



Oral Lymphatic Transport Is an Underused Design Space for Lipophilic Natural Products with Poor Aqueous Solubility and Extensive First-Pass Loss

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ABSTRACT

Poor aqueous solubility and extensive presystemic metabolism frequently constrain the oral development of lipophilic natural products, yet formulation strategies are commonly evaluated through dissolution and plasma exposure without explicitly considering whether intestinal lymphatic transport could become a design variable. This translational framework examines when oral lymphatic delivery should be considered during natural-product lead selection and formulation development rather than treated as an incidental pharmacokinetic phenomenon. Current evidence indicates that intestinal lymphatic transport depends on coordinated gastrointestinal solubilization, epithelial uptake, intracellular lipid processing, association with chylomicron-related pathways, lacteal access, and formulation-specific behavior. High lipophilicity is therefore permissive rather than sufficient: intestinal instability, inadequate lipid association, inappropriate dose or vehicle composition, and inefficient chylomicron incorporation can prevent meaningful lymphatic exposure. Conversely, lipid vehicles, nanostructured carriers, and lipid-mimetic prodrug strategies can alter pathway engagement and, in selected cases, reduce initial hepatic first-pass delivery. The framework proposed here distinguishes intrinsic from engineered lymphatic eligibility and organizes development around exposure liabilities, pathway compatibility, formulation leverage, route-specific evidence, and translational verification. It further separates increased systemic exposure from demonstrated lymphatic transport and treats computational or in-vitro prediction as prioritization evidence rather than mechanistic proof. The principal implication is that lymphatic delivery should be evaluated selectively, where chemical and biopharmaceutical liabilities plausibly align with lipid-mediated intestinal transport. Species differences, physiological variability, formulation dependence, limited predictive datasets, and difficult route attribution remain major boundaries requiring prospective experimental validation.

Key Words: *Intestinal lymphatic transport, Natural products, Lipid-based formulations, First-pass metabolism, Oral bioavailability, Translational pharmacokinetics*

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INTRODUCTION

Oral development of lipophilic natural products is often framed as a solubility problem followed by a metabolic problem: insufficient dissolution restricts absorption, while compounds that do cross the intestinal epithelium may undergo extensive intestinal or hepatic first-pass loss. That

sequence encourages formulation programs to maximize apparent solubilization and systemic exposure without asking whether part of the absorbed dose could be deliberately redirected through intestinal lymph. Contemporary understanding instead places the intestinal lymphatic network within an active biological system that can participate in the transport of dietary lipids, drugs, lipid

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conjugates, and delivery systems [1]. For selected orally administered molecules, lymphatic entry offers an alternative to immediate portal delivery and can therefore change the relationship between gastrointestinal absorption and initial hepatic exposure [2].

This possibility is more consequential than simply adding another absorption pathway. Modern oral delivery strategies increasingly exploit biological routes that connect the gastrointestinal tract with post-gastrointestinal destinations, indicating that oral formulation design need not be restricted to optimizing luminal dissolution and transepithelial flux alone [3]. For natural-product leads, the relevant question is therefore not whether lymphatic transport can occur in principle, but whether the candidate's dominant liabilities create a situation in which lymphatic exposure would solve a meaningful developability problem. A poorly soluble compound with extensive first-pass metabolism may be attractive, whereas a similarly lipophilic compound whose exposure is limited principally by instability, low permeability, dose burden, or rapid systemic clearance may gain little from lymphatic redirection.

Translation further requires separating mechanistic plausibility from quantitative prediction. Semi-physiological pharmacokinetic models incorporating gastrointestinal lymphatic absorption have shown that route-associated disposition can be represented across species for selected tool compounds [4]. Such modeling supports the feasibility of treating lymphatic uptake as an explicit pharmacokinetic process, but it does not establish that the route can yet be predicted prospectively for chemically diverse natural products. The contribution proposed here is consequently a lymphatic-transport design framework in which lymphatic exposure is treated as a conditional lead-selection and formulation opportunity. The framework asks first what limits oral exposure, then whether the molecule is intrinsically compatible with intestinal lipid pathways or can be made compatible through formulation or chemical engineering, and finally what evidence is required before improved plasma exposure can reasonably be attributed to lymphatic transport.

Physiology of intestinal lymphatic transport

The intestinal lymphatic route begins within a physiological system evolved for lipid handling rather than drug delivery. Following digestion, lipid-derived species can enter enterocytes, undergo intracellular processing, and contribute to the assembly and secretion of chylomicron-rich particles that are preferentially transferred toward intestinal lacteals rather than directly into portal blood. Entry into lacteals is not adequately described as passive leakage through a continuously open

conduit. Experimental evidence indicates that chylomicrons themselves can influence lacteal endothelial permeability, with regulated junctional behavior affecting intestinal lipid absorption [5]. This makes lacteal access a biological gate whose state may influence drug transport even after a candidate has achieved luminal solubilization and epithelial entry.

