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# A Potent Phytochemical Is Not Yet a Developable Lead: Ranking Solubility, Permeability, Stability, Metabolic Liability, and Supply Constraints Before Optimization

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## ABSTRACT

Potent phytochemicals can attract optimization effort before the properties that determine whether their activity can be translated into reproducible exposure, stable handling, tractable disposition, and sustainable material access are known. This article develops a proposed pre-optimization decision model for ranking such candidates across solubility, permeability, chemical stability, metabolic liability, and supply constraints without collapsing these dimensions into a single drug-likeness score. The model treats potency as necessary but insufficient evidence and distinguishes measured liabilities from predictions, intrinsic properties from context-dependent behavior, and remediable problems from liabilities for which no credible corrective route is evident. Particular emphasis is placed on interactions: increasing apparent solubility may not increase absorption if thermodynamic activity or permeability falls; structural flexibility can change exposed polarity; chemical degradation can make nominal assay concentration misleading; metabolism can disconnect parent-compound potency from the species that actually circulate; and formulation, dose, physiology, or production technology can reverse candidate order. The proposed architecture therefore ranks candidates conditionally, using evidence confidence, liability severity, interaction structure, and plausible compensability rather than universal numerical weights. Its purpose is to identify which phytochemicals justify optimization, which require targeted de-risking first, and which should be deprioritized pending new evidence. It does not predict clinical success, establish universal thresholds, or replace experimental validation, and it requires prospective testing across independent natural-product series.

**Keywords:** Phytochemicals, Developability, Solubility, Permeability, Metabolic stability, Lead prioritization

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## Introduction

Natural products remain a major source of pharmacologically useful structures, while natural-product-derived drugs and chemical probes also occupy chemical and structural regions that are not fully represented by conventional small-molecule collections [1, 2]. That opportunity creates a recurring selection problem: the compound producing the strongest biological response in an assay is not necessarily the compound best positioned for optimization. Natural-product discovery often begins with an activity signal, but development requires a different question—whether enough intact material can reach and persist in the relevant biological context, and whether the candidate can be generated, handled, characterized, and improved reproducibly. Potency is therefore a property of a compound–assay relationship under specified conditions, not an intrinsic declaration that the molecule can generate useful exposure under a different biological or pharmaceutical context.

Retrospective analyses of pharmaceutical discovery programs show that lead progression is accompanied by systematic attention to physicochemical and developability properties rather than potency alone [3]. Likewise, comparisons of successful hit-to-clinical-candidate pairs indicate that medicinal-chemistry optimization commonly changes several molecular properties simultaneously [4]. These observations do not prove that any particular property trajectory causes success, nor do they establish a phytochemical-specific recipe. They do, however, support an important distinction for natural-product selection: activity ranking and development ranking answer different questions. The former asks which compound is most active under a defined assay; the latter asks which candidate presents the most defensible path toward interpretable exposure and tractable optimization. These rankings can agree, but there is no reason to assume that they must.

Curcumin illustrates why this distinction matters. Its extensive biological literature coexists with well-described concerns involving chemical behavior, assay interpretation, exposure, and medicinal-chemistry tractability [5]. The lesson is not that phytochemicals are intrinsically problematic, or that one difficult compound represents an entire chemical class. Rather, conspicuous potency or mechanistic interest should not substitute for early evidence about the properties that condition whether potency can matter beyond the initial experiment. This caution is especially relevant because natural products and their derivatives have made substantial historical contributions to drug discovery [6]; premature rejection would be as poorly justified as premature progression. The objective is therefore not to impose conventional small-molecule stereotypes on natural-product chemistry, but to make development-relevant uncertainty explicit before optimization resources are committed.

This article proposes a developability decision model for use before intensive optimization. “Developability” is used here in a deliberately bounded sense: the degree to which a candidate has sufficiently interpretable physicochemical, stability, disposition, and resupply characteristics to justify further lead-directed work. It is not synonymous with clinical developability, regulatory acceptability, manufacturing readiness, or eventual therapeutic success. The model keeps potency analytically separate from solubility, permeability, chemical stability, metabolic liability, and supply, then asks how those dimensions interact, how confidently each is known, whether a liability appears compensable, and whether changing experimental, formulation, physiological, or production context could reverse candidate order. The contribution is methodological rather than predictive: a proposed conditional architecture for making progression, targeted de-risking, or deprioritization more transparent before extensive optimization begins.

*Potency versus developability in natural-product selection*

Lead-optimization data from large pharmaceutical portfolios show that successful chemical series evolve across multiple molecular properties rather than activity alone [7]. Broad compound-collection analyses likewise connect permeability and bioavailability behavior with distributions of physicochemical properties [8]. For phytochemical selection, the implication is not that corporate property ranges should be copied as universal acceptance windows. It is that potency should enter a larger evidence structure. An impressive activity value remains an assay observation whose developmental significance depends on whether the molecule can remain available in the relevant phase, cross necessary barriers, survive long enough to exist as the intended chemical entity, and avoid disposition that makes the tested parent a poor proxy for exposure. The same measured potency can therefore carry very different development significance for two molecules.

This distinction becomes sharper for structurally complex candidates. Experimental work on chameleonic compounds has shown that dynamically exposed polarity can change the relationship among conformation, solubility, and permeability [9]. A static descriptor can consequently mischaracterize the molecular state that matters at a membrane or in an aqueous environment. Macrocyclic drug research similarly shows that large, flexible architectures can achieve useful behavior outside simple rule-based expectations, but only under favorable conformational and physicochemical conditions [10]. Natural-product candidates should therefore not be penalized merely for occupying unusual chemical space. Conversely, unusual chemical space increases the cost of assuming that familiar two-dimensional descriptors or simple thresholds fully explain behavior.

The proposed model consequently treats potency and developability as orthogonal evidence axes at the start of selection. Potency answers, “Does the candidate produce the desired response under the assay conditions?” Developability asks, “Is there a credible path by which that response can remain interpretable when concentration, matrix, route, metabolism, and material access change?” A candidate can therefore be highly potent but weakly developable, modestly potent but unusually tractable, or uncertain on either axis. Importantly, “weakly

developable" is not equivalent to "reject": a liability may be technically remediable, contextually irrelevant, or based on uncertain evidence. Likewise, high potency does not grant an unlimited liability budget.

This framing avoids two symmetrical errors. One is discarding complex natural products because they violate simplified property expectations developed largely from conventional drug space. The other is advancing them because biological potency is allowed, implicitly, to compensate for every other uncertainty. Before optimization, the more discriminating question is not which candidate has the highest activity alone, but which activity signal remains credible after its first confrontation with the conditions required for further development.

*Properties that change the meaning of potency*

For orally considered candidates, dissolution or solubility and permeability must be interpreted jointly because the process limiting absorption can change with formulation and gastrointestinal conditions [11-13]. Improving the concentration of drug held in solution therefore does not guarantee a proportional increase in absorbed drug. Experimental and mechanistic evidence shows that pH-dependent dissolution, membrane transport, thermodynamic driving forces, and gastrointestinal conditions can change together, allowing an apparently favorable intervention on one axis to produce little net benefit when another becomes limiting. A potency value obtained at a nominal assay concentration is developmentally informative only when the achievable free or dissolved concentration remains plausible in the intended context. Solubility is thus not simply a pass–fail descriptor attached after potency measurement; it helps determine whether the potency claim describes an exposure that can realistically be recreated.

Static physicochemical rules require similar qualification. Analyses based on measured properties show that simple heuristics can conceal substantial variation within apparently comparable drug-like space [14]. In beyond-rule-of-five chemical space, computational access to relevant physicochemical behavior becomes more sensitive to molecular representation and conformational state [15]. Chameleonicity can also be measured experimentally using chromatographic approaches designed to capture changes in exposed polarity [16]. These findings do not render conventional descriptors useless. They instead indicate that confidence in a developability judgment should decrease when the descriptor is a poor representation of the molecular state governing solvation, partitioning, or membrane passage. For complex phytochemicals, descriptor value and descriptor adequacy are therefore separate questions.

