Molecular Docking, Molecular Dynamics, and Machine Learning in Phytopharmacology: An Umbrella Review of Computational Evidence for Natural Product Therapeutics

Sofía Martínez[1]*, Carlos Gómez[1], Lucia Navarro[2]

[1]Department of AI for Anticancer Phytochemicals, Faculty of Pharmacy, Complutense University of Madrid, Madrid, Spain.
[2]Department of Machine Learning for Bioactive Natural Products, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain.

ABSTRACT

Phytopharmacology and natural product therapeutics remain important areas of drug discovery because medicinal plants, phytochemicals, marine metabolites, microbial products, and natural product scaffolds continue to provide biologically meaningful chemical diversity. Computational methods are increasingly used to prioritize this chemical space, but the interpretive strength of in silico evidence varies across molecular docking, molecular dynamics, machine learning, network pharmacology, ADMET prediction, toxicity screening, and virtual screening workflows. This umbrella review synthesizes review-level evidence on how these computational approaches are used to support natural product therapeutic prioritization while distinguishing computational plausibility from pharmacological proof. The review focuses on molecular docking as a method for ligand–target prioritization, binding-site hypothesis generation, and virtual screening; molecular dynamics as a method for examining interaction stability, conformational behavior, and post-docking plausibility; and machine learning as a method for bioactivity prediction, target prediction, ADMET modeling, toxicity prediction, QSAR, database mining, and lead prioritization. Cross-method synthesis is used to evaluate whether convergent computational evidence strengthens hypothesis generation or risks reinforcing uncertainty when methods share biased inputs, poorly curated structures, weak target assumptions, or limited validation. The review identifies recurring gaps in methodological reporting, reproducibility, dataset quality, applicability-domain assessment, experimental confirmation, and translational interpretation. Overall, computational phytopharmacology can support rational prioritization and mechanism-oriented hypothesis generation, but therapeutic claims require reproducible workflows, verified chemical structures, transparent evidence synthesis, pharmacological validation, and translationally relevant experimental confirmation.

Key Words: *Phytopharmacology, Natural products, Molecular docking, Molecular dynamics, Machine learning, Umbrella review*

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INTRODUCTION

Natural products remain a major foundation for drug discovery because they provide structurally diverse and biologically active scaffolds that have repeatedly contributed to pharmacologically relevant compounds. Contemporary phytopharmacology extends this tradition by examining medicinal plants, phytochemicals, marine and microbial metabolites, and natural product-inspired scaffolds as sources of therapeutic hypotheses. However,

Corresponding author: Sofía Martínez
Address: Department of AI for Anticancer Phytochemicals, Faculty of Pharmacy, Complutense University of Madrid, Madrid, Spain.
E-mail: ✉ sofia.martinez@ucm.es
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natural product discovery also faces persistent challenges, including compound complexity, supply limitations, structural characterization issues, target uncertainty, pharmacokinetic liabilities, toxicity concerns, and the need for robust validation before therapeutic interpretation [1, 2].

Computational methods have become increasingly prominent in natural product research because they can help organize complex chemical spaces, prioritize candidate compounds, infer possible targets, and generate testable mechanism hypotheses. Artificial intelligence and cheminformatics approaches have expanded the capacity to explore natural product libraries, compare molecular representations, and triage compounds before resource-intensive experimental work [3]. In this context, computational phytopharmacology is best understood as a hypothesis-generating and prioritization domain rather than as a substitute for wet-lab pharmacology.

The current computational natural product literature is distributed across several partially overlapping methodological traditions. Molecular docking reviews emphasize ligand–target fit and binding-site plausibility, molecular dynamics reviews focus on conformational behavior and interaction stability, and machine-learning reviews address prediction, classification, prioritization, and database-scale pattern recognition. Recent reviews of artificial intelligence for natural product drug discovery further show that these methods increasingly depend on data quality, model interpretability, reliable structure annotation, and experimental follow-up [4].

This umbrella review aims to synthesize review-level evidence on molecular docking, molecