ADMET Prediction for Plant-Derived Molecules: A State-of-the-Art Review of In Silico Safety, Bioavailability, Toxicity, and Developability Models

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ABSTRACT

Plant-derived molecules remain central to pharmacological discovery because they occupy chemically diverse regions of bioactive chemical space, yet their development is frequently constrained by solubility, permeability, metabolic instability, off-target toxicity, formulation barriers, and uncertain translational performance. In silico ADMET prediction has therefore become an important early-stage strategy for prioritizing phytochemicals, natural products, secondary metabolites, and herbal bioactives before resource-intensive experimental evaluation. This state-of-the-art review examines current computational approaches for predicting safety, bioavailability, pharmacokinetic behavior, toxicity, and developability-relevant liabilities in plant-derived molecules. The review emphasizes molecular representation strategies, including descriptors, fingerprints, SMILES, molecular graphs, and learned embeddings, together with rule-based filters, QSAR, machine learning, deep learning, graph neural networks, multitask models, applicability-domain methods, interpretability tools, and uncertainty-aware prediction. Endpoint coverage is considered across absorption, solubility, permeability, oral bioavailability, distribution, plasma protein binding, blood–brain barrier penetration, CYP450 interaction, transporter effects, clearance, half-life, hepatotoxicity, cardiotoxicity, hERG liability, genotoxicity, mutagenicity, carcinogenicity, reproductive toxicity, skin sensitization, and acute toxicity. The synthesis highlights that computational ADMET models can support early triage, risk flagging, hypothesis generation, and prioritization, but their outputs should not be interpreted as confirmed safety, bioavailability, toxicity, or clinical developability. The main contribution is a developability-oriented framework that links plant-derived chemical diversity with endpoint-specific model selection, validation safeguards, experimental confirmation, and translational readiness. Future progress will depend on better natural-product datasets, scaffold-aware validation, uncertainty reporting, explainability, reproducibility, and integration with pharmacology, toxicology, formulation science, and medicinal chemistry.

Key Words: *ADMET prediction, Plant-derived molecules, Natural products, In silico toxicology, Bioavailability, Developability*

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INTRODUCTION

Plant-derived molecules occupy a distinctive position in pharmaceutical sciences because they combine pharmacological relevance with chemical features that often differ from conventional synthetic screening libraries. Their polyfunctional scaffolds, stereochemical richness, glycosylated structures, macrocyclic motifs, and high oxygenation can support biological activity, but the same features can also complicate absorption, distribution, metabolism, excretion, toxicity, and formulation.

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Computational ADMET prediction has become useful in this setting because tools that estimate pharmacokinetic properties, drug-likeness, and medicinal chemistry friendliness can help identify early liabilities before extensive experimental work is undertaken [1].

A state-of-the-art assessment of plant-derived molecule ADMET prediction must therefore move beyond generic enthusiasm for computational screening. Natural-product ADME prediction is shaped by the fact that many available tools were developed primarily from drug-like or general chemical datasets rather than from experimentally validated plant metabolite collections. As a result, predictions may be informative for early prioritization but require cautious interpretation when applied to structurally complex phytochemicals, herbal bioactives, or secondary metabolites that fall outside the training distribution of conventional models [2].

Natural-product libraries can be profiled computationally for ADME/Tox patterns, and such profiling can reveal broad trends in physicochemical suitability, permeability-related risk, and toxicity alerts across phytochemical chemical space. However, these outputs remain screening-level evidence because database-derived predictions do not establish experimental pharmacokinetics, toxicological safety, biological exposure, or clinical developability. Computational profiling is most defensible when it is used to prioritize candidates, identify possible liabilities, and guide subsequent experimental testing rather than to confirm safety or efficacy [3].

This review aims to synthesize current advances in ADMET prediction for plant-derived molecules with emphasis on in silico safety, bioavailability, toxicity, pharmacokinetic behavior, and developability models. The guiding questions are how current model classes are used for plant-derived molecule triage, which endpoints are most relevant to developability, how molecular representations influence prediction reliability, and what validation safeguards are needed before computational outputs can inform translational decisions. This aim is important because natural products continue to contribute substantially to drug discovery, making early developability assessment a practical requirement rather than a peripheral modeling exercise [4].