Chemical stability introduces a different interpretive problem. Early hydrolytic-stability screening can distinguish compounds that degrade under conditions relevant to discovery workflows [17]. If substantial degradation occurs during preparation, storage, assay incubation, or subsequent handling, the nominal concentration no longer necessarily represents the concentration of intact parent compound responsible for the observed signal. An unstable candidate can consequently create two problems at once: a genuine development liability and uncertainty about what chemical species generated the original potency. Stability is therefore not merely a downstream formulation concern; it can determine whether potency has been assigned to a chemically well-defined exposure.

Metabolic liability further separates assay potency from in vivo relevance. Metabolic stability is routinely considered during lead development because rapid turnover can restrict parent exposure [18]. At the same time, retrospective assessment of ADMET prediction tools shows that predicted endpoints remain model- and domain-dependent rather than interchangeable with experimental measurements [19]. Berberine provides a natural-product example in which parent compound and metabolites exhibit distinct biodistribution and pharmacokinetic profiles [20]. The generalizable point is not that other phytochemicals reproduce berberine disposition, but that parent-compound potency should not automatically be treated as the pharmacologically relevant chemical exposure once metabolism begins.

These distinctions define the evidence that should qualify potency before candidates are compared across dimensions. **Table 1** classifies the principal evidence types and the particular interpretive error each is intended to prevent.

**Table 1.** Evidence classes that qualify pharmacological potency before pre-optimization ranking

| Evidence class | What potency alone misses | Proposed early evidence | Key interaction or boundary | Proposed decision consequence |
|---|---|---|---|---|
| **Solubility and dissolution** | Achievable dissolved exposure | Context-matched solubility and dissolution | pH, dose, formulation, precipitation | Separate exposure limitation from weak activity |

| | | | | |
|---|---|---|---|---|
| **Permeability and dynamic polarity** | Barrier access of the relevant molecular state | Experimental permeability plus state-sensitive descriptors | Conformation, thermodynamic activity, membrane environment | Avoid static-descriptor overconfidence |
| **Chemical stability** | Persistence of intact parent during testing | Time-resolved degradation measurements | Matrix, pH, temperature, preparation history | Reinterpret potency when nominal exposure is unstable |
| **Metabolic stability and transformation** | Persistence and chemical identity after biotransformation | Turnover data with metabolite characterization when needed | Enzyme system, species, tissue, parent–metabolite contribution | Separate parent potency from exposure plausibility |
| **Prediction confidence** | Reliability of an estimated property | Domain-aware prediction followed by experimental challenge | Applicability domain and uncertainty | Lower confidence without converting uncertainty into failure |

**Note:** Evidence classes reflect literature-supported distinctions; the early-evidence and decision-consequence columns are proposed components of the decision model.

*Candidate trade-offs across development dimensions*

Developability dimensions become most informative when treated as interacting constraints rather than independent checkboxes. Half-life, for example, emerges from clearance and distribution processes and is not inherently improved simply by maximizing one contributing property [21]. A candidate with slower apparent turnover may gain exposure but could also acquire undesirable persistence or distribution depending on the intended pharmacology. The same reasoning applies before human pharmacokinetics are known: property direction should be interpreted against intended route, dose, site of action, duration of exposure, and therapeutic context rather than assigned a universal positive or negative sign. Development ranking therefore requires interpretation of relationships among properties, not merely measurement of their isolated values.

Clearance prediction further illustrates why confidence must accompany rank. Multispecies machine-learning models can estimate intrinsic clearance while quantifying prediction uncertainty, but their performance remains conditional on represented species and chemical domain [22]. A predicted liability should therefore not receive the same evidential weight as a reproducible experimental liability, and a highly uncertain estimate should not be silently converted into a negative experimental result. In the proposed framework, evidence confidence is a second axis beside liability severity. Two candidates with apparently similar clearance risk may consequently warrant different decisions if one estimate is supported by measurements in a relevant system while the other is extrapolated beyond the model's well-supported domain.

