics, microbial xenobiotic metabolism, conjugate disposition, tissue pharmacokinetics, and metabolite bioanalysis is integrated into a proposed exposure-weighted molecular-ensemble framework. The framework treats predicted metabolites, measured circulating species, tissue-accessible molecules, and experimentally supported target ligands as different evidential states rather than interchangeable evidence of mechanism. It also explains why parent-only screening or docking may prioritize a chemically plausible but biologically mis-specified ligand. The argument remains bounded: parent compounds can be pharmacologically relevant, local gastrointestinal mechanisms may not require systemic exposure, conjugates are not uniformly active or inactive, and metabolite prediction does not establish formation or target engagement. Mechanistic attribution should follow the molecular species that plausibly reaches the biology being explained.

Key Words: Natural products, Metabolites, Biotransformation, Pharmacokinetics, Gut microbiome, Target engagement

eIJPPR 2025; 15(1):58-66

HOW TO CITE THIS ARTICLE: Tanaka K, Kobayashi Y, Nakamura T. The Active Molecule May Not Be the Phytochemical You Swallow: Reframing Natural Product Pharmacology Around Metabolites, Biotransformation, and Systemic Exposure. Int J Pharm Phytopharmacol Res. 2025;15(1):58-66. <https://doi.org/10.51847/tT8VUvB394>

INTRODUCTION

Natural products remain a chemically diverse foundation for modern drug discovery, but contemporary natural-product research increasingly depends on integration of chemical characterization, pharmacology, analytical measurement, and biological mechanism rather than treating an isolated structure as a complete pharmacological explanation [1]. This requirement

becomes especially important after oral administration. A molecule placed in a capsule, food matrix, extract, or dosing solution enters a biological system in which its chemical identity may change before the proposed target is encountered.

For many dietary polyphenols, intestinal and microbial transformations generate downstream molecules chemically distinct from the swallowed structures [2]. The resulting problem is not adequately captured by the phrase

Corresponding author: Kenji Tanaka

Address: Department of Pharmacokinetics and Metabolite Pharmacology, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.

E-mail: ✉ tanaka.kenji@mol.f.u-tokyo.ac.jp

Received: 07 November 2024; **Revised:** 23 December 2024; **Accepted:** 09 January 2025

This is an **open access** journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.



“poor bioavailability.” Bioavailability stated only for a parent compound can obscure a more basic question: which molecular species are actually present after absorption and metabolism? Human evidence shows substantial interindividual variability in the metabolism and bioavailability of polyphenol-derived metabolites [3]. The same nominal dose can therefore generate different systemic chemical environments.

This perspective uses oral identity for the structure administered or ingested, exposure identity for molecular species demonstrably present in the biological compartment relevant to a claim, and pharmacological identity for species sufficiently available at the proposed site of action to remain credible participants in the mechanism. These identities can coincide, but they should not be assumed to do so.

The argument is not that metabolites universally replace parent compounds. Parent molecules, host metabolites, microbial products, conjugates, and locally regenerated species should instead be treated as competing or coexisting hypotheses whose relevance depends on formation, concentration, distribution, and biological competence. The central problem is therefore one of molecular attribution across exposure, particularly when an orally administered structure is connected directly to an in-vitro effect or computational target prediction without demonstrating the intervening chemistry.

The parent-compound assumption in natural product research

The parent-compound assumption arises when the molecule administered experimentally is carried forward

as though it were necessarily the principal in-vivo ligand. The assumption may be subtle: an oral intervention is named by its parent constituent, pharmacokinetics are interpreted without adequate molecular speciation, and later docking or mechanistic experiments use that parent structure. The resulting narrative can be internally coherent while containing an untested identity transition between ingestion and target exposure.

Curcumin illustrates why this requires qualification. Formulation strategies can alter measured exposure, but interpretation depends on which curcuminoid-related species are quantified and what those measurements establish about the chemical forms actually circulating [4]. Showing that a formulation increases “bioavailability” does not by itself establish increased exposure of the molecular species used in a mechanistic assay.

Quercetin provides a complementary example. Human exposure involves extensive phase-II metabolism, and the parent and its conjugates should not be treated as pharmacologically interchangeable solely because they share a precursor relationship [5]. A conjugate may have different transport, distribution, intrinsic activity, or capacity for local deconjugation. Conversely, detecting a conjugate does not establish that the conjugate itself mediates the biological effect.

The distinction is therefore evidential rather than semantic. Naming the swallowed phytochemical identifies an input molecule; it does not automatically identify the systemically exposed or mechanistically relevant molecule. **Table 1** organizes these identity states and the evidentiary errors that arise when they are collapsed.