Plant-derived molecules and developability challenges

Plant-derived molecule development is constrained by the same ADMET expectations that shape synthetic drug discovery, but the underlying chemical-space problem is different. Natural-product databases contain structurally diverse metabolites that may include unusual ring systems, dense stereochemistry, multiple hydrogen-bonding groups, sugar residues, conjugated polyphenolic scaffolds, and complex substitution patterns. These features can support biological recognition while also challenging solubility, membrane permeability, metabolic stability, and computational model fit. Natural-product database reviews show that the usefulness of in silico screening depends heavily on the quality, completeness, curation, and structural consistency of the chemical data used for prediction [5].

Open natural-product collections have improved the feasibility of large-scale computational screening by making phytochemical structures more accessible for cheminformatics and ADMET workflows. Such resources allow researchers to compare compound libraries, explore chemical diversity, calculate descriptors, and submit structures to ADMET platforms for early prioritization. Nevertheless, the existence of a searchable structure does not mean that the compound has reliable endpoint labels, standardized assay data, or experimentally verified pharmacokinetic and toxicity information. Open structural databases therefore support screening breadth, but they do not remove the need for endpoint-specific evidence [6].

Recent expansion and curation of natural-product databases strengthens the foundation for computational developability assessment by improving access to larger and more organized plant-derived chemical spaces. This development is particularly valuable for ADMET prediction because model applicability depends partly on whether the query molecule resembles the chemical space represented in model training or validation data. However, expanded structure coverage should not be confused with expanded biological or toxicological annotation; many plant-derived molecules remain under-characterized with respect to permeability, transporter interaction, metabolic fate, plasma protein binding, clearance, and toxicity endpoints [7].

Plant-derived ADMET case studies illustrate how computational profiling is commonly used to prioritize phytochemicals, flag possible safety risks, and assess drug-likeness before experimental testing. Such studies are useful because they connect molecular structures to predicted pharmacokinetic and toxicity properties in a practical screening workflow. Their limitation is that predicted ADMET suitability does not prove oral exposure, metabolic stability, low toxicity, or developability in vivo. For plant-derived molecules, in silico ADMET results should therefore be interpreted as decision-support evidence that helps determine which compounds deserve further pharmacology, toxicology, formulation, and medicinal chemistry evaluation [8].

Table 1 summarizes the major developability challenges that affect plant-derived molecules and explains how ADMET prediction can support early-stage prioritization without replacing experimental validation.

Table 1. Developability Challenges for Plant-Derived Molecules in ADMET Prediction: Chemical Complexity, Bioavailability Constraints, Pharmacokinetic Liabilities, Safety Risks, Model-Relevance Issues, and Validation Needs

Developability challenge	Plant-derived molecule feature involved	ADMET domain affected	Why it matters for development	In silico assessment approach	Interpretation limitation	Experimental validation need	Translational implication	Research priority
Structural complexity	Multiple rings, stereocenters, oxygenated scaffolds, conjugated systems	Cross-cutting ADMET	Complex structures may fall outside conventional model training space	Descriptor, fingerprint, and graph-based profiling	Similarity to training data may be uncertain	Confirm key ADMET endpoints experimentally	Prediction confidence may be lower for unusual scaffolds	Build and validate natural-product-aware ADMET datasets
Glycosylation and high polarity	Sugar residues, many hydrogen-bond donors and acceptors	Absorption, permeability, bioavailability	Polar structures may show limited passive permeability	Solubility, permeability, oral bioavailability, and transporter prediction	Models may not capture enzymatic cleavage or gut metabolism	Caco-2, PAMPA, intestinal uptake, and metabolism assays	Oral exposure may require formulation or prodrug strategies	Integrate gut metabolism and transporter data
Polyphenolic scaffolds	Phenolic groups, tannin-like motifs, redox-active structures	Absorption, metabolism, toxicity	Polyphenols may show poor permeability, rapid conjugation, or assay interference	Physicochemical profiling, metabolism prediction, toxicity-alert screening	Predicted activity may be confounded by promiscuity or assay artifacts	Metabolic stability, conjugation, and cytotoxicity assays	Candidate ranking should consider exposure and specificity	Develop models sensitive to assay interference and conjugation
Macrocycles and rigid scaffolds	Large rings, constrained conformations	Permeability, distribution, metabolism	Macrocycles may violate simple drug-likeness rules but still be bioactive	Conformation-aware descriptors, graph models, and permeability prediction	Rule-based filters may over-penalize noncanonical structures	Permeability, solubility, and plasma protein binding studies	Noncanonical scaffolds need endpoint-specific evaluation	Improve conformational and 3D-aware ADMET modeling
Solubility limitation	Hydrophobic cores, aromatic density, crystallinity	Absorption, formulation, bioavailability	Low solubility can limit exposure despite potency	Aqueous solubility and formulation-risk prediction	Calculated solubility may not reflect salt form, excipients, or solid state	Equilibrium solubility, dissolution, and formulation studies	Poor solubility may require formulation intervention	Connect prediction with formulation-relevant data
Permeability limitation	High polarity, ionizable groups, bulky substituents	Absorption, distribution	Poor permeability can restrict oral and tissue exposure	Caco-2, passive permeability, P-gp substrate prediction	Transporter and metabolism effects may be assay-context dependent	Cell-based permeability and transporter assays	Early triage should distinguish passive and active transport	Expand transporter-labeled phytochemical datasets
Metabolic instability	Labile esters, phenols, glycosides, conjugation-prone groups	Metabolism, clearance, half-life	Rapid metabolism may reduce systemic exposure	CYP450, phase II metabolism, metabolic stability, and metabolite prediction	Many models emphasize CYP inhibition over complete metabolic fate	Microsomal stability, hepatocyte assays, metabolite identification	Predicted metabolic risk should guide experimental metabolism studies	Improve phase II and metabolite-formation modeling
Off-target toxicity	Electrophilic motifs, redox activity, membrane disruption,	Toxicity and safety	Natural origin does not guarantee safety	Toxicity-alert, hepatotoxicity, hERG, mutagenicity, and acute	Toxicity predictions are endpoint-specific and	In vitro and in vivo toxicology confirmation	Safety screening must precede translational claims	Build endpoint-specific toxicology

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	promiscuous binding			toxicity prediction	assay-dependent			validation pipelines
Chemical-space mismatch	Natural-product scaffolds underrepresented in drug-like datasets	Model validation	Predictions may be unreliable outside model domain	Applicability-domain analysis, similarity assessment, uncertainty estimation	Domain warnings may be absent or incomplete	External validation on relevant phytochemical sets	Low-confidence predictions should not drive high-stakes decisions	Require domain reporting for plant-derived molecules
Compound availability and reproducibility	Low abundance, isolation difficulty, batch variability	Developability, validation	Limited material can delay experimental confirmation	Prioritization using ADMET and developability filters	Prediction cannot solve sourcing or standardization problems	Purity, identity, stability, and batch reproducibility testing	Computational triage should consider feasibility of follow-up	Link ADMET screening with supply and standardization criteria

ADMET modeling approaches

Modern ADMET modeling platforms increasingly integrate multiple endpoints into a single computational workflow, allowing researchers to estimate physicochemical properties, absorption, distribution, metabolism, excretion, and toxicity-related liabilities from molecular structure. Multi-endpoint platforms are useful for plant-derived molecule screening because they allow the same phytochemical structure to be evaluated across several developability dimensions. Their practical value is strongest when predictions are treated as endpoint-specific alerts rather than as a single composite judgment of drug-likeness or safety [9].

Recent platform updates illustrate the shift from isolated endpoint calculators toward broader ADMET decision-support systems that combine expanded endpoint coverage, improved model infrastructure, and workflow accessibility. This matters for plant-derived molecules because early triage often requires simultaneous consideration of solubility, permeability, metabolic interaction, transporter behavior, toxicity alerts, and uncertainty. Even so, platform breadth does not eliminate the need to check whether a phytochemical lies within the model's applicability domain or whether the endpoint was validated on chemically relevant examples [10].

Scalable machine learning ADMET systems are especially relevant for large natural-product libraries because they can rapidly prioritize compounds before experimental resources are committed. These systems may combine descriptors, fingerprints, graph-derived features, and multitask learning to estimate multiple endpoints across large chemical collections. For plant-derived molecule development, the main advantage is throughput; the main risk is that large-scale prediction may generate confident-looking outputs for compounds whose structural features are weakly represented in the training data [11].

Graph-based molecular property frameworks and attention-based ADMET models illustrate the growing importance of learned molecular representations. Message-passing neural network software supports reproducible molecular property modeling workflows when users provide appropriate datasets, training protocols, and validation strategies [12]. Attention-based graph neural networks using SMILES-derived molecular structures show how ADMET prediction can move beyond fixed descriptors toward learned representations, although reliability still depends on endpoint quality, chemical-space coverage, validation design, and interpretability [13].

Table 2 compares major computational ADMET modeling approaches used for plant-derived molecules by input representation, prediction endpoint, validation strategy, interpretability, and practical utility.