Absorption is similarly conditional. In vitro measurements can contribute to prediction of oral absorption, yet translation remains dependent on the biological system and assumptions linking assay outputs to in vivo behavior [23]. Physiologically based biopharmaceutics modeling further shows that regional intestinal absorption can vary with local physiology and compound properties [24]. Lipid-based formulation studies demonstrate another layer of coupling: digestion can change not only solubilization but also thermodynamic activity and permeability, undermining a simple assumption that “more solubilized” necessarily means “more absorbed” [25]. These observations establish why a candidate ranking must be allowed to change when formulation or physiological context changes rather than treating such changes as noise around a fixed intrinsic order.

The resulting decision problem is relational. A solubility liability may be tolerable when exposure can be increased without materially impairing permeability; a permeability limitation may carry different importance for a candidate intended to act locally rather than systemically. Rapid parent metabolism could be less damaging when pharmacologically relevant metabolites contribute to exposure, but more consequential when activity depends specifically on the parent. Conversely, individually moderate liabilities can compound one another: incomplete dissolution can reduce the amount available for transport, while rapid metabolic removal can further erode the fraction reaching a distant target.

The model proposed here consequently avoids a simple additive penalty score. It instead treats interaction strength, context, evidence confidence, and plausible compensability as conditions determining whether a liability is independently limiting, jointly limiting, tolerable under the intended use case, or sufficiently uncertain to require targeted de-risking. This distinction prepares the ranking step for a central possibility developed later: the order

of candidates is not fixed, because new evidence, a changed formulation, a different exposure objective, or a credible route around a material constraint can legitimately reverse it.

*A pre-optimization ranking strategy*

A pre-optimization ranking system should combine development-relevant evidence without pretending that unlike liabilities share a universal numerical scale. Multiparameter computational optimization demonstrates that several objectives can be considered simultaneously rather than maximizing a single endpoint [26]. The proposed model adopts that logic but does not import any published weighting function. For each phytochemical, it asks four questions in parallel: how severe is the observed or predicted liability; how strong is the evidence supporting it; does it interact materially with another development dimension; and is there a credible route by which the liability could be reduced without creating a worse one? Potency remains visible but does not function as a compensating score that can erase failure elsewhere.

Predicted evidence must be handled separately from measured evidence. Contemporary in silico ADME methods can support early prioritization, but their applicability depends on endpoint, training domain, representation, and validation context [27]. The proposed ranking therefore uses predictions principally to direct measurements and identify uncertainty. A candidate should not be demoted as though a prediction were an experimentally established failure, nor promoted because a favorable estimate lacks an uncertainty flag. Where measured data are unavailable, the appropriate state is unresolved rather than good or bad. This distinction makes evidence confidence part of the decision architecture instead of concealing it inside a property value.

A second principle is comparative rather than absolute. Computational approaches for evaluating lead-optimization progress show that improvement can be judged across several properties rather than one activity measure [28]. Before optimization, the analogous question is whether one candidate dominates another on the dimensions that matter for the intended use, or whether advantages are offset by liabilities whose importance cannot yet be ranked confidently. This permits three proposed decision states: progression when activity is credible and no major unaddressed constraint dominates; targeted de-risking when the candidate remains attractive but a decision-changing uncertainty is resolvable; and deprioritization when a material liability is well supported and lacks a credible compensating path.

A further safeguard is to prevent averaging from hiding a dominant constraint. A candidate that performs moderately well on four dimensions should not automatically outrank one with a single uncertain liability, nor should exceptional potency offset a demonstrated inability to maintain chemically defined exposure. The model therefore uses conditional gates before any overall comparison. A liability becomes potentially decision-dominant when it directly compromises interpretation of activity, blocks the intended exposure route, or makes reliable material access implausible under the current evidence. By contrast, a liability remains negotiable when its relevance depends on an unresolved context or when a specific remediation can be tested without assuming success. This gate structure is proposed rather than validated; its purpose is to preserve clinically and pharmaceutically meaningful distinctions that would disappear if every property were normalized and averaged.

The ranking must also be interaction-sensitive. Formulation studies show that strategies designed to improve oral delivery can alter solubility and permeability in different directions [29]. A numerical sum could therefore reward a nominal gain while obscuring a coupled loss. The proposed architecture instead triggers reassessment whenever an intervention changes the conditions under which another dimension was measured. **Figure 1** summarizes this conditional logic and shows why candidate order is provisional rather than intrinsic

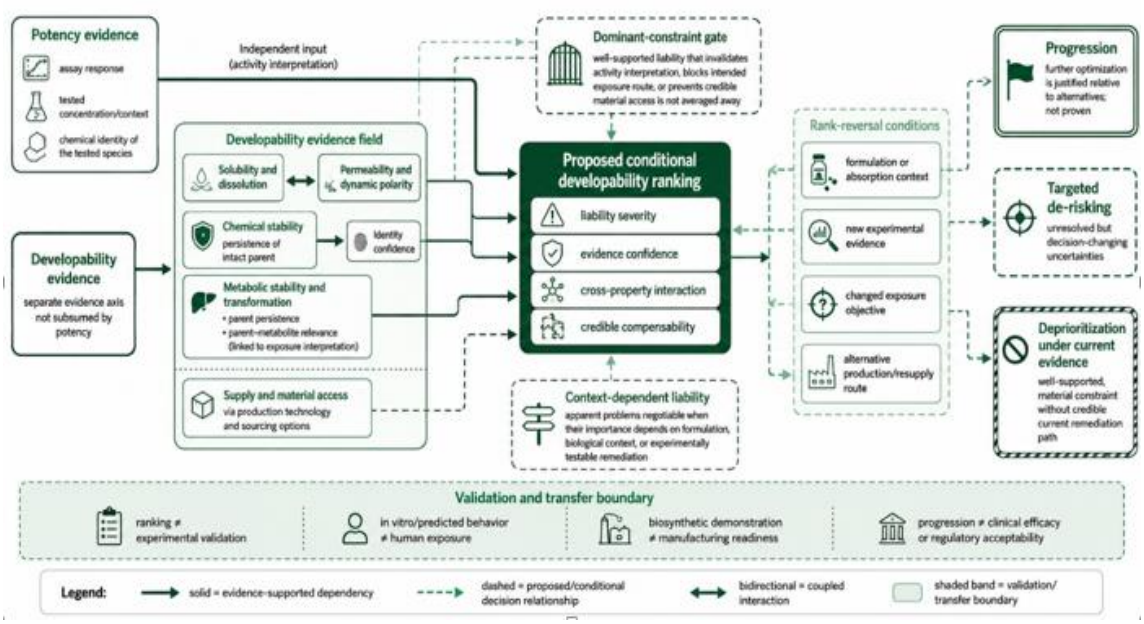


**Figure 1.** Conditional developability ranking from potency evidence to progression, de-risking, or deprioritization

Caption. Original proposed decision architecture. Potency enters separately from development evidence. Evidence-supported dependencies connect solubility–permeability coupling, chemical identity/stability, metabolic transformation, and supply feasibility to candidate interpretation. Dashed connectors denote the proposed integration of liability severity, evidence confidence, interaction, and compensability into conditional ranking. Rank-reversal branches return formulation, exposure context, new measurements, or resupply options to reassessment. The lower boundary separates prioritization from experimental validation, clinical inference, and manufacturing-readiness claims.

Alt text. Left-to-right branching decision architecture in which potency and development evidence remain separate, converge on an interaction-sensitive ranking core, branch through rank-reversal conditions, and reach progression, targeted de-risking, or deprioritization gates above an explicit validation and transfer boundary.

*When candidate rankings reverse*

Candidate rank should be expected to change when a liability previously treated as fixed becomes technically alterable. Synthetic biology has created routes for producing natural products and modifying their biosynthetic systems, demonstrating that dependence on native extraction is not always immutable [30]. Supply should therefore be assessed as both a present constraint and a question of credible remediation. A scarce candidate with an incompletely known pathway differs from one whose biosynthesis can already be reconstructed, just as a readily isolated compound differs from a candidate requiring unstable, low-yield, or ecologically problematic sourcing. The proposed model does not equate theoretical biosynthetic possibility with practical supply; it asks how mature the evidence for an alternative route actually is.

Plant chassis approaches broaden the range of possible production systems but also expose pathway, host, yield, and engineering constraints [31]. Consequently, supply is unusual among the five development dimensions: it can improve without changing the pharmacologically active structure at all. A candidate originally ranked below a more abundant analogue may become competitive if a robust production route emerges, whereas a structurally attractive molecule can fall in rank when reproducible access proves less tractable than initial isolation suggested. Such reversals should be documented rather than retrospectively described as inconsistency.

The principle is supported by distinct demonstrations of heterologous biosynthesis. Cannabinoids, medicinal tropane alkaloids, and the complex anticancer natural product vinblastine have each been produced through engineered biological systems [32-34]. These examples establish feasibility for selected pathways, not universal economic scalability. Their decision-model significance is narrower: material access is a conditional property of the compound plus its production technology, and technological evidence can change a previously rational prioritization.

Rank reversal also occurs without changing supply. Formulation can alter coupled absorption determinants; new stability or clearance measurements can replace an uncertain prediction; and a change in intended route or exposure objective can alter which liability dominates. The appropriate response is not continuous reshuffling after every minor observation. Re-ranking is warranted when new information changes a decision-relevant assumption: the severity of a limiting liability, confidence that it is real, its interaction with another property, or the credibility of remediation. **Table 2** distinguishes these rank-changing conditions from evidence that should merely refine confidence.

**Table 2.** Conditions that can legitimately reverse a pre-optimization phytochemical ranking

| Rank-changing condition | What changes | Proposed interpretation | What does not follow |
|---|---|---|---|
| **Formulation or absorption context** | Coupled solubility, activity, or permeability | Reassess exposure-limiting dimension | Formulation has clinically "rescued" the candidate |
| **New experimental evidence** | Confidence in stability, permeability, or clearance liability | Replace uncertain estimate with measured state | One assay establishes in vivo behavior |
| **Alternative production route** | Credibility of material resupply | Reassess supply as a remediable constraint | Demonstrated biosynthesis equals scale readiness |
| **Changed exposure objective** | Relevance of local versus systemic access or parent persistence | Reassess which liability is decision-limiting | Property direction becomes universally favorable |

**Note:** Decision consequences are proposed. The matrix contains no universal thresholds or numerical weights.

*Decision boundaries for progression or deprioritization*

A decision boundary should represent an evidential state, not a universal property cutoff. For supply, pathway discovery and engineering maturity determine whether an alternative production route is sufficiently credible to affect prioritization [35]. A severe constraint with a demonstrated route around it is different from an equally severe constraint supported only by speculation about future engineering. The same distinction applies to formulation and metabolism: compensability should mean a plausible, testable remediation supported by relevant evidence, not the assertion that medicinal chemistry can probably fix the problem later.

Computational prioritization can expand and accelerate natural-product discovery, but its utility remains dependent on data quality, representation, applicability, and experimental validation [36]. The proposed model therefore places a visible boundary between ranking and validation. Progression means that further optimization is justified relative to alternatives; it does not mean that developability has been demonstrated. Targeted de-risking means that a candidate remains competitive if a decision-changing uncertainty can be resolved efficiently. Deprioritization means that current evidence does not justify comparable optimization effort, not that the compound lacks scientific or pharmacological value.

Chemical instability should cross a stronger boundary when reproducible testing shows that the nominal parent exposure is unreliable [17]. Metabolic liability requires qualification by the experimental system and cannot automatically be translated into human exposure [18]. Predicted clearance should retain explicit uncertainty when chemical or species domains limit confidence [22]. Likewise, a serious supply constraint can move back toward progression when a credible production route becomes available [30]. These examples illustrate the central proposed rule: progression depends jointly on liability severity, confidence, interaction, and compensability, while any one of these can remain uncertain enough to justify a de-risking experiment rather than an irreversible decision.

*Implications for natural-product lead discovery*

The practical implication is to move decision-changing measurements earlier, before potency has accumulated enough organizational momentum to become a de facto progression criterion. Retrospective development trends support attention to multiple properties during candidate evolution [3]. Early hydrolytic-stability screening can reveal liabilities that would otherwise complicate interpretation [17], while metabolic-stability assessment can identify turnover concerns before extensive optimization [18]. For natural-product programs, these measurements are most useful when framed as comparative questions: which candidate's apparent advantage survives a realistic test of exposure, identity, and persistence, and which uncertainty is most likely to change the next decision?

This sequencing does not require complete ADME characterization before chemistry begins. It requires discriminating between information that is merely interesting and information capable of changing candidate order. A poorly soluble but permeable candidate may warrant a focused formulation experiment; an unstable compound may require confirmation that intact parent produced the original activity; an apparent metabolic liability may require a more relevant biological system; and a supply-limited scaffold may require early consideration of semisynthesis, pathway reconstruction, or alternative production. Synthetic-biology evidence supports treating resupply as an engineering question in appropriate cases [30], while pathway maturity remains a substantive constraint on how confidently such remediation can be assumed [35].

Uncertainty should also be reported as part of rank rather than hidden behind point predictions. Multispecies clearance modeling illustrates the value of explicit uncertainty estimates [22], and broader ADME modeling literature emphasizes applicability and validation limits [27]. Natural-product AI similarly offers powerful prioritization capabilities without converting prediction into experimental confirmation [36]. A useful pre-optimization record should therefore state not only which candidate ranks first, but which evidence makes that ranking stable and what observation would most plausibly reverse it.

Prospective evaluation should test the proposed model against potency-only selection and simpler additive ranking. Independent natural-product series should be ranked before optimization, followed by orthogonal measurements of solubility, permeability, chemical stability, metabolic behavior, and material access appropriate to the intended route and context. Evaluation should examine rank stability, decision-changing prediction errors, sensitivity to proposed boundaries, and whether targeted de-risking resolves uncertainty efficiently. Such work could refine or reject individual elements of the architecture. Until then, its value is organizational: it makes explicit the assumptions that are otherwise embedded informally in decisions about which potent phytochemical deserves the next experiment.

## Conclusion

A potent phytochemical becomes a credible lead candidate only when its activity is considered together with the conditions required to reproduce, interpret, and sustain that activity during development. The proposed model separates potency from developability and evaluates solubility, permeability, chemical stability, metabolic liability, and supply as distinct but interacting dimensions. It further separates liability severity from evidence confidence, recognizes that properties can constrain one another, and treats compensability as a testable proposition rather than an automatic license to continue optimization.

This architecture changes the purpose of early developability assessment. Instead of asking whether a molecule satisfies a generic collection of favorable properties, it asks whether the current evidence supports progression relative to competing candidates, whether a specific uncertainty should be resolved before optimization, or whether a well-supported constraint currently outweighs the activity advantage. Because formulation, biological context, new measurements, or production technology can alter the governing constraint, rankings are conditional and should be revisited only when decision-relevant assumptions change.

The model remains a proposed decision framework rather than a prospectively validated predictor. It supplies no universal thresholds, numerical weights, guarantees of exposure, manufacturing feasibility, clinical efficacy, or regulatory acceptability. Its appropriate use is earlier and narrower: to prevent potency from silently dominating candidate selection while preserving promising natural products whose apparent liabilities are uncertain, context-dependent, or credibly remediable. Prospective comparison across independent natural-product series is required to determine whether this structured approach improves candidate selection over simpler potency-driven or additive methods.

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