Table 1. Molecular identity constructs that should remain distinct in oral natural-product pharmacology

Construct	Meaning in this perspective	Evidence needed before mechanistic interpretation	Main error if collapsed
Ingested parent compound	Species administered or consumed	Verified composition and identity	Assuming administration establishes target exposure
Detected derivative	Transformed species observed after administration	Structure-resolved analytical identification	Treating detection as proof of activity
Phase-II conjugate	Covalently modified metabolite with distinct disposition	Intact-species measurement; transport or activity evidence where relevant	Treating conjugation as synonymous with inactivity or activity
Exposure-relevant species	Molecule quantitatively present in the biological compartment pertinent to the claim	Concentration and compartment-specific evidence	Equating systemic abundance with target availability
Candidate pharmacological entity — proposed	Parent or derivative whose identity, exposure, and biological competence jointly justify mechanistic testing	Convergent chemical, pharmacokinetic, and pharmacological evidence	Treating precursor relationships as pharmacological equivalence

Note: The final row is a proposed interpretive construct and does not rank metabolites above parent compounds.

Intestinal transformation before systemic entry

For an orally administered natural product, the gastrointestinal tract is not simply a conduit between dose

and plasma. Dissolution, luminal chemistry, epithelial passage, enterocyte metabolism, biliary processes, and microbial transformation can alter the molecular population available for systemic distribution. Pharmacokinetic investigation should therefore follow chemical species rather than only nominal ingredients.

Human work with pomegranate-derived constituents demonstrates how targeted LC–MS/MS can distinguish parent-related and downstream molecules after ingestion rather than collapsing exposure into an undifferentiated extract-level measure [6]. Such analytical separation does not establish which detected molecule is pharmacologically active, but it provides the chemical attribution required before that question can be answered. Microbial transformation adds another layer because natural products and gut microorganisms interact bidirectionally. Microorganisms can transform natural-product constituents, while the compounds and their metabolites may also modify the microbial environment [7]. “Intestinal metabolism” should therefore not be used as shorthand for a single pathway. Host epithelial enzymes and microbial enzymes occupy different biological settings and can generate different products.

The mechanistic implication is temporal as well as chemical. A parent may be abundant in the intestinal lumen yet scarce after absorption; another species may appear after enterocyte or hepatic transformation; and microbial products may emerge after later colonic processing. A mechanistic experiment conducted only with the swallowed molecule therefore tests one candidate within a changing chemical population. For a luminal target, that candidate may be correct. For a systemic target, pre-systemic transformation becomes part of molecular attribution.

Microbial metabolism as a generator of new pharmacologically relevant molecules

Microbial metabolism can be viewed as chemical synthesis occurring within a host-associated ecological system. Gut bacteria perform defined transformations on dietary polyphenols that alter functional groups, scaffold size, polarity, and subsequent host handling [8]. These products need not be considered merely degraded remnants of their precursors; some are distinct molecular entities whose pharmacological properties may differ substantially.

The chemistry is also individualized. Polyphenol-related gut metabolotypes describe recurring differences in the capacity to generate downstream products, although their stability and determinants vary with population and context [9]. More direct experimental work supports the underlying principle that xenobiotic transformation is distributed unevenly across microbial organisms and communities. Mapping across cultured human gut bacteria

demonstrated broad but chemically specific drug-transforming capacities, whereas individualized community experiments showed that different microbiomes can generate different outcomes from the same xenobiotic substrate [10, 11]. These studies do not establish identical behavior for every phytochemical, but they support person-dependent metabolic identity as a mechanistically credible possibility.

Microbial transformation also matters because a downstream molecule can acquire target relationships that cannot be inferred from the precursor. Some microbiota-derived metabolites function as ligands for host xenobiotic receptors [12]. The relevant mechanistic question therefore shifts from whether an ingested molecule has a plausible target to whether any species generated from the exposure possesses the identity, concentration, localization, and biological competence required for the proposed effect.

Urolithin A provides an instructive example. It is a microbiota-derived molecule that has been administered directly and characterized as a distinct systemic entity in humans [13]. Direct supplementation can also produce more consistent exposure than reliance on endogenous formation from dietary precursors, thereby reducing variability associated with microbial production capacity [14]. Urolithin A is not a universal model for microbial metabolites, but it illustrates why a metabolite may become the experimentally appropriate pharmacological object.

Phase I and Phase II metabolism reshape the circulating chemical space

Following absorption, natural-product-derived molecules enter another transformation regime. Oxidation, reduction, hydrolysis, glucuronidation, sulfation, methylation, and related reactions can substantially alter the chemical population detected in blood and excreta. The relevant analytical unit is therefore not simply “the phytochemical in plasma,” but the set of molecular forms produced by host disposition.

Human metabolomics demonstrates the breadth of this phenomenon. Characterization of sulfated and glucuronidated polyphenol metabolites reveals a substantial phase-II chemical space following dietary exposure [15]. Their presence does not establish pharmacological importance, but it directly challenges interpretations that treat systemic exposure as synonymous with unconjugated parent compound.

Conjugates also possess their own disposition biology. Uptake and efflux transporters can participate in the movement of glucuronide and sulfate metabolites across intestinal, hepatic, renal, and other cellular interfaces [16]. Conjugation is therefore not adequately described as a terminal chemical “off switch.” It can alter permeability,

transporter dependence, clearance, tissue distribution, and the possibility of later deconjugation.

The pharmacological consequence is that potency should be interpreted against the species and concentrations biology actually encounters. Critical assessment of phenolic acids and their phase-II conjugates shows why mechanistic conclusions become fragile when experiments use a different molecular species or concentrations poorly aligned with human exposure [17]. A convincing cellular effect at an experimentally convenient concentration is not equivalent to evidence that the same mechanism operates after oral administration.

Metabolite-aware bioanalysis therefore becomes part of mechanistic reasoning. Contemporary recommendations emphasize purposeful identification and quantification of metabolites when their exposure may influence efficacy or safety interpretation [18]. Applied to natural products, the principle is straightforward: before assigning systemic pharmacology to the swallowed structure, determine which structures the organism actually presents to the relevant biological system.

Conjugates, deconjugation, and tissue-specific reactivation

Conjugation creates a difficult interpretive problem because three possibilities are often compressed into one category: an intact conjugate may possess biological activity, it may primarily represent a transported or cleared metabolite, or it may serve as a precursor from which another species is regenerated. These possibilities cannot be distinguished from the label “glucuronide” or “sulfate” alone.

Analytical treatment can further distort interpretation. Curcumin studies show that β -glucuronidase treatment may incompletely hydrolyze complex conjugates, meaning that workflows designed to estimate “total curcumin” may not faithfully reconstruct sample composition [19]. Hydrolysis-based measurements are therefore transformations of the specimen rather than direct observations of what circulated intact. This does not invalidate such approaches, but their products should not be mistaken automatically for the molecular species present in vivo.

Local deconjugation creates the opposite problem. A circulating conjugate may be relatively inactive in plasma yet provide substrate for tissue-specific regeneration. In a preclinical bone system, β -glucuronidase catalyzed deconjugation of curcumin glucuronide and regeneration of unconjugated curcumin [20]. Related work in resorptive bone models supports the possibility that dietary-polyphenol metabolism can differ within a tissue microenvironment from what would be inferred from circulating composition alone [21].

These findings support a conditional mechanism, not a universal explanation for poorly exposed phytochemicals. Tissue reactivation depends on the conjugate, enzyme environment, transport, disease context, and local kinetics. A circulating conjugate may therefore be the relevant species, an elimination product, or a mobile precursor whose importance emerges only after local conversion.

Which molecular species actually reach the proposed target?

Systemic detection is not equivalent to target-site availability. Tissue binding, permeability, active transport, and clearance can generate differences between plasma and tissue exposure; under identifiable disposition mechanisms, unbound tissue concentration may diverge from plasma concentration [22, 23]. Human hepatic-distribution work further shows that organ concentrations can be predicted and compared with empirical observations rather than simply inferred from plasma values [24]. Spatial mass-spectrometry methods can add another layer by localizing drug and metabolite distributions within tissues [25].

The mechanistic question should therefore progress through distinct evidentiary levels: what was swallowed, what was formed, what circulated, what entered the relevant tissue, and what molecular species was available to the proposed target. No level universally substitutes for another. **Table 2** separates these exposure states, while **Figure 1** shows how competing molecular identities move through successive evidence boundaries without presuming that metabolites are intrinsically more important than their parent compounds.

Table 2. Exposure states that should be distinguished before assigning a molecular mechanism

Exposure state	What the observation establishes	What remains unresolved
Plasma detection	The molecular species entered sampled systemic circulation	Free concentration and target access
Quantified systemic exposure	Concentration–time behavior of the measured species	Tissue distribution and local transformation
Tissue occurrence	Presence in the relevant organ or compartment	Intracellular and unbound availability
Spatial localization	Anatomical distribution within tissue	Direct molecular engagement
Target-accessible species — proposed	Exposure evidence is compatible with access to the proposed target	Whether engagement produces functional pharmacology

Note: The proposed final category does not define a validated exposure threshold.