The pathway also operates within a variable physiological environment. Experimental work on dietary lipids demonstrates sexual dimorphism in intestinal absorption and lymphatic lipid transport [6]. Although those observations cannot be converted directly into a quantitative drug effect, they establish that lipid-associated lymphatic handling is context dependent. Physiological state, feeding conditions, lipid digestion, intestinal motility, chylomicron production, and lymph flow can therefore modify the environment in which a lymphotropic formulation is evaluated.

At the system level, intestinal lacteals connect mucosal absorption with mesenteric lymphatics and broader metabolic and immune functions [7]. For drug development, this architecture creates several sequential requirements: the compound must remain available within the gastrointestinal tract, reach the absorptive epithelium, partition appropriately into cellular lipid-processing pathways, survive intracellular processing in a transport-compatible form, and reach lymph in sufficient quantity to alter downstream exposure. Failure at any stage can make a theoretically attractive physicochemical profile pharmacokinetically irrelevant. The framework proposed here therefore treats intestinal lymphatic transport as a multigate process, not as a binary property of a molecule. Lipophilicity or lipid solubility may facilitate entry into this sequence, but neither defines the entire route.

Lipophilicity, solubility, and association with lipid pathways

The common shorthand that “very lipophilic drugs enter lymph” is useful only as an initial heuristic. Direct comparison of cannabidiol, cannabigerol, cannabichromene, and cannabinol shows that molecular properties and formulation jointly influence lymphatic transport rather than producing a uniform effect across structurally related cannabinoids [8]. This distinction matters for natural products because compounds that share botanical origin, broad scaffold class, or low aqueous solubility can nevertheless differ in lipid solubility, ionization, dose, membrane permeability, metabolic susceptibility, and compatibility with chylomicron-associated intracellular processing. The relevant design variable is therefore not lipophilicity in isolation but lipid-pathway compatibility under gastrointestinal conditions.

Counterexamples sharpen this boundary. Ivacaftor is highly lipophilic, yet experimental pharmacokinetic assessment in rats indicated only a minor contribution of intestinal lymphatic transport to its disposition [9]. High hydrophobicity can consequently coexist with insufficient lymphatic mass transfer to produce a developmentally important effect. A candidate may partition strongly into lipid phases while still failing because the administered dose exceeds transport capacity, because drug remains sequestered within nonabsorbed colloidal structures, or because the intracellular pathway favors portal rather than chylomicron-associated exit.

Chemical stability creates another independent gate. A highly lipophilic protease-inhibitor prodrug administered in a lipid-based formulation showed lymphatic uptake limited by instability within the intestine [10]. Favorable partitioning therefore cannot rescue a molecule that disappears before productive uptake or conversion occurs. For candidate selection, the proposed implication is to replace a single physicochemical threshold with a conjunction of questions: Is poor aqueous solubility genuinely limiting? Does the compound remain intact through luminal and epithelial transit? Can it associate with digesting lipids without becoming unavailable for absorption? Is there plausible entry into chylomicron-related processing? And is the expected lymphatic flux large enough to matter relative to portal absorption and metabolic loss? Only when these conditions align does lipophilicity become a useful design advantage rather than a descriptive property.

Formulation-dependent promotion of lymphatic uptake

Formulation can alter several of these gates simultaneously, but “lipid based” is not a mechanistically uniform category. Rapeseed oleosomes, naturally organized intracellular oil bodies, increased the intestinal lymphatic delivery and oral bioavailability of cannabidiol relative to comparator conditions in preclinical work [11]. Their relevance lies not only in providing lipid mass but in

presenting the drug within a particular lipid architecture during digestion. Thus, formulation structure may influence the sequence from gastrointestinal dispersion to lipid processing rather than acting solely through an increase in apparent solubility.

Lipid identity also matters. Comparative administration of cannabidiol with different vegetable oils demonstrated that vehicle composition affected both intestinal lymphatic transport and systemic bioavailability [12]. The implication is that replacing one digestible oil with another cannot be considered pharmacokinetically neutral merely because both are capable of solubilizing the compound. Fatty-acid composition, digestion kinetics, colloidal products, and associated minor constituents may change how much drug remains available for epithelial uptake and how strongly absorbed drug enters chylomicron-associated pathways. Consequently, formulation optimization should interrogate composition and digestive behavior rather than maximizing drug loading alone.

Nanostructured carriers offer another route to modify presentation. In a double-catheterized rat model, curcumin-loaded nanostructured lipid carriers produced direct evidence of intestinal lymphatic drug transport together with enhanced systemic exposure [13]. Such evidence is stronger for route attribution than plasma exposure alone, because an increase in systemic concentration can also arise from improved dissolution, permeability, reduced degradation, altered metabolism, or combinations of these mechanisms. Across direct preclinical studies, molecular structure, carrier architecture, and lipid-vehicle composition alter lymphatic delivery in compound- and formulation-dependent rather than interchangeable ways [8, 11, 12]. The manuscript therefore proposes that formulation selection should be matched to the specific transport bottleneck being addressed instead of escalating generically from oil solution to increasingly complex lipid systems.

These formulation-dependent decisions and their competing interpretive risks are summarized in **Table 1**.

Table 1. Choosing a lymphatic formulation by the bottleneck it is intended to modify

Formulation decision	Transport problem addressed	Potential advantage supported by preceding evidence	Principal trade-off or uncertainty	Proposed decision implication
Preserve an organized lipid architecture	Drug is soluble in lipid but pathway engagement is uncertain	Oleosome presentation can enhance lymphatic and systemic CBD delivery	Carrier composition and digestion may contribute independently of the oil core	Compare architecture, not only lipid dose
Change digestible lipid source	Existing oil solubilizes drug but produces suboptimal exposure	Vegetable-oil identity can alter CBD lymphatic transport and bioavailability	Effects cannot be assigned to fatty-acid composition alone	Screen lipid composition under matched drug dose and digestion conditions
Use a nanostructured lipid carrier	Poorly soluble natural product requires sustained lipid-associated presentation	Curcumin NLCs can produce directly measurable lymphatic transport in rats	Higher plasma exposure may still contain nonlymphatic contributions	Pair systemic PK with route-specific measurements

Escalate formulation complexity	Simpler lipid systems appear insufficient	Additional architecture may modify dispersion, digestion, uptake, or intracellular processing	Complexity can improve the wrong bottleneck and complicate translation	Escalate only after identifying the limiting transport step
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note: The final column is an original proposed decision synthesis derived from the preceding mechanistic and formulation evidence. The matrix does not establish universal formulation rankings or quantitative thresholds.

Avoidance of first-pass metabolism

The most compelling reason to seek intestinal lymphatic transport is not simply to increase absorption, but to alter where absorbed drug enters the systemic circulation. Portal absorption exposes drug to the liver before it reaches the wider circulation, whereas material transported through intestinal lymph reaches the venous circulation after passage through the lymphatic network. For natural products whose oral exposure is constrained by substantial hepatic extraction, this difference can be pharmacokinetically important. However, lymphatic delivery should be described as avoidance of initial hepatic first-pass delivery rather than abolition of presystemic metabolism, because degradation and metabolism may still occur in the lumen, enterocyte, lymph, or systemic circulation.

Scutellarin illustrates why this opportunity should include engineered rather than only intrinsic lymphatic eligibility. Triglyceride-mimetic prodrugs increased its oral bioavailability by promoting intestinal lymphatic transport and reducing first-pass loss [14]. The relevant lesson is not that a particular triglyceride scaffold should be generalized to all natural products, but that a parent compound whose own physicochemical properties are poorly aligned with lymph transport may be redesigned to enter lipid-processing pathways. Chemical modification can therefore become an exposure-engineering strategy when formulation alone cannot create sufficient pathway association.

Prodrug architecture nevertheless remains mechanistically consequential. Optimization of triglyceride prodrugs of mycophenolic acid showed that conjugation through different positions can markedly change lymphatic transport [15]. A 2026 translational study extended this principle further: an oral allopregnanolone prodrug exploited lymphatic transport to bypass substantial liver metabolism and enabled oral exposure in animals and humans [16]. Together, these studies justify a distinction between parent-drug properties and properties of the administered transport construct. The proposed framework therefore evaluates first whether the therapeutic moiety suffers a first-pass liability large enough to matter, and then whether a formulation or reversible chemical design can redirect a useful fraction of absorbed material without

creating unacceptable instability, delayed release, or new safety liabilities.

Natural product candidates most likely to benefit

The natural products most likely to benefit are not simply the most hydrophobic molecules. A useful candidate profile combines a meaningful oral-exposure liability with a plausible lymphatic solution. Cannabidiol exemplifies this distinction: its poor aqueous solubility and formulation-sensitive oral exposure can be improved using nanostructured lipid carriers [17], but increased systemic exposure from such a formulation does not by itself establish that lymphatic transport caused the improvement. The candidate-selection question should therefore begin with the mechanism of failure. A compound limited primarily by dissolution and extensive first-pass metabolism presents a stronger rationale than one limited by irreversible intestinal degradation, extremely low permeability, or rapid systemic clearance after absorption. Direct higher-species evidence strengthens this assessment. In a conscious pig model with thoracic lymph duct cannulation, cannabidiol was measurable in lymph after oral administration and its lymphatic behavior depended on formulation [18]. The study does not establish the human lymphatic fraction, but it demonstrates that route-specific measurements can be obtained outside rodent models and that species or formulation effects may materially alter interpretation. This matters for phytochemicals because botanical origin does not define a uniform physicochemical or metabolic class.

The manuscript therefore proposes two candidate categories. Intrinsically lymph-compatible candidates are parent molecules whose lipophilicity, lipid solubility, gastrointestinal stability, dose, and metabolic liabilities plausibly allow useful chylomicron-associated transport. Engineered lymph-compatible candidates are compounds for which the parent is poorly matched to the route but a lipid formulation, carrier architecture, or reversible lipid-mimetic prodrug could create pathway compatibility. **Table 2** integrates the evidence layers needed to distinguish these categories without conflating improved formulation performance with demonstrated route engagement.

Table 2. Evidence layers for deciding whether a natural product is intrinsically or engineerably lymph-compatible

Evidence layer	What it resolves	Evidence status before a lymphatic claim	Decision consequence
Oral-liability diagnosis	Whether poor solubility and first-pass loss are dominant constraints	Required clinical or preclinical PK/biopharmaceutic characterization	Proceed only if changing absorption route could solve a material problem
Physicochemical and stability profile	Whether the parent can survive and partition into lipid-processing environments	Supportive, not route proof	Favors intrinsic eligibility when aligned
Formulation response	Whether lipid presentation changes exposure or pathway association	Suggestive unless route is measured	Supports formulation optimization but not causal attribution
Direct lymph measurement	Whether drug or active prodrug actually enters intestinal lymph	Strong route-specific evidence	Upgrades mechanistic confidence
Prodrug or carrier engineering	Whether pathway compatibility can be created deliberately	Compound- and construct-specific	Supports engineered eligibility when parent properties are insufficient
Cross-species or human translation	Whether route contribution persists beyond one model	Highest translational layer available	Determines whether the strategy merits later-stage development

note: The ordering is an original proposed evidence hierarchy. It does not define mandatory regulatory stages or quantitative acceptance thresholds.

Predicting lymphatic transport and systemic exposure

Prediction could make this design space more efficient by identifying candidates before resource-intensive lymph-cannulation studies. A graph-transformer model developed from historical in-vivo lymphatic transport data demonstrates that molecular structure can be used to estimate transport potential even when available datasets are limited [19]. Its value is therefore most defensible as prioritization: it may help identify chemical patterns worth testing, but sparse historical datasets, heterogeneous experimental methods, narrow chemical coverage, and formulation dependence prevent model output from being treated as route confirmation.

Systemic pharmacokinetic modeling presents a related but distinct challenge. A PBPK analysis of halofantrine under post-prandial conditions showed that lymphatic involvement may need to be represented indirectly when the modeling platform does not explicitly simulate intestinal lymphatic uptake [20]. A model may reproduce plasma concentration-time behavior while remaining non-

identifiable with respect to the actual absorption route. For natural products, where metabolism, enterohepatic processes, food effects, and formulation-dependent solubilization can all change exposure simultaneously, fit quality must therefore be separated from mechanistic validity.

The proposed prediction strategy uses computational and in-vitro tools as successive hypothesis filters rather than substitutes for route-specific experiments. Molecular prediction can rank intrinsic plausibility; formulation models can test whether digesting lipids or chylomicron-like compartments change apparent uptake; PBPK can evaluate whether a hypothesized lymphatic contribution is compatible with systemic disposition. Each layer should increase or decrease confidence without erasing uncertainty inherited from the preceding layer. **Figure 1** expresses this as a constrained spiral in which apparent progress is allowed only when a specific evidential checkpoint has been passed.

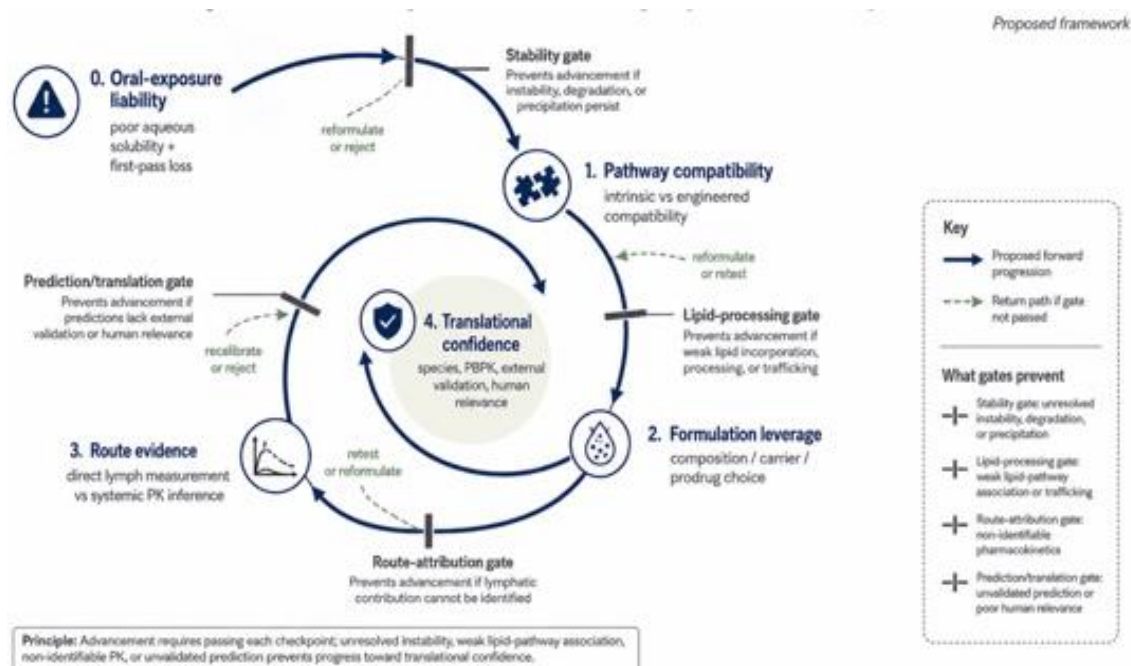


Figure 1. From oral-exposure liability to defensible lymphatic-transport confidence

The lymphatic-transport design framework

The proposed framework converts the preceding evidence into a development sequence rather than a score. The first decision is problem diagnosis: confirm that poor aqueous solubility, inadequate oral exposure, and clinically or experimentally meaningful first-pass loss are sufficiently important that rerouting absorption could add value. A compound whose exposure is dominated by irreversible gastrointestinal degradation or post-absorptive systemic clearance should not be advanced merely because it is lipophilic. The second decision is pathway eligibility: determine whether the parent is intrinsically compatible with intestinal lipid processing or whether compatibility would need to be engineered.

The third decision is intervention matching. Modified dissolution systems can distinguish aqueous release from uptake into an artificial chylomicron-like compartment and therefore provide an intermediate assay for lymphotropic products [21]. In-vitro models incorporating artificial chylomicrons can also discriminate formulation enhancers and inhibitors [22]. These approaches can reduce experimental search space, but they remain surrogates. Their appropriate function in the framework is to falsify weak options early, compare formulations under controlled

conditions, and generate mechanistic hypotheses for in-vivo testing.

The fourth decision is route attribution. Mechanistically visualized triglyceride-mimetic prodrugs show that processing and lymphatic transport can be interrogated directly rather than inferred solely from elevated plasma exposure [23]. Direct lymph measurements, or rigorously validated alternatives, should therefore carry greater evidential weight than formulation-induced AUC changes. The fifth decision is translation: test whether the transport advantage survives changes in dose, food state, formulation, sex, species, and eventual human physiology. Importantly, failure at a late checkpoint should trigger reconsideration of the preceding assumption rather than automatic escalation of formulation complexity. A candidate may therefore be rejected at any gate without implying that the molecule lacks pharmacological value; the rejection applies only to the suitability of lymphatic transport as its oral-delivery strategy.

Table 3 converts these steps into an assumption–risk–remedy matrix. It is intended as a proposed falsification-oriented design aid: each assumption earns progression only when an experiment addresses the corresponding risk.

Table 3. Assumptions that can falsely promote a natural product into a lymphatic-development program

Working assumption	Risk if wrong	Evidence-based or proposed remedy
Poor oral exposure is mainly a solubility/first-pass problem	Lymphatic rerouting addresses the wrong liability	Diagnose dissolution, stability, permeability, metabolism, and systemic clearance before route engineering
High lipophilicity implies pathway compatibility	Candidate is retained despite negligible lymph flux	Require evidence of lipid-processing or chylomicron-associated behavior

Better lipid solubilization means better absorption	Drug remains colloiddally trapped or unavailable	Separate total solubilization from absorbable drug and test in vivo
Higher plasma exposure demonstrates lymph transport	Nonlymphatic mechanisms are misattributed	Add direct lymph measurement or validated route-dissection evidence
In-vitro or computational ranking predicts in-vivo success	Model-domain error propagates into development	Use models as filters and prospectively challenge top-ranked candidates
More complex formulation is inherently superior	Complexity increases without solving the limiting gate	Escalate only when a defined bottleneck justifies the intervention

note: The assumption–risk relationships synthesize the manuscript evidence; the remedies constitute the proposed framework and are not prospectively validated decision rules.

Trade-offs with absorption, variability, and safety

Lymphatic targeting creates trade-offs because the formulation must support both absorption and route engagement. In comparative CBD studies, natural sesame oil outperformed predigested lipid formulations and purified triglycerides for lymphatic transport and systemic bioavailability [24]. This finding cautions against assuming that a formulation closer to the nominal products of lipid digestion will necessarily be superior. Natural oils may differ in digestion kinetics, colloidal evolution, minor constituents, and capacity to maintain drug in an absorbable state. Formulation simplification and formulation sophistication can therefore fail for opposite reasons.