Table 2. Computational ADMET Modeling Approaches for Plant-Derived Molecules: Molecular Representations, Model Families, Prediction Endpoints, Validation Strategies, Strengths, Limitations, Interpretability, and Developability Utility

Modeling approach	Molecular representation	Typical ADMET endpoint	Learning or inference strategy	Validation approach	Main strength	Main limitation	Interpretability concern	Developability utility
Rule-based filters	Physicochemical descriptors, structural alerts, threshold rules	Drug-likeness, solubility risk, permeability	Expert-derived rules and property cutoffs	Comparison with known drug-like or toxicophore patterns	Fast, transparent, easy to apply early	May over-penalize noncanonical natural products	Rules may simplify complex exposure and	Useful for initial triage and flagging obvious liabilities

		risk, toxicity alerts					toxicity mechanisms	
QSAR models	Descriptors, fingerprints, structural fragments	Solubility, permeability, CYP inhibition, toxicity endpoints	Statistical or machine learning relationship between structure and endpoint	Internal validation, external test sets, applicability-domain assessment	Mature and endpoint-specific	Reliability declines outside training domain	Descriptor contribution may be hard to map biologically	Supports endpoint-specific prioritization when domain fit is checked
Molecular descriptor models	Topological, physicochemical, electronic, and constitutional descriptors	ADME and toxicity endpoints	Regression or classification from calculated molecular features	Cross-validation and external validation	Captures interpretable molecular properties	Descriptor selection can bias results	Mechanistic meaning may be partial	Helps connect structure features with developability risk
Molecular fingerprint models	Binary or count-based structural fingerprints	Toxicity, metabolism, transporter interaction, bioavailability	Similarity-based or supervised learning	Scaffold split or external validation preferred	Efficient for large libraries	Fragment patterns may miss stereochemical and conformational effects	Fingerprint bits may not be chemically intuitive	Useful for rapid screening of natural-product databases
Pharmacophore-based modeling	3D feature arrangements, hydrogen-bonding patterns, hydrophobic features	Target-related liability, transporter or enzyme interaction when relevant	Feature-matching or supervised pharmacophore classification	Retrospective ligand validation and prospective testing	Can reflect spatial recognition patterns	Depends on conformer quality and ligand set relevance	Model may overfit known ligand features	Helpful for hypothesis generation around interaction liabilities
Machine learning classifiers	Descriptors, fingerprints, hybrid molecular features	CYP inhibition, P-gp interaction, hERG liability, hepatotoxicity, broad toxicity	Random forest, support vector machine, gradient boosting, ensemble learning	Internal validation, external validation, scaffold-aware testing	Strong practical performance in many endpoint tasks	Sensitive to dataset bias and label heterogeneity	Feature importance may not fully explain prediction	Supports scalable endpoint-specific risk flagging
Deep learning models	Learned embeddings, molecular graphs, sequence-like molecular inputs	Multi-endpoint ADMET prediction	Neural networks, multitask architectures, representation learning	Benchmark datasets, holdout sets, external validation where available	Learns complex nonlinear patterns	Data-hungry and vulnerable to domain shift	Black-box behavior can reduce decision confidence	Useful for large-scale triage when uncertainty is reported
Graph neural networks	Molecular graph nodes, bonds, atom and bond features	ADME, toxicity, molecular property prediction	Message passing, graph attention, graph convolution	Benchmark comparison and external testing	Represents molecular connectivity directly	May still miss 3D conformation, stereochemistry, and assay context	Attention weights are not always mechanistic explanations	Valuable for structurally diverse phytochemical screening
SMILES-based models	Molecular strings or SMILES-derived graphs	Multi-endpoint ADMET	Sequence learning, graph conversion, attention mechanisms	Benchmark and endpoint-specific validation	Easy input format and scalable processing	SMILES ambiguity and representation choices can affect learning	Learned tokens may be difficult to interpret chemically	Useful for automated database-scale prediction workflows

Transformer-based molecular models	Molecular strings, learned tokens, molecular embeddings, multimodal inputs	General molecular property and ADMET endpoint prediction	Self-attention and pretrained molecular representation learning	External validation and domain-transfer testing required	Can learn reusable molecular representations	Requires large, high-quality datasets and careful fine-tuning	Attention does not guarantee causal interpretation	Promising for transfer learning across sparse ADMET endpoints
Multitask learning	Shared molecular features across several endpoints	Broad ADMET panels	Joint learning of related endpoint tasks	Endpoint-level and task-level validation	Can exploit relationships among endpoints	Poor labels in one task can affect others	Shared representations may obscure endpoint-specific drivers	Useful for integrated developability screening
Transfer learning	Pretrained molecular embeddings or models adapted to ADMET tasks	Sparse ADMET endpoints, toxicity endpoints	Pretraining followed by endpoint-specific fine-tuning	External testing in target chemical space	May help when endpoint labels are limited	Transfer may fail across dissimilar chemical spaces	Source-task influence may be opaque	Useful for rare or under-labeled plant-derived endpoints
Applicability-domain methods	Similarity metrics, distance to training set, confidence region	Any ADMET endpoint	Domain estimation around model training space	External validation and domain-error analysis	Helps identify unreliable predictions	Domain definitions differ across models	Domain warnings may be hard for non-specialists to interpret	Essential for chemically diverse natural products
Explainable AI and uncertainty estimation	Feature attribution, confidence intervals, calibrated probabilities, uncertainty scores	Toxicity, ADME, multi-endpoint decision support	Post hoc explanation, uncertainty-aware modeling, calibrated prediction	Calibration, explanation stability, external validation	Improves decision transparency	Explanations may not be mechanistic proof	Misleading explanations can create false confidence	Supports translational triage and prioritization decisions

Absorption, distribution, metabolism, and excretion prediction

Absorption prediction for plant-derived molecules begins with the recognition that solubility, permeability, ionization, polarity, and transporter interaction jointly shape whether a compound can reach systemic exposure after oral administration. Broad ADMET web services can estimate multiple absorption-related and pharmacokinetic endpoints from molecular structure, including properties relevant to solubility, permeability, blood–brain barrier penetration, metabolism, and toxicity. For plant-derived molecules, these predictions are most useful when they are interpreted as an integrated profile rather than as isolated pass-or-fail outputs, because a compound with acceptable predicted solubility may still be limited by efflux, metabolism, instability, or formulation barriers [14].

Metabolism prediction is especially important for phytochemicals because many plant-derived structures contain phenolic, glycosidic, ester, lactone, or other metabolically labile groups. CYP450 inhibition models can help flag possible metabolic interaction liabilities, including the possibility that a plant-derived molecule may alter the metabolism of co-administered drugs. Such predictions are valuable for prioritizing experimental CYP inhibition, induction, and metabolic stability studies, but they should not be treated as direct evidence of in vivo drug–drug interaction risk because enzyme expression, concentration, metabolites, transporter coupling, and tissue context influence actual pharmacokinetic outcomes [15].

Transporter prediction is another central ADME concern because intestinal uptake, efflux, biliary handling, and tissue distribution can be strongly affected by transporter recognition. P-glycoprotein substrate and inhibitor prediction can support early interpretation of whether a plant-derived molecule may show restricted intestinal absorption, limited brain penetration, altered tissue exposure, or transporter-mediated interaction potential. Rule-based or decision-tree transporter models can offer more interpretable outputs than fully opaque models, but their endpoint specificity means that P-glycoprotein prediction alone cannot represent the full transporter landscape relevant to absorption, distribution, and excretion [16].

Distribution, clearance, and half-life prediction should be interpreted as screening guidance rather than confirmed pharmacokinetic behavior. Plant-derived molecules may

bind strongly to plasma proteins, partition into tissues, undergo rapid conjugation, or be eliminated through pathways that are incompletely represented in general training datasets. Applicability-domain-aware ADMET tools are therefore important because they help users recognize when a query molecule may be too dissimilar from training compounds for confident interpretation. In plant-derived chemical space, model-domain assessment is not a technical detail; it is a prerequisite for responsible prioritization before experimental pharmacokinetic evaluation [17].

Toxicity and safety screening

Toxicity prediction for plant-derived molecules must start from the principle that natural origin does not establish safety. Computational toxicity servers can help flag potential liabilities such as acute toxicity, hepatotoxicity, mutagenicity, carcinogenicity, immunotoxicity, or other endpoint-specific alerts, but these outputs are hypotheses for further testing rather than toxicological confirmation. This distinction is especially important for phytochemicals because structural alerts, redox activity, electrophilicity, promiscuous binding, assay interference, or metabolite-mediated effects may not be fully captured by a single model or endpoint panel [18].

Updated toxicity platforms have expanded the practical scope of in silico safety screening by adding broader endpoint coverage and more accessible workflows for chemical hazard prioritization. For plant-derived molecules, such systems can support early exclusion of high-risk candidates, selection of compounds for targeted toxicology assays, and comparison of related analogues or extracts at the molecular level. Nevertheless, toxicity predictions remain sensitive to dataset quality, endpoint definition, assay heterogeneity, and chemical-space coverage, meaning that predicted non-toxicity should not be interpreted as proof of biological safety [19].