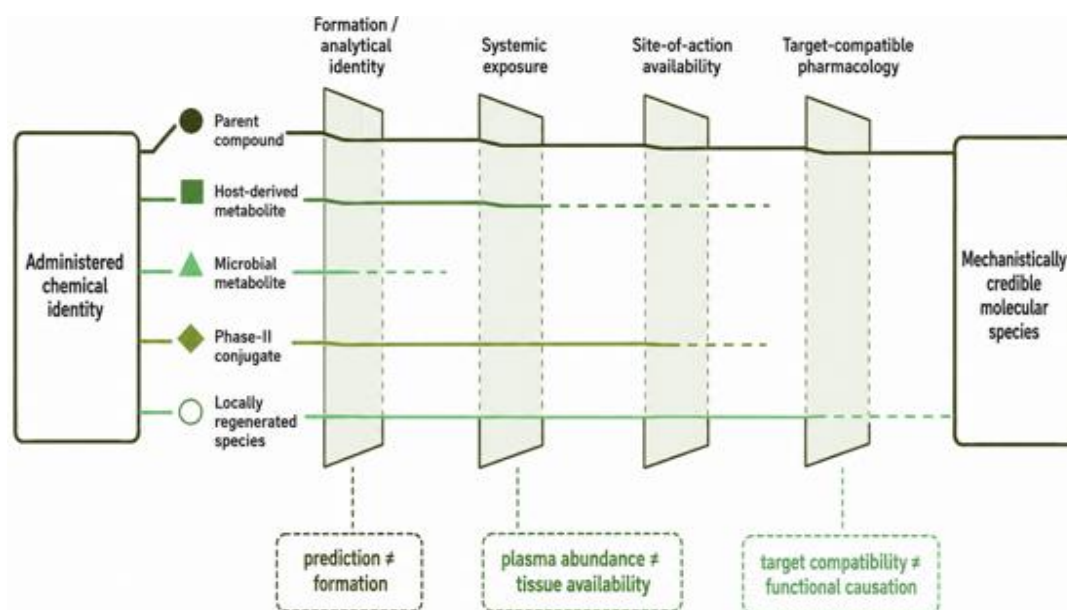


Figure 1. Exposure identity as the bridge between ingestion and mechanistic attribution

Why parent-compound docking can misidentify the relevant ligand

Docking evaluates whether a specified molecular structure is geometrically and energetically compatible with a modeled binding site, but it does not establish that the structure exists at that target after oral administration [26]. A technically sound docking experiment can therefore answer the wrong pharmacological question if metabolism has changed the ligand population relevant *in vivo*.

Metabolite-prediction models provide one route for expanding that candidate space. Contemporary deep-learning approaches can generate plausible downstream metabolite structures [27], and machine-learning systems can predict defined transformations such as quinone formation [28]. These tools are valuable because they challenge the assumption that the administered parent is the only structure worth modeling.

Their output nevertheless remains hypothetical. A predicted metabolite should not replace the parent in a mechanistic model simply because software generates it, and a docking score for a predicted metabolite does not establish formation, exposure, binding, or functional activity. The stronger strategy is to treat parent and metabolite structures as candidate ligands whose priority changes as analytical and pharmacokinetic evidence accumulates.

This distinction exposes an important form of model mis-specification: a docking calculation may be computationally correct for the supplied ligand yet pharmacologically irrelevant because the ligand is absent from the target environment. Conversely, a parent-compound model remains entirely appropriate when parent exposure and target access are supported. The issue is therefore not “parent versus metabolite docking,” but

whether the molecular representation given to the model matches the chemical species presented to the biology.

Reconstructing natural product pharmacology around exposure-weighted molecular ensembles

This perspective proposes an exposure-weighted molecular ensemble as the unit of mechanistic reconstruction. The ensemble contains molecular species that remain plausible after consideration of formation, measured exposure, biological location, and pharmacological compatibility. Depending on the compound and biological question, its members may include the parent, microbial products, host metabolites, conjugates, or locally regenerated species.

“Exposure-weighted” does not imply a numerical score. It describes an evidentiary ordering in which a predicted species supported by no measurements should carry less mechanistic weight than a directly identified and quantitatively exposed species, while neither automatically becomes the causal ligand. PBPK modeling can help test whether hypothesized pharmacology occurs within physiologically plausible exposure ranges, as illustrated for urolithin A [29], but modeled exposure does not establish target engagement.