The same non-equivalence appears when in-vitro solubilization is compared with in-vivo performance. Adding medium-chain triglyceride facilitated micellar solubilization of cannabidiol in vitro, yet pure sesame oil retained superior in-vivo performance [25]. Thus, optimizing the easiest measurable surrogate may move the formulation away from the biological process that ultimately governs exposure. For the proposed framework, an in-vitro gain should be interpreted as evidence that one barrier has changed, not that total absorption or lymphatic transport has improved.

Variability is also intrinsic to the strategy. Food state, lipid dose, digestive capacity, chylomicron production, lymph flow, sex, disease, and formulation manufacturing can all alter pathway engagement. Safety must therefore be evaluated at the level of the complete delivery construct. Large lipid loads, excipients, persistent nanoparticles, or prodrug-derived lipid species may introduce tolerability or metabolic liabilities even if the parent natural product is familiar. The framework does not treat “natural” origin as evidence of safety, nor does it assume that increasing lymphatic exposure is always desirable. A viable strategy must improve the intended exposure problem without creating disproportionate formulation burden, unpredictable route variability, or new local and systemic risks.

Translational and experimental requirements

The central experimental requirement is credible route attribution. Cycloheximide-based chylomicron-flow

blockade has been used as a convenient proxy for intestinal lymphatic transport, but direct comparison with lymph-cannulation approaches demonstrated limitations in assuming equivalence between the methods [26]. Pharmacological blockade can perturb physiology beyond the intended pathway, whereas cannulation is technically demanding and may itself alter fluid balance or feeding. Method choice should therefore be justified according to the claim being made: screening may tolerate a surrogate, whereas a statement that lymphatic transport materially explains systemic exposure requires stronger route-specific evidence.

Study design must also anticipate pharmacokinetic variability. Repeated preclinical work with abiraterone showed that substantial variability can influence conclusions drawn from short comparative pharmacokinetic designs [27]. For lymphatic studies, this problem is compounded because biological variation can affect both the amount absorbed and the fraction assigned to the lymph route. Prospective designs should therefore use adequate within-study controls, matched dosing and feeding conditions, explicit formulation characterization, prespecified sampling strategies, and replication sufficient to separate formulation effects from biological noise without inventing universal sample-size rules.

Translation should proceed by evidence convergence. A compelling program would combine gastrointestinal stability, digestion or dispersion studies, direct or validated lymph measurements, systemic pharmacokinetics, metabolic profiling, and mechanistically justified modeling. Candidates that remain promising should be challenged across dose and food states, then across species selected for physiological relevance rather than convenience alone. Computational predictions should be tested on compounds not used to construct the model, and formulation decisions should be revisited if mechanistic evidence contradicts plasma exposure. Human studies become justified only when the expected benefit—such as meaningful avoidance of first-pass loss—outweighs the added formulation or prodrug complexity.

Limitations

This framework is constrained by the same measurement and mechanistic uncertainties that motivate it. Apparent

formulation solubilization can overstate the fraction of drug that is molecularly available for absorption; work with surfactant-based formulations has shown that molecularly dissolved drug can be more relevant to oral absorption than total solubilized drug [28]. That evidence is not specific to lymph transport, but it cautions against interpreting colloidal drug loading as effective delivery. Lipid digestion, colloidal partitioning, epithelial permeability, intracellular metabolism, and lymph incorporation remain experimentally separable processes. A second limitation is transferability. Lipid attachment itself does not guarantee substantial lymphatic uptake: in rats, the lipidated GLP-1 agonist liraglutide and non-lipidated exenatide showed similarly low lymphatic uptake after subcutaneous administration [29]. This is a deliberately cross-context boundary rather than direct evidence about oral natural products. It shows why molecular lipidation cannot be treated as a universal lymphatic switch. The proposed framework is therefore a decision structure for organizing evidence and rejecting weak assumptions, not a validated predictor of which natural products will achieve clinically useful lymphatic exposure. Its value must be tested prospectively across chemically diverse natural products, formulation classes, species, and eventually human pharmacokinetic settings.

CONCLUSION

Oral intestinal lymphatic transport deserves consideration as a deliberate design space when a lipophilic natural product combines poor aqueous solubility with substantial first-pass loss, but the opportunity is conditional rather than generic. The central contribution of this framework is to separate exposure liability, pathway compatibility, formulation leverage, route attribution, prediction, and translation into distinct decisions. It also distinguishes intrinsically lymph-compatible compounds from candidates that may require engineered compatibility through lipid carriers or reversible prodrug design. The framework rejects several shortcuts: high lipophilicity is not route proof; greater solubilization is not necessarily greater absorption; increased plasma exposure is not synonymous with lymphatic transport; computational fit is not mechanistic validation; and lipid attachment does not guarantee useful lymphatic uptake. A defensible development program therefore progresses only when each relevant gate is supported by evidence appropriate to the claim. This approach does not establish prospective performance, therapeutic superiority, or universal eligibility. Instead, it provides a falsifiable translational logic for deciding when intestinal lymphatic transport merits further investment and when a natural-product lead

should remain within conventional oral-development strategies.

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REFERENCES

- [1] Reddiar SB, Xie Y, Abdallah M, Han S, Hu L, Feeney OM, et al. Intestinal lymphatic biology, drug delivery, and therapeutics: Current status and future directions. *Pharmacol Rev.* 2024;76(6):1326-98. doi:10.1124/pharmrev.123.001159
- [2] Zhang Z, Lu Y, Qi J, Wu W. An update on oral drug delivery via intestinal lymphatic transport. *Acta Pharm Sin B.* 2021;11(8):2449-68. doi:10.1016/j.apsb.2020.12.022
- [3] Han R, He H, Lu Y, Lu H, Shen S, Wu W. Oral targeted drug delivery to post-gastrointestinal sites. *J Control Release.* 2024;370:256-76. doi:10.1016/j.jconrel.2024.04.047
- [4] Tao X, Sadekar S, Leipold D, Ferl GZ, Stefanich EG, Kamath AV. Leveraging buprenorphine and halofantrine as tool molecules to develop a novel semi-physiologically based pharmacokinetic model accounting for gastro-intestinal lymphatic absorption and enabling cross-species translation. *AAPS J.* 2025;27(3):67. doi:10.1208/s12248-025-01053-6
- [5] Zarkada G, Chen X, Zhou X, Lange M, Zeng L, Lv W, et al. Chylomicrons regulate lacteal permeability and intestinal lipid absorption. *Circ Res.* 2023;133(4):333-49. doi:10.1161/CIRCRESAHA.123.322607
- [6] Liu M, Shen L, Yang Q, Nauli AM, Bingamon M, Wang DQH, et al. Sexual dimorphism in intestinal absorption and lymphatic transport of dietary lipids. *J Physiol.* 2021;599(22):5015-30. doi:10.1113/JP281621
- [7] Cifarelli V, Eichmann A. The intestinal lymphatic system: Functions and metabolic implications. *Cell Mol Gastroenterol Hepatol.* 2019;7(3):503-13. doi:10.1016/j.jcmgh.2018.12.002
- [8] Ryšánek P, Jelínek P, Housar H, Kozlík P, Křížek T, Nováková A, et al. Effect of quantitative structural properties and drug formulation in four cannabinoids (cannabidiol, cannabigerol, cannabichromene, and cannabinol) on their lymphatic transport after enteral administration in rats. *Mol Pharm.* 2025;22(8):4544-55. doi:10.1021/acs.molpharmaceut.4c01357