Cardiotoxicity and hepatotoxicity represent two high-priority safety domains for developability assessment. hERG inhibition prediction is useful because hERG liability is a widely recognized computational alert for cardiac safety risk, but hERG prediction is not equivalent to comprehensive cardiotoxicity assessment because cardiac risk can involve multiple ion channels, metabolites, exposure levels, and physiological contexts [20]. Hepatotoxicity prediction similarly requires endpoint-specific models and cautious interpretation, because liver injury can arise through diverse mechanisms including reactive metabolites, mitochondrial stress, bile-acid transport disruption, oxidative stress, immune-mediated injury, and dose-dependent exposure effects [21].

A state-of-the-art view of plant-derived molecule toxicity prediction must therefore integrate endpoint coverage with uncertainty, interpretability, and experimental confirmation. AI-based toxicity prediction has advanced rapidly, but its translational use remains constrained by label inconsistency, data imbalance, limited mechanistic transparency, and incomplete external validation across diverse chemical scaffolds. For plant-derived molecules, the safest interpretation is that computational toxicity models can prioritize experiments, identify plausible liabilities, and improve early triage, while in vitro and in vivo toxicology remain necessary for safety confirmation [22].

Model validation and translational readiness

Reliable ADMET prediction depends on validation practices that match the decision being made. Internal validation can help detect overfitting during model development, but it is insufficient when predictions are used to prioritize chemically unusual plant-derived molecules. External validation, applicability-domain assessment, transparent reporting, and reproducible workflows are needed to determine whether a model is likely to perform on new phytochemical scaffolds. Applicability-domain-aware QSAR frameworks demonstrate why prediction reliability should be evaluated in relation to chemical similarity, training-space coverage, and endpoint-specific model limits [23].

Uncertainty estimation and explainability are increasingly important because ADMET predictions are often used to decide which molecules progress to experimental testing. A probability score, classification label, or predicted endpoint value is more useful when accompanied by uncertainty information, calibration evidence, and interpretable molecular features that explain why the model produced the output. Explainable uncertainty quantification is particularly relevant for deep learning models, where high predictive performance on benchmark datasets may not guarantee reliability for structurally complex or underrepresented natural products [24].

Translational readiness also requires a clear distinction between screening-level prediction, preclinical relevance, clinical safety, and regulatory acceptability. A predicted permeability class does not prove oral bioavailability; a predicted lack of hERG liability does not establish cardiac safety; and a predicted favorable ADMET profile does not demonstrate developability. Responsible interpretation requires linking model outputs to follow-up experiments, including solubility and dissolution testing, permeability assays, metabolic stability studies, CYP and transporter assays, plasma protein binding, hepatotoxicity panels, genotoxicity testing, and appropriate in vivo pharmacokinetic or toxicology studies when development decisions justify them.

For plant-derived molecules, validation should also account for chemical identity, stereochemical specification, purity, batch consistency, and biological context. Many phytochemicals occur in mixtures, undergo degradation, or are transformed by gut microbiota and host metabolism, so the modeled parent compound may not be the only biologically relevant species. Translational use of ADMET prediction is therefore strongest when computational outputs are embedded within a broader developability workflow that includes analytical chemistry, pharmacology, toxicology, formulation, medicinal chemistry, and reproducible experimental confirmation.

Table 3 synthesizes validation and translational-readiness requirements for using ADMET predictions in plant-derived molecule development.

Table 3. Validation and Translational-Readiness Requirements for ADMET Prediction of Plant-Derived Molecules: Applicability Domain, External Validation, Experimental Confirmation, Interpretability, Uncertainty, Reproducibility, and Implementation Needs

Validation or readiness requirement	Modeling stage affected	Underlying concern	Quality-control action	Evidence needed	Interpretability requirement	Translational risk if ignored	Mitigation strategy	Future research need
Applicability-domain assessment	Prediction and interpretation	Plant-derived scaffolds may differ from training compounds	Report similarity, domain status, or confidence region	Chemical-space comparison against training data	Explain whether the molecule is inside or outside model domain	False confidence in out-of-domain predictions	Treat out-of-domain outputs as low-confidence screening alerts	Natural-product-specific domain benchmarks
External validation	Model evaluation	Internal validation may overestimate performance	Test on independent compounds and scaffold-diverse sets	Endpoint-specific external test results	Explain performance limits by endpoint and scaffold	Poor generalization to new phytochemicals	Require independent validation before decision use	Curated external ADMET sets for phytochemicals
Scaffold-aware evaluation	Model benchmarking	Random splits can inflate performance when analogues overlap	Use scaffold split or structure-aware validation	Performance across structurally distinct scaffolds	Identify structural classes with lower reliability	Over-ranking familiar scaffolds and underestimating novelty risk	Combine random, temporal, and scaffold-aware testing	Standardized scaffold-validation protocols
Endpoint-specific benchmarking	Model comparison	ADMET endpoints differ in assay quality and mechanism	Benchmark models separately for each endpoint	Endpoint-level metrics and assay definitions	Explain endpoint boundaries and label sources	Treating broad ADMET prediction as uniformly reliable	Use endpoint-by-endpoint decision thresholds	Better benchmark datasets for sparse endpoints
Experimental confirmation	Post-prediction decision stage	Prediction is not biological confirmation	Prioritize assays based on predicted risk	Permeability, solubility, metabolism, toxicity, and PK data	Link predicted feature to experimental hypothesis	Advancing unsafe or non-exposed candidates	Use prediction to guide, not replace, experiments	Prospective validation studies in plant-derived molecules
Uncertainty estimation	Prediction reporting	Point predictions may hide low confidence	Report calibrated probability, confidence interval, or uncertainty score	Calibration and uncertainty-performance analysis	Explain how uncertainty should affect action	Overinterpreting uncertain model outputs	Use uncertainty thresholds for triage	Routine uncertainty reporting in ADMET tools
Explainability	Model interpretation	Black-box predictions may be hard to act upon	Provide feature attribution, structural alerts, or rationale	Stable and chemically meaningful explanations	Distinguish explanation from mechanistic proof	Misguided optimization or false mechanistic inference	Pair explanations with experimental	Explanation methods validated for ADMET endpoints

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							mechanism studies	
Reproducibility	Model use and reporting	Predictions may vary across versions, settings, or input forms	Report tool version, input structure, parameters, and preprocessing	Re-runnable workflows and archived inputs	Clarify assumptions and preprocessing decisions	Irreproducible prioritization decisions	Standardize reporting templates	FAIR ADMET prediction reporting standards
Chemical identity control	Input preparation	Stereochemistry, tautomer state, salt form, and glycosides affect prediction	Curate structures before modeling	Verified structures and standardized representations	Explain structural choices used for prediction	Wrong molecular input leads to wrong ADMET inference	Use expert curation and multiple relevant forms	Better tools for natural-product structure standardization
Translational integration	Development decision-making	Model output alone cannot define developability	Combine ADMET prediction with pharmacology, toxicology, formulation, and medicinal chemistry	Integrated evidence package	Explain how each evidence type contributes	Premature claims of safety or developability	Stage-gated decision framework	Prospective workflows linking prediction to development outcomes

State-of-the-art synthesis

The state-of-the-art evidence base indicates that ADMET prediction for plant-derived molecules is most mature as an early screening and prioritization strategy rather than as a confirmatory developability tool. Computational toxicity methods for bioactive natural products can help organize safety concerns, identify candidate liabilities, and support rational selection of follow-up experiments, but their outputs must be interpreted in light of endpoint specificity, chemical-space coverage, and experimental uncertainty. This is particularly important because plant-derived compounds may be structurally complex, biologically promiscuous, or metabolically transformed into active or toxic species that are not captured by parent-compound prediction alone [25].

Next-generation ADMET prediction is moving toward broader endpoint integration, machine learning and deep learning workflows, uncertainty-aware decision support, and more explicit attention to translational use. These developments are promising for plant-derived molecule research because they can connect natural-product libraries with scalable screening, endpoint-specific risk flagging, and more systematic developability assessment. However, the strongest future direction is not simply larger or more complex models; it is better alignment among data quality, molecular representation, validation design, interpretability, uncertainty estimation, experimental confirmation, and practical development decisions [26].

Figure 1 presents a state-of-the-art synthesis framework linking plant-derived chemical diversity, ADMET model inputs, endpoint prediction, validation safeguards, and translational readiness.

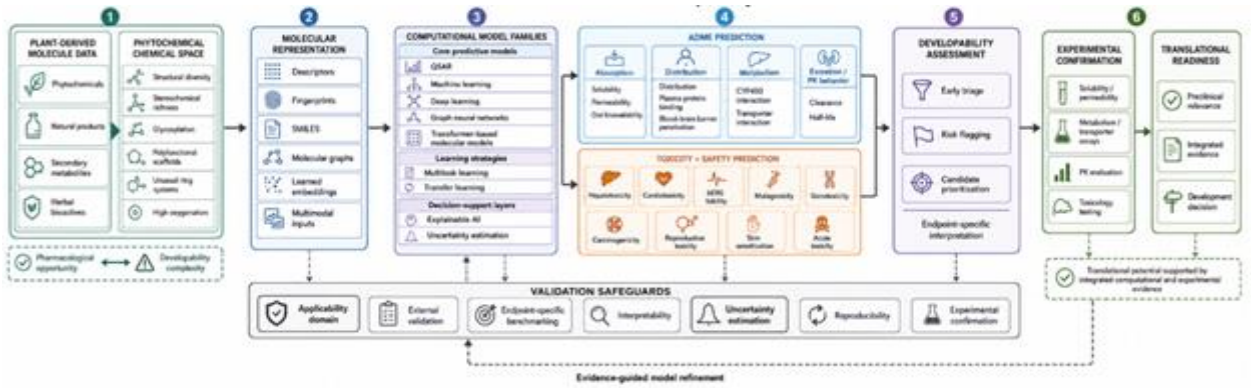

Figure 1. State-of-the-Art Framework for ADMET Prediction and Developability Assessment of Plant-Derived Molecules

Alt-text description: A conceptual framework showing plant-derived molecules and phytochemical data flowing into molecular representation strategies such as descriptors, fingerprints, SMILES, molecular graphs, and learned embeddings. These inputs feed into computational models such as QSAR, machine learning, deep learning, graph neural networks, transformer-based models, multitask learning, and explainable AI. Model outputs are organized into absorption, distribution, metabolism, excretion, toxicity, safety screening, and developability assessment, with validation safeguards and translational-readiness checkpoints before experimental and preclinical use.

Across endpoint domains, absorption and basic physicochemical prediction appear comparatively mature because solubility, permeability, drug-likeness, and related descriptors are widely implemented in practical ADMET platforms. Metabolism and transporter predictions are also increasingly useful, especially for CYP450 inhibition and P-glycoprotein interaction, but they remain incomplete proxies for metabolic stability, metabolite formation, induction, tissue-specific transporter behavior, and in vivo clearance. For plant-derived molecules, the key synthesis point is that ADME prediction is strongest when it identifies specific experimental questions rather than when it is used to rank compounds by a generalized notion of "good" or "bad" pharmacokinetics.

Toxicity prediction is advancing through broader endpoint panels and more sophisticated model families, but it remains limited by heterogeneous labels, endpoint-specific mechanisms, class imbalance, and uncertain transferability to natural-product chemical space. hERG and hepatotoxicity prediction are useful examples of endpoint-focused safety modeling, yet neither can stand in for comprehensive toxicology. Mutagenicity, genotoxicity, carcinogenicity, reproductive toxicity, skin sensitization, and acute toxicity prediction require the same caution: computational alerts can support triage, but experimental toxicology determines whether the predicted concern is biologically meaningful under relevant exposure conditions.

The practical state-of-the-art is therefore an integrated, stage-gated workflow. Plant-derived structures should first be curated and standardized, then represented using complementary molecular descriptors, fingerprints, SMILES, graphs, and learned embeddings. Predictions should then be interpreted endpoint by endpoint, checked against applicability domain and uncertainty, and prioritized according to the specific development question. Compounds with promising predicted profiles should still undergo experimental confirmation, while compounds with predicted liabilities should be examined for whether the liability is plausible, modifiable, exposure-dependent, or an artifact of model-domain mismatch. This integrated approach keeps ADMET prediction useful while avoiding overclaiming.

CONCLUSION

This state-of-the-art review positions ADMET prediction for plant-derived molecules as a decision-support strategy for in silico safety, bioavailability, toxicity, pharmacokinetic, and developability assessment. Computational models can support early prioritization, risk flagging, and hypothesis generation, especially when they integrate molecular representation, endpoint-specific prediction, applicability-domain assessment, uncertainty estimation, interpretability, and reproducible reporting. However, predicted ADMET suitability is not equivalent to confirmed safety, exposure, toxicity, or clinical developability. Reliable development of plant-derived molecules requires computational prediction to be integrated with pharmacology, toxicology, formulation science, medicinal chemistry, analytical validation, and experimental pharmacokinetic evidence.

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