The ensemble must also accommodate uncertainty in provenance. Human gastrointestinal comparisons show that colonic processing and endogenous precursor metabolism can complicate attribution of phenolic metabolites to an ingested source [30]. Thus, detecting a downstream molecule does not always identify where it came from, and shared metabolic products may arise from dietary, microbial, or endogenous pathways.

The framework is deliberately revisable. A parent initially prioritized by structural plausibility may lose weight if it is

not detectably exposed. A predicted metabolite may gain relevance after direct measurement. A conjugate may become more important if transporter or tissue evidence supports access, or less important if it remains confined to elimination pathways. The central objective is not to identify one “winner” prematurely, but to preserve the molecular competition until exposure and mechanism discriminate among candidates.

The distinction between sequential evidence qualification and competitive evidence updating is important. **Figure 1** depicts the evidentiary boundaries that a candidate molecular species must confront, whereas **Figure 2** shows how the relative standing of several candidates can change as different kinds of evidence accumulate. The two figures therefore address different parts of the argument rather than duplicating the same framework

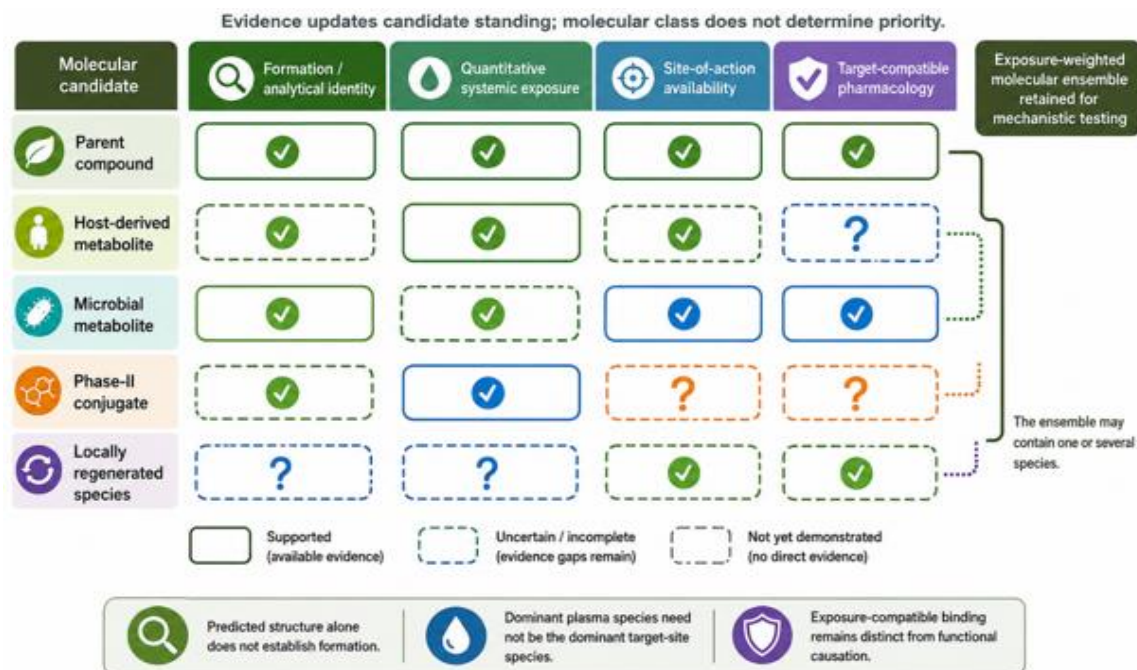


Figure 2. Competitive evidence updating within an exposure-weighted molecular ensemble

Linking metabolite prediction, bioanalysis, and target modeling

Prediction, bioanalysis, tissue measurement, and target modeling answer different questions. Computational metabolism can generate candidate structures [27]. Metabolite bioanalysis can establish whether those structures are present and quantify exposure [18]. Spatial methods can refine localization [25]. Natural-product target-identification strategies can then test candidate molecular engagement using orthogonal biochemical, biophysical, proteomic, or related approaches [31]. The proposed workflow therefore depends on evidential continuity. A mechanistic claim becomes stronger when the modeled ligand can be traced from plausible formation through direct detection and exposure-compatible concentration to target-relevant testing. A discontinuity at any stage should remain visible rather than being bridged by assumption.

This is especially important for computational prioritization. Metabolite prediction can reduce the chance that a biologically relevant ligand is ignored, but unlimited enumeration can also expand false-positive chemical space. Analytical data should therefore constrain

computational candidate sets whenever feasible. Conversely, untargeted or broad-spectrum bioanalysis may reveal unexpected species that deserve subsequent modeling. The relationship should be iterative: prediction informs measurement, measurement restricts modeling, and target experiments adjudicate between surviving candidates.