- [9] Pozniak J, Ryšánek P, Smrčka D, Kozlík P, Křížek T, Šmardová J, et al. Ivacaftor pharmacokinetics and lymphatic transport after enteral administration in rats. *Front Pharmacol.* 2024;15:1331637. doi:10.3389/fphar.2024.1331637
- [10] Xie Y, Lu Z, Styles IK, Reddiar SB, Phillips ARJ, Windsor JA, et al. Lymphatic uptake of a highly lipophilic protease inhibitor prodrug from a lipid-based formulation is limited by instability in the intestine. *J Pharm Sci.* 2024;113(8):2342-51. doi:10.1016/j.xphs.2024.03.029
- [11] Ji L, Feng W, Chen H, Chu Y, Wong A, Zhu Y, et al. Rapeseed oleosomes facilitate intestinal lymphatic delivery and oral bioavailability of cannabidiol. *Int J Pharm.* 2025;668:124947. doi:10.1016/j.ijpharm.2024.124947
- [12] Feng W, Qin C, Abdelrazig S, Bai Z, Raji M, Darwish R, et al. Vegetable oils composition affects the intestinal lymphatic transport and systemic bioavailability of co-administered lipophilic drug cannabidiol. *Int J Pharm.* 2022;624:121947. doi:10.1016/j.ijpharm.2022.121947
- [13] Chi H, Zhang X, Chen Z, Chen Q, Yang B, Deng H, et al. Lymph-targeted delivery of CUR-NLCs enhances oral bioavailability: Evidence from a double-catheterized rat model. *Pharmaceutics.* 2025;17(11):1484. doi:10.3390/pharmaceutics17111484
- [14] Wang X, Zhang C, Han N, Luo J, Zhang S, Wang C, et al. Triglyceride-mimetic prodrugs of scutellarin enhance oral bioavailability by promoting intestinal lymphatic transport and avoiding first-pass metabolism. *Drug Deliv.* 2021;28(1):1664-72. doi:10.1080/10717544.2021.1960928
- [15] Hu L, Quach T, Zheng D, Leong NJ, Sharma G, Lim SF, et al. Optimizing triglyceride prodrugs of a model immunomodulator: Conjugation through the phenol of mycophenolic acid (MPA) markedly promotes lymphatic drug transport. *Mol Pharm.* 2025;22(3):1555-67. doi:10.1021/acs.molpharmaceut.4c01272
- [16] Simpson JS, Quach T, Han S, Hu L, Trevaskis NL, Leong NJ, et al. An oral allopregnanolone prodrug bypasses liver metabolism via lymphatic transport enabling bioavailability in animals and humans. *Sci Transl Med.* 2026;18(842). doi:10.1126/scitranslmed.adu2352
- [17] Taha IE, ElSohly MA, Radwan MM, Elkanayati RM, Wanas A, Joshi PH, et al. Enhancement of cannabidiol oral bioavailability through the development of nanostructured lipid carriers: In vitro and in vivo evaluation studies. *Drug Deliv Transl Res.* 2025;15(8):2722-32. doi:10.1007/s13346-024-01766-9
- [18] Rizov V, Lukáč P, Mlček M, Kozlík P, Křížek T, Jelínek P, et al. Cannabidiol lymphatic transport after oral administration assessed using a novel thoracic lymph duct cannulated conscious pig model. *Drug Deliv.* 2026;33(1):2608913. doi:10.1080/10717544.2025.2608913
- [19] Li Y, Liu R, Ji Z, Gao L, Wang X, Zhang J, et al. Predicting lymphatic transport potential using graph transformer based on limited historical data from in vivo studies. *J Control Release.* 2025;384:113847. doi:10.1016/j.jconrel.2025.113847
- [20] Yousef M, Mosa FES, Barakat KH, Davies NM, Löbenberg R. Indirect modeling of post-prandial intestinal lymphatic uptake of halofantrine using PBPK approaches: Limitations and implications. *Pharmaceutics.* 2025;17(9):1228. doi:10.3390/pharmaceutics17091228
- [21] Yousef M, Park C, Bou Chacra NA, Davies NM, Löbenberg R. Novel first-generation dissolution models to investigate the release and uptake of oral lymphotropic drug products. *AAPS PharmSciTech.* 2024;25(6):187. doi:10.1208/s12249-024-02866-y
- [22] Yousef M, O'Croinin C, Le TS, Park C, Zuo J, Bou Chacra N, et al. In vitro predictive model for intestinal lymphatic uptake: Exploration of additional enhancers and inhibitors. *Pharmaceutics.* 2024;16(6):768. doi:10.3390/pharmaceutics16060768
- [23] Yan S, Li L, Cui H, Zhong C, Gao X, Chen C. Visualized triglyceride-mimetic prodrugs: Preparation, effect evaluation and mechanistic investigation of lymphatic transport. *Eur J Pharm Sci.* 2026;222:107548. doi:10.1016/j.ejps.2026.107548
- [24] Feng W, Qin C, Chu Y, Berton M, Lee JB, Zgair A, et al. Natural sesame oil is superior to pre-digested lipid formulations and purified triglycerides in promoting the intestinal lymphatic transport and systemic bioavailability of cannabidiol. *Eur J Pharm Biopharm.* 2021;162:43-9. doi:10.1016/j.ejpb.2021.02.013
- [25] Feng W, Qin C, Cipolla E, Lee JB, Zgair A, Chu Y, et al. Inclusion of medium-chain triglyceride in lipid-based formulation of cannabidiol facilitates micellar solubilization in vitro, but in vivo performance remains superior with pure sesame oil vehicle. *Pharmaceutics.* 2021;13(9):1349. doi:10.3390/pharmaceutics13091349
- [26] Ryšánek P, Grus T, Lukáč P, Kozlík P, Křížek T, Pozniak J, et al. Validity of cycloheximide chylomicron flow blocking method for the evaluation of lymphatic transport of drugs. *Br J Pharmacol.* 2021;178(23):4663-74. doi:10.1111/bph.15644

- [27] Královičová J, Bartůněk A, Hofmann J, Křížek T, Kozlík P, Roušarová J, et al. Pharmacokinetic variability in pre-clinical studies: Sample study with abiraterone in rats and implications for short-term comparative pharmacokinetic study designs. *Pharmaceutics*. 2022;14(3):643. doi:10.3390/pharmaceutics14030643
- [28] Holzem FL, Parrott N, Schaffland JP, Brandl M, Bauer-Brandl A, Stillhart C. Oral absorption from surfactant-based drug formulations: The impact of molecularly dissolved drug on bioavailability. *J Pharm Sci*. 2024;113(10):3054-64. doi:10.1016/j.xphs.2024.07.017
- [29] Reddiar SB, Abdallah M, Styles IK, Müllertz OO, Trevaskis NL. Lymphatic uptake of the lipidated and non-lipidated GLP-1 agonists liraglutide and exenatide is similar in rats. *Eur J Pharm Biopharm*. 2024;200:114339. doi:10.1016/j.ejpb.2024.114339