Phytochemical Intelligence for Drug Discovery: Connecting Virtual Screening, Target Prediction, ADMET Profiling, and Mechanism-Based Candidate Prioritization

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ABSTRACT

Phytochemicals and plant-derived molecules remain central to drug discovery because they offer chemically diverse scaffolds, biological complexity, and mechanistic breadth that can complement synthetic libraries. However, the computational prioritization of phytochemicals is often fragmented across isolated docking studies, target-prediction outputs, network analyses, and ADMET filters. This article proposes "phytochemical intelligence" as a conceptual framework for integrating virtual screening, target prediction, ADMET profiling, mechanism-based filtering, and candidate prioritization into a transparent decision-support logic for early-stage drug discovery. The framework positions virtual screening as a hypothesis-generating layer for identifying candidate molecular interactions, target prediction as a mechanism-inference layer for linking compounds to plausible biological targets, and ADMET profiling as a developability-oriented filter for identifying pharmacokinetic and safety liabilities. Mechanism-based prioritization is then used to distinguish weak computational hits from candidates with convergent evidence across molecular fit, target plausibility, pathway relevance, safety risk, assay feasibility, and translational readiness. The framework emphasizes that computational evidence can support prioritization, but cannot establish bioactivity, safety, therapeutic efficacy, or clinical relevance without experimental validation. Its main contribution is a structured decision architecture that separates prediction, plausibility, validation, and translational readiness while enabling reproducible evidence integration. Practically, phytochemical intelligence can help natural product researchers, medicinal chemists, pharmacologists, and computational scientists select stronger candidates for experimental testing, avoid overreliance on single-method outputs, and design more coherent validation strategies. Future research should focus on transparent reporting, uncertainty assessment, benchmarked prediction models, experimentally confirmed mechanisms, and interdisciplinary workflows that connect computational triage with pharmacological and translational development.

Key Words: *Phytochemical intelligence, Drug discovery, Virtual screening, Target prediction, ADMET profiling, Candidate prioritization*

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INTRODUCTION

Phytochemicals and plant-derived molecules occupy a distinctive position in drug discovery because natural products have repeatedly contributed scaffolds, pharmacophores, and molecular architectures that are difficult to reproduce through conventional synthetic-library design. Their value does not arise from an assumption that plant origin implies safety or efficacy, but

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from the chemical diversity, stereochemical complexity, and biological history embedded in natural-product chemical space. This continuing relevance makes phytochemicals attractive starting points for early-stage discovery, while also demanding rigorous approaches for triage, validation, and developability assessment [1].

A central challenge in natural product discovery is that chemical richness does not automatically translate into drug-discovery efficiency. Retrospective analysis of natural-product discovery trends shows that productive exploration depends on how candidate space is sampled, interpreted, and connected to biologically meaningful questions. For phytochemical research, this creates a need to move beyond descriptive compound lists or isolated activity claims toward systematic evidence organization that can identify which candidates deserve experimental resources and which remain weakly supported hypotheses [2].

Modern natural product research increasingly relies on computational approaches to complement extraction, structural characterization, medicinal chemistry, pharmacology, and mechanism-of-action studies. Molecular docking, pharmacophore modeling, ligand-based screening, target prediction, machine learning, pathway interpretation, and ADMET prediction can each provide useful evidence, but their value depends on how their outputs are interpreted and integrated. When computational outputs are treated as independent proof rather than decision-support evidence, the resulting claims can become overstated or poorly connected to translational development [3].

This article proposes phytochemical intelligence as a conceptual framework for organizing computational and pharmacological evidence about plant-derived molecules. The framework asks how virtual screening, target prediction, ADMET profiling, mechanism-based filtering, and candidate prioritization can be connected into a transparent selection logic that distinguishes computational hits from biologically plausible and validation-ready candidates. It also emphasizes that computational prioritization must complement, not replace, compound isolation, structural confirmation, target engagement assays, pharmacological validation, toxicology, pharmacokinetics, formulation development, preclinical testing, clinical evaluation, and regulatory review [1, 4].

Phytochemical intelligence in drug discovery

Phytochemical intelligence can be defined as an evidence-integration approach that organizes computational, chemical, pharmacological, and translational information about plant-derived molecules to support candidate prioritization. It is not a single algorithm, database, docking protocol, or ADMET tool. Instead, it is a decision architecture for asking whether a phytochemical candidate has enough convergent evidence to justify further experimental testing. This definition is grounded in the recognition that phytochemicals can contribute to drug discovery, but only when their biological relevance, chemical tractability, safety profile, and validation needs are assessed with appropriate caution [5].

The first function of phytochemical intelligence is to convert virtual screening from a stand-alone ranking exercise into an evidence stream within a broader prioritization workflow. In natural-product bioprospecting, virtual screening can help search chemically diverse libraries, compare candidate ligands, and generate hypotheses about molecular recognition. However, a high-ranking screening result should be interpreted as a prioritization signal rather than confirmation of pharmacological activity. Within phytochemical intelligence, screening evidence is therefore useful only when linked to target plausibility, chemical quality, ADMET feasibility, and follow-up validation [6].

The second function is to connect phytochemical candidates to plausible protein interactions and biological mechanisms. Computational prediction of protein interactions for natural products can help identify potential targets, guide mechanistic hypotheses, and prioritize compounds for target-focused assays. Yet target-prediction evidence is strongly shaped by available training data, similarity assumptions, target coverage, and method-specific biases. Phytochemical intelligence therefore treats predicted targets as provisional biological hypotheses that require orthogonal support from pathway context, bioactivity evidence, and experimental confirmation [7].

The third function is to interpret mechanism-of-action plausibility without overstating prediction. In silico target prediction can reveal possible molecular targets of familiar natural products and can suggest mechanistic explanations that were not initially obvious from traditional pharmacological observation. Within the proposed framework, such evidence is valuable because it helps transform a candidate from an isolated chemical hit into a mechanistic hypothesis. Nevertheless, predicted target association remains distinct from confirmed target engagement, pathway modulation, pharmacological efficacy, or therapeutic relevance [8].

Virtual screening and target prediction

Virtual screening provides the entry point for many computational phytochemical discovery workflows because it can organize large candidate spaces before experimental testing. Ultra-large screening platforms demonstrate that computational search can operate at scales that are not practical for conventional assay-first

approaches, enabling the prioritization of molecules for more focused analysis. For phytochemicals, this scalability is useful when natural-product libraries are chemically diverse, structurally complex, or derived from multiple sources, but screening reliability still depends on library quality, molecular preparation, target structure quality, scoring assumptions, and reproducibility [9].

Molecular docking is one of the most common structure-based strategies used to estimate whether a candidate ligand may fit a binding site and form plausible interactions with a protein target. Ultra-large library docking has shown that computational screening can help identify candidate chemotypes for experimental follow-up, but docking scores alone do not prove binding, selectivity, cell activity, druggability, or therapeutic potential. In a phytochemical intelligence framework, docking should therefore contribute to candidate triage only when the result is chemically plausible, structurally interpretable, and compatible with additional evidence streams [10].

Natural-product-based docking studies can be useful when they are positioned as hypothesis-generating analyses rather than definitive pharmacological demonstrations. Docking can support the comparison of phytochemical candidates, exploration of binding poses, assessment of interaction hypotheses, and selection of compounds for assays. However, candidate prioritization should not rely on docking alone, because docking workflows may be affected by protein flexibility, ligand protonation, water networks, scoring-function limitations, and incomplete representation of biological context. For this reason, docking evidence should be combined with pharmacophore reasoning, ligand-based similarity, target prediction, ADMET profiling, and validation planning [11].

Target prediction, reverse docking, drug–target interaction prediction, and network pharmacology extend virtual screening by linking phytochemicals to possible biological targets and pathways. These methods can help generate mechanism-of-action hypotheses, identify target clusters, and connect candidate compounds to disease-relevant biological processes. Their interpretive strength increases when virtual screening, natural-product protein-interaction prediction, and validation-aware target-prediction strategies converge on coherent biological hypotheses; nevertheless, predicted binding or target association must remain clearly separated from experimentally confirmed mechanism of action [6, 7, 12].