Consequences for mechanistic claims and lead selection

Mechanistic language should reflect the strongest completed link in the evidence chain. Detection supports presence, not activity. Docking supports structural compatibility, not target engagement [26]. In-vitro potency is most informative when the tested species and concentration are compatible with human exposure [17]. Tissue asymmetry can further change which molecule deserves experimental priority [23].

The same discipline affects lead selection. A parent compound with strong assay potency but negligible relevant exposure may be less informative as a systemic mechanistic lead than an exposed derivative with compatible pharmacology. Yet the reverse can also occur: a parent may persist, reach the tissue, and remain the most

credible ligand. The framework therefore ranks evidence concordance, not molecular class.

Table 3 translates this principle into manuscript-derived dimensions for exposure-qualified lead reasoning. These

dimensions are not a scoring algorithm and should not be interpreted as validated thresholds.

Table 3. Proposed dimensions for exposure-qualified natural-product lead selection

Dimension	Stronger evidential position	Weak position requiring qualification
Chemical identity	Species directly characterized	Structure only computationally inferred
Formation	Detected after relevant exposure	Metabolite merely predicted
Exposure	Quantified at biologically plausible concentration	Presence reported without quantitative context
Site availability	Tissue or unbound exposure supported	Plasma total concentration used uncritically as surrogate
Pharmacology	Same species tested at exposure-compatible levels	Parent tested while another species dominates measured exposure
Target evidence	Orthogonal engagement evidence	Docking or target prediction alone

Note: These dimensions are proposed for organizing evidence, not for producing a validated lead-selection score.

Boundary cases: local gastrointestinal activity and nonabsorbed compounds

Systemic exposure is not always the relevant criterion. A poorly absorbed natural-product constituent may act within the intestinal lumen or mucosa, interact with microorganisms, or modify local physiology without substantial plasma exposure [7]. In such cases, demanding systemic metabolite exposure would mis-specify the mechanism in the opposite direction.

Multiple active identities may also coexist. A parent may act locally while microbial or host-derived products act systemically, and transporter-dependent conjugates may contribute differently across organs [16]. Pharmacology should therefore not be forced into a one-compound/one-mechanism model when the biological situation supports several molecular actors.

Other hard cases include transient reactive metabolites, species that cannot be measured reliably, metabolites arising from both endogenous and dietary sources, and tissue-specific regeneration that is difficult to sample directly. These cases do not invalidate exposure-aware reasoning; they define where confidence must remain limited.

The proposed framework therefore rejects both parent-only and metabolite-only dogmas. The relevant molecular identity is determined by the biological claim being tested. For local gastrointestinal pharmacology, the swallowed parent may be the correct exposure-relevant molecule. For a distant systemic target, transformation and site-of-action availability become correspondingly more important.

Experimental priorities for identifying the pharmacologically active species

Future mechanistic studies should characterize intact molecular species wherever feasible and avoid assuming that hydrolysis-derived “total” concentrations reconstruct the circulating mixture [19]. When plasma is an inadequate surrogate, free or tissue exposure should be investigated,

with spatial localization added when it provides information unavailable from bulk measurements [22].

Computational metabolite generation should guide analytical searches rather than substitute for them [27]. Once candidate species are measured, parent and relevant derivatives should be compared at exposure-compatible concentrations using the same target and functional systems where practical. Orthogonal target-identification approaches can then strengthen or challenge the assignment of the molecular species responsible for an observed phenotype [31].

Where local regeneration is proposed, mechanistic perturbation is especially important. Altering the relevant deconjugation process provides stronger evidence than inferring parent activity from the abundance of a circulating precursor [20]. Similar logic applies to microbial transformation: manipulating or stratifying the transformation capacity can help distinguish a precursor effect from a downstream-metabolite effect.

CONCLUSION

The molecule named on a natural-product intervention is a starting chemical identity, not automatically the molecular identity responsible for a systemic mechanism. Oral processing can generate parent compounds, microbial products, host metabolites, conjugates, and locally regenerated species whose relevance changes with exposure and biological location.

This perspective proposes that mechanistic pharmacology be reconstructed around exposure-weighted molecular ensembles rather than an assumed parent ligand. The approach does not privilege metabolites by default and does not convert prediction, plasma detection, tissue localization, docking, or target identification into interchangeable proof. Each resolves a different uncertainty.

The practical consequence is a stricter standard of molecular attribution: follow candidate molecules from formation through exposure to the biology being explained. Where that chain is incomplete, mechanistic language should remain provisional. Where the parent genuinely reaches the relevant system, it should remain central. Where another species better satisfies the evidence, pharmacology should follow that molecule instead.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

- [1] Atanasov AG, Zotchev SB, Dirsch VM; International Natural Product Sciences Taskforce; Supuran CT. Natural products in drug discovery: Advances and opportunities. *Nat Rev Drug Discov.* 2021;20(3):200-16. doi:10.1038/s41573-020-00114-z
- [2] Cheng H, Zhang D, Wu J, Liu J, Zhou Y, Tan Y, et al. Interactions between gut microbiota and polyphenols: A mechanistic and metabolomic review. *Phytomedicine.* 2023;119:154979. doi:10.1016/j.phymed.2023.154979
- [3] Favari C, Rinaldi de Alvarenga JF, Sánchez-Martínez L, Tosi N, Mignogna C, Cremonini E, et al. Factors driving the inter-individual variability in the metabolism and bioavailability of (poly)phenolic metabolites: A systematic review of human studies. *Redox Biol.* 2024;71:103095. doi:10.1016/j.redox.2024.103095
- [4] Kroon MAGM, van Laarhoven HWM, Swart EL, van Tellingen O, Kemper EM. A pharmacokinetic study and critical reappraisal of curcumin formulations enhancing bioavailability. *iScience.* 2025;28(6):112575. doi:10.1016/j.isci.2025.112575
- [5] Williamson G, Clifford MN. A critical examination of human data for the biological activity of quercetin and its phase-2 conjugates. *Crit Rev Food Sci Nutr.* 2025;65(9):1669-705. doi:10.1080/10408398.2023.2299329
- [6] Wang YH, Mondal G, Khan W, Gurley BJ, Yates CR. Development of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for characterizing pomegranate extract pharmacokinetics in humans. *J Pharm Biomed Anal.* 2023;233:115477. doi:10.1016/j.jpba.2023.115477
- [7] Zhang NN, Jiang ZM, Li SZ, Yang X, Liu EH. Evolving interplay between natural products and gut microbiota. *Eur J Pharmacol.* 2023;949:175557. doi:10.1016/j.ejphar.2023.175557
- [8] Alqudah S, Claesen J. Mechanisms of gut bacterial metabolism of dietary polyphenols into bioactive compounds. *Gut Microbes.* 2024;16(1):2426614. doi:10.1080/19490976.2024.2426614
- [9] Hu J, Mesnage R, Tuohy KM, Heiss C, Rodriguez-Mateos A. (Poly)phenol-related gut metabolites and human health: An update. *Food Funct.* 2024;15(6):2814-35. doi:10.1039/d3fo04338j
- [10] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature.* 2019;570(7762):462-7. doi:10.1038/s41586-019-1291-3
- [11] Javdan B, Lopez JG, Chankhamjon P, Lee YJ, Hull R, Wu Q, et al. Personalized mapping of drug metabolism by the human gut microbiome. *Cell.* 2020;181(7):1661-79.e22. doi:10.1016/j.cell.2020.05.001
- [12] Dvořák Z, Li H, Mani S. Microbial metabolites as ligands to xenobiotic receptors: Chemical mimicry as potential drugs of the future. *Drug Metab Dispos.* 2023;51(2):219-27. doi:10.1124/dmd.122.000860
- [13] Andreux PA, Blanco-Bose W, Ryu D, Burdet F, Ibberson M, Aebischer P, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat Metab.* 2019;1(6):595-603. doi:10.1038/s42255-019-0073-4
- [14] Singh A, D'Amico D, Andreux PA, Dunngalvin G, Kern T, Blanco-Bose W, et al. Direct supplementation with Urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. *Eur J Clin Nutr.* 2022;76(2):297-308. doi:10.1038/s41430-021-00950-1
- [15] Tsiara I, Hervás Povo B, Alotaibi W, Young Tie Yang P, Rodriguez-Mateos A, Globisch D. Characterizing the sulfated and glucuronidated (poly)phenol metabolome for dietary biomarker discovery. *J Agric Food Chem.* 2025;73(11):6702-10. doi:10.1021/acs.jafc.4c12596
- [16] Järvinen E, Deng F, Kiander W, Sinokki A, Kidron H, Sjöstedt N. The role of uptake and efflux transporters in the disposition of glucuronide and sulfate conjugates. *Front Pharmacol.* 2022;12:802539. doi:10.3389/fphar.2021.802539
- [17] Williamson G, Clifford MN. A critical examination of human data for the biological activity of phenolic acids and their phase-2 conjugates derived from

- dietary (poly)phenols, phenylalanine, tyrosine and catecholamines. *Crit Rev Food Sci Nutr*. 2025;65(27):5324-83. doi:10.1080/10408398.2024.2410874
- [18] Li W, Vazvaei-Smith F, Dear G, Boer J, Cuyckens F, Fraier D, et al. Metabolite bioanalysis in drug development: Recommendations from the IQ Consortium Metabolite Bioanalysis Working Group. *Clin Pharmacol Ther*. 2024;115(5):939-53. doi:10.1002/cpt.3144
- [19] Luis PB, Kunihiro AG, Funk JL, Schneider C. Incomplete hydrolysis of curcumin conjugates by β -glucuronidase: Detection of complex conjugates in plasma. *Mol Nutr Food Res*. 2020;64(6). doi:10.1002/mnfr.201901037
- [20] Kunihiro AG, Luis PB, Brickey JA, Frye JB, Chow HHS, Schneider C, et al. Beta-glucuronidase catalyzes deconjugation and activation of curcumin-glucuronide in bone. *J Nat Prod*. 2019;82(3):500-9. doi:10.1021/acs.jnatprod.8b00873
- [21] Kunihiro AG, Luis PB, Frye JB, Chew W, Chow HHS, Schneider C, et al. Bone-specific metabolism of dietary polyphenols in resorptive bone diseases. *Mol Nutr Food Res*. 2020;64(14). doi:10.1002/mnfr.202000072
- [22] Zang R, Barth A, Wong H, Marik J, Shen J, Lade J, et al. Design and measurement of drug tissue concentration asymmetry and tissue exposure-effect (tissue PK-PD) evaluation. *J Med Chem*. 2022;65(13):8713-34. doi:10.1021/acs.jmedchem.2c00502
- [23] Zhang D, Hop CECA, Patilea-Vrana G, Gampa G, Seneviratne HK, Unadkat JD, et al. Drug concentration asymmetry in tissues and plasma for small molecule-related therapeutic modalities. *Drug Metab Dispos*. 2019;47(10):1122-35. doi:10.1124/dmd.119.086744
- [24] Yin M, Balhara A, Marie S, Tournier N, Gáborik Z, Unadkat JD. Successful prediction of human hepatic concentrations of transported drugs using the proteomics-informed relative expression factor approach. *Clin Pharmacol Ther*. 2024;115(3):595-605. doi:10.1002/cpt.3123
- [25] Chen Y, Liu Y, Li X, He Y, Li W, Peng Y, et al. Recent advances in mass spectrometry-based spatially resolved molecular imaging of drug disposition and metabolomics. *Drug Metab Dispos*. 2023;51(10):1273-83. doi:10.1124/dmd.122.001069
- [26] Sadybekov AV, Katritch V. Computational approaches streamlining drug discovery. *Nature*. 2023;616(7958):673-85. doi:10.1038/s41586-023-05905-z
- [27] Zhu K, Huang M, Wang Y, Gu Y, Li W, Liu G, et al. MetaPredictor: In silico prediction of drug metabolites based on deep language models with prompt engineering. *Brief Bioinform*. 2024;25(5). doi:10.1093/bib/bbae374
- [28] Sandhu H, Garg P. Machine learning enables accurate prediction of quinone formation during drug metabolism. *Chem Res Toxicol*. 2023;36(12):1876-90. doi:10.1021/acs.chemrestox.3c00162
- [29] Aichinger G, Stevanoska M, Beekmann K, Sturla SJ. Physiologically-based pharmacokinetic modeling of the postbiotic supplement Urolithin A predicts its bioavailability is orders of magnitude lower than concentrations that induce toxicity, but also neuroprotective effects. *Mol Nutr Food Res*. 2023;67(15). doi:10.1002/mnfr.202300009
- [30] Cáceres-Jiménez S, Pereira-Caro G, Dobani S, Pourshahidi K, Gill CIR, Moreno-Rojas JM, et al. Interpretation of plasma pharmacokinetics and urinary excretion of phenolic metabolites and catabolites derived from (poly)phenols following ingestion of mango by ileostomists and subjects with a full gastrointestinal tract: Complications associated with endogenous and ingested phenylalanine and tyrosine. *Food Funct*. 2025;16(19):7761-78. doi:10.1039/d5fo02745d
- [31] Pan X, Jiang S, Zhang X, Wang Z, Wang X, Cao L, et al. Recent strategies in target identification of natural products: Exploring applications in chronic inflammation and beyond. *Br J Pharmacol*. 2025;182(20):4841-60. doi:10.1111/bph.17356