Computational drug-discovery workflows are strongest when screening and target-prediction outputs are embedded in iterative cycles of evaluation, refinement, and validation. Rather than treating virtual screening as a terminal ranking step, phytochemical intelligence uses it as the first layer of a decision pipeline. A candidate may progress when its screening evidence is supported by target plausibility, pathway relevance, acceptable predicted developability, feasible assay design, and clear validation requirements. Conversely, a high-scoring molecule with weak mechanistic support, poor predicted safety, uncertain chemical identity, or no feasible validation route should remain a low-confidence computational hit [13].

ADMET profiling and mechanistic filtering

ADMET profiling functions as a developability-oriented filtering layer within phytochemical intelligence. A phytochemical candidate may appear promising in a docking or target-prediction workflow, but still be unsuitable for further development if it is predicted to have poor oral bioavailability, low solubility, limited permeability, problematic metabolism, or unfavorable drug-likeness. Tools that estimate pharmacokinetic and medicinal chemistry properties can therefore help identify early liabilities before experimental resources are committed to low-feasibility candidates [14].

ADMET evidence should not be treated as a single pass-or-fail label. Instead, it should be interpreted as a set of endpoint-specific signals that inform candidate ranking. A molecule with moderate screening evidence but a relatively balanced predicted ADMET profile may be more suitable for follow-up than a high-scoring docking hit with multiple predicted liabilities. Multi-endpoint ADMET prediction supports this type of decision logic by encouraging simultaneous attention to absorption, distribution, metabolism, excretion, toxicity, and optimization concerns [15].

Comprehensive ADMET profiling also helps connect candidate selection to developability rather than only to molecular recognition. In phytochemical drug discovery, predicted oral bioavailability, solubility, permeability, metabolic stability, CYP450 interactions, transporter interactions, and toxicity alerts can be used to identify candidates that require medicinal chemistry optimization, formulation strategies, or deprioritization. ADMET and toxicity tools can support early filtering, but their outputs remain prediction-level evidence and cannot establish pharmacokinetic suitability, safety, or clinical acceptability without experimental confirmation [14, 16, 17].

Mechanistic filtering should integrate biological plausibility with pharmacokinetic and safety feasibility. A candidate with plausible target engagement and pathway relevance may still be weak if it carries substantial predicted toxicity risk, chemical instability, or poor synthetic accessibility. Machine-learning-based toxicity estimation can contribute to this filtering process by adding toxicity and developability penalties to candidate ranking,

but these predictions should be interpreted as risk signals rather than definitive toxicological findings [18].

Candidate prioritization logic

Candidate prioritization is the decision layer that converts heterogeneous computational evidence into an ordered set of experimental priorities. In phytochemical intelligence, ranking should not be driven by a single docking score, target probability, pathway count, or ADMET output. Instead, prioritization should combine virtual screening strength, target prediction confidence, mechanism plausibility, ADMET feasibility, toxicity risk, chemical tractability, assay feasibility, and translational relevance. Machine learning can support this process across discovery tasks when models are trained, evaluated, and interpreted with attention to data quality and domain relevance [19].

Artificial intelligence and computational modeling can improve early-stage decision support by identifying patterns across chemical structures, predicted targets, biological annotations, and developability features. However, these methods should be used to support human scientific judgment rather than replace it. In a phytochemical intelligence workflow, an AI-supported ranking becomes meaningful only when the evidence behind the ranking is transparent enough to guide experimental design and mechanistic testing [20].

Deep learning and representation-learning approaches add further capacity by modeling molecular graphs, fingerprints, descriptors, SMILES strings, and other molecular representations. These methods may help identify relationships that are difficult to capture with simpler similarity or rule-based approaches, but their outputs can be difficult to interpret and may be sensitive to training-set bias, endpoint definition, and chemical-domain coverage. Candidate prioritization should therefore include uncertainty assessment and should avoid treating model confidence as equivalent to biological truth [21].

A practical prioritization logic can distinguish four candidate states. Weak computational hits have isolated support, such as a favorable docking pose without target plausibility or ADMET feasibility. Promising computational hits show convergence across screening and preliminary target evidence. Mechanism-supported candidates have coherent target, pathway, and biological plausibility signals. Validation-ready candidates combine plausible mechanism, acceptable predicted developability, manageable safety risk, chemical tractability, and a feasible experimental validation route. AI-era drug design requires this type of interpretable, expert-guided decision structure, especially because unrealistic expectations about computational discovery can obscure the difference between prediction and validated pharmacology [22]. **Table 1** presents a mechanism-based candidate prioritization matrix for integrating virtual screening, target prediction, ADMET profiling, validation needs, and translational risk in phytochemical drug discovery.

Table 1. Mechanism-Based Candidate Prioritization Matrix for Phytochemical Intelligence in Drug Discovery: Virtual Screening Evidence, Target Prediction Confidence, ADMET Filtering, Biological Plausibility, Validation Needs, Translational Risk, and Decision Logic

Prioritization dimension	Evidence source	Decision question	Favorable signal	Risk signal	Validation requirement	Interpretation limitation	Translational implication	Candidate-prioritization action
Phytochemical identity and data provenance	Plant source records, compound databases, structural annotation, literature evidence	Is the candidate chemically defined and traceable?	Clear structure, source traceability, consistent annotation	Ambiguous identity, duplicate records, uncertain stereochemistry	Structural confirmation, purity assessment, source verification	Database records may be incomplete or inconsistent	Poor provenance weakens downstream interpretation	Prioritize only chemically traceable candidates
Molecular representation quality	Descriptors, fingerprints, SMILES, graph representation, conformer preparation	Is the molecule represented accurately for modeling?	Correct ionization, stereochemistry, tautomer handling, conformer quality	Incorrect protonation, missing stereochemistry, unrealistic conformation	Expert curation and reproducible preparation workflow	Model output depends strongly on input representation	Poor representation can create misleading predictions	Reprocess or exclude poorly represented candidates
Virtual screening evidence	Docking, pharmacophore screening, ligand-based screening,	Does the candidate show plausible molecular recognition?	Coherent binding hypothesis across	Isolated docking score, strained pose, implausible interactions	Biophysical or biochemical binding assay	Screening does not prove binding or bioactivity	Useful for triage, not confirmation	Advance only if supported by other

	structure-based screening		screening approaches					evidence streams
Target prediction confidence	Reverse docking, drug–target interaction prediction, similarity inference	Are predicted targets biologically plausible?	Convergence across methods and target biology	Unsupported target assignment, database bias, broad promiscuity	Target engagement assay and orthogonal target validation	Predicted targets are hypotheses, not confirmed mechanisms	Guides assay selection and mechanism testing	Rank higher when target evidence is coherent
Pathway and mechanism plausibility	Network pharmacology, pathway mapping, mechanism-of-action inference	Does the target set map to a plausible biological mechanism?	Mechanistically coherent pathway context	Overconnected networks, nonspecific pathway enrichment	Pathway perturbation assay, cellular mechanism verification	Network topology may reflect database bias	Helps move from hit lists to biological hypotheses	Prioritize candidates with mechanistic coherence
ADMET feasibility	ADME prediction, drug-likeness assessment, pharmacokinetic alerts	Is the candidate likely to be developable enough for follow-up?	Balanced predicted solubility, permeability, metabolism, and bioavailability	Poor solubility, low permeability, metabolic liabilities	In vitro ADME and pharmacokinetic testing	Prediction is endpoint-specific and model-dependent	Supports early developability triage	Penalize candidates with multiple severe liabilities
Toxicity and safety risk	Toxicity prediction, hERG alerts, hepatotoxicity and genotoxicity signals	Does the candidate present unacceptable predicted safety risk?	No major predicted safety alerts or manageable risk	Multiple toxicity alerts or high-risk endpoint flags	Toxicology assays and safety pharmacology testing	Toxicity prediction cannot establish safety	Prevents premature advancement of risky candidates	Deprioritize or require strong mitigation strategy
Chemical tractability	Synthetic accessibility, isolation feasibility, analog design potential	Can the candidate be obtained and optimized?	Feasible isolation, synthesis, or analog development	Scarce source, unstable compound, poor tractability	Re-isolation, synthesis, stability testing	Computational promise may be irrelevant if compound access is poor	Determines practical follow-up feasibility	Prioritize candidates that can be produced and modified
Assay feasibility	Target assays, phenotypic assays, cellular models, mechanistic readouts	Can the hypothesis be tested experimentally?	Clear assay path and measurable endpoint	No assay route, unclear target readout, unsuitable model	Fit-for-purpose assay design	Feasible assay does not guarantee translational relevance	Converts prediction into testable pharmacology	Advance candidates with clear validation route
Translational readiness	Integrated evidence, reproducibility, uncertainty, medicinal chemistry fit	Is the candidate ready for deeper experimental development?	Convergent evidence, manageable uncertainty, validation plan	Fragmented evidence, high uncertainty, overclaiming risk	Iterative experimental validation and model refinement	Early prioritization is not preclinical proof	Supports structured progression decisions	Advance as validation-ready only with convergent evidence

Computational ranking must also contain an explicit safeguard against overclaiming. A candidate should not be described as therapeutic, safe, druggable, or mechanism-confirmed merely because it performs well in a computational workflow. The prioritization output should instead specify the candidate's evidence status: screening-supported, target-hypothesized, mechanism-plausible, ADMET-flagged, validation-ready, or deprioritized. This terminology protects the framework from the common error of interpreting computational prioritization as experimental validation or translational proof [23].

Proposed conceptual framework

The proposed phytochemical intelligence framework is an integrated pipeline that begins with phytochemical data sources and ends with evidence-weighted candidate prioritization for experimental validation. Its first layer is data construction: plant-derived compounds must be represented through curated structures, standardized molecular formats, and traceable source information. Its second layer is computational screening, where docking, pharmacophore screening, ligand-based screening, structure-based screening, and similarity analysis generate preliminary interaction hypotheses. Its third layer is target and mechanism inference, where reverse docking, drug–target interaction prediction, network pharmacology, and pathway interpretation connect candidates to plausible biological mechanisms. Network pharmacology is particularly useful here when it is used to explore causal and systems-level relationships rather than to inflate unsupported mechanism claims [24].

The fourth layer is ADMET and toxicity filtering, which evaluates oral bioavailability, solubility, permeability, metabolism, CYP450 interaction, transporter interaction, toxicity prediction, hERG liability, hepatotoxicity, and safety alerts. The fifth layer is evidence weighting, where each candidate is assessed according to convergent evidence rather than a single favorable metric. The sixth layer is prioritization, where candidates are classified according to biological plausibility, developability risk, validation need, and translational readiness. Network pharmacology databases and compound–target–disease resources can support this process when their provenance, coverage, and inference limits are made explicit [25].

Figure 1 illustrates the proposed phytochemical intelligence framework connecting virtual screening, target prediction, ADMET profiling, mechanism-based filtering, validation safeguards, and candidate prioritization.

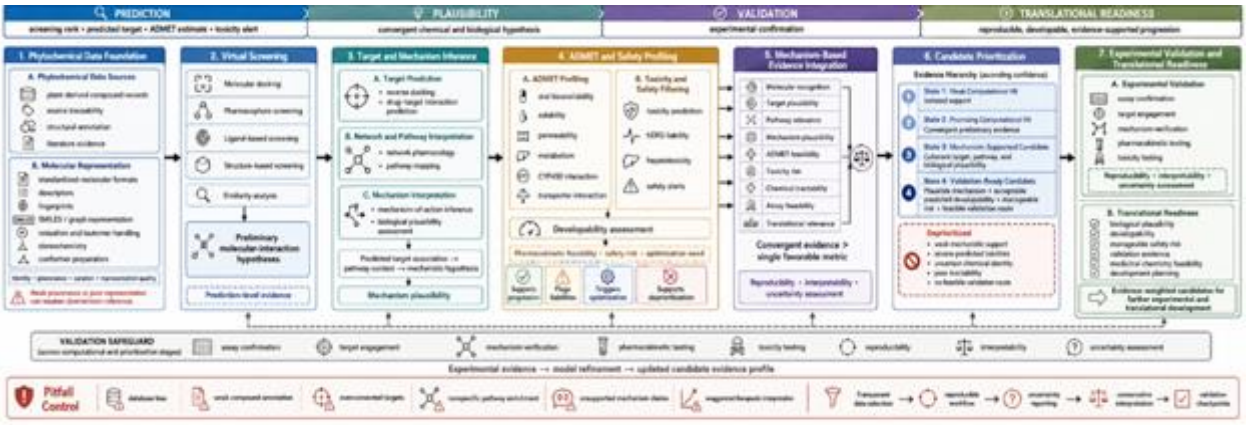

Figure 1. Phytochemical Intelligence Framework for Mechanism-Based Candidate Prioritization in Drug Discovery

Alt-text description

A conceptual framework showing phytochemical data flowing into molecular representation, virtual screening, target prediction, network pharmacology, ADMET profiling, toxicity filtering, and mechanism-based evidence integration. These evidence streams converge into a candidate prioritization module that ranks compounds according to biological plausibility, safety risk, developability, validation requirements, and translational readiness, with feedback loops from experimental validation to model refinement.

A central feature of the framework is its distinction among prediction, plausibility, validation, and translational readiness. Prediction refers to computational outputs such as screening rank, target association, ADMET estimate, or toxicity alert. Plausibility emerges when multiple outputs form a coherent biological and chemical hypothesis. Validation requires experimental confirmation through compound identity checks, binding assays, target engagement studies, mechanism verification, pharmacological testing, pharmacokinetic studies, and toxicity assays. Translational readiness requires a stronger level of evidence that includes reproducibility, medicinal chemistry feasibility, safety assessment, and development planning.

The framework also requires feedback loops. Experimental findings should not simply confirm or reject computational rankings; they should refine the models, update the candidate evidence profile, and improve future screening decisions. Curated bioactivity data can strengthen this feedback process by allowing predicted target interactions to be checked against experimentally reported activity where available. In phytochemical intelligence, such resources support evidence integration by helping teams avoid unsupported target claims and by improving the traceability of candidate-selection decisions [26].

Finally, the framework includes an explicit pitfall-control layer. Natural-product network pharmacology and mechanism-inference workflows can be vulnerable to database bias, overconnected targets, nonspecific pathway

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enrichment, weak compound annotation, and exaggerated therapeutic interpretation. Therefore, phytochemical intelligence should require transparent database selection, reproducible workflows, clear uncertainty reporting, conservative language, and validation checkpoints before mechanism-based claims are advanced. Without these safeguards, an apparently integrated computational workflow may still produce weak or misleading candidate rankings [27].

Practical implications

For natural product drug discovery, phytochemical intelligence provides a practical way to move from broad compound libraries to structured experimental priorities. Open natural-product databases can support reproducible library construction by providing accessible compound records that can be standardized, filtered, and prepared for screening workflows. Their value is greatest when researchers document compound provenance, structural curation, stereochemical assumptions, and preprocessing decisions before screening begins [28].

For phytopharmacology and medicinal chemistry, the framework helps reduce overreliance on isolated computational indicators. A docking score should not be interpreted without target plausibility, a predicted target should not be treated as a confirmed mechanism, an ADMET output should not be treated as a safety conclusion, and a network diagram should not be treated as therapeutic validation. Open knowledge-management initiatives can improve this process by making natural-product information more traceable, reusable, and connected to source and structural evidence [29].

For translational development, the framework encourages interdisciplinary collaboration among natural product chemists, computational scientists, pharmacologists, toxicologists, and medicinal chemists. A sample-centric and knowledge-driven computational workflow can connect natural-product sources, structural annotation, bioactivity evidence, and prioritization logic, but it still requires experimental validation and iterative refinement before candidates can be considered pharmacologically meaningful. In practice, phytochemical intelligence should be implemented as a transparent decision-support workflow that links computational screening to testable hypotheses, not as a substitute for drug development [30].

CONCLUSION

Phytochemical intelligence offers a conceptual framework for connecting virtual screening, target prediction, ADMET profiling, mechanistic filtering, and candidate prioritization in natural product drug discovery. Its central contribution is a structured decision logic that distinguishes weak computational hits from candidates supported by convergent evidence across molecular recognition, target plausibility, pathway relevance, safety risk, developability, validation feasibility, and translational readiness. The framework can support hypothesis generation and experimental prioritization, but its value depends on careful interpretation, transparent reporting, uncertainty assessment, reproducibility, pharmacological plausibility, medicinal chemistry integration, and rigorous experimental validation. It should therefore be used as a disciplined evidence-integration strategy rather than as a claim that computational methods alone can establish efficacy, safety, mechanism of action, or clinical relevance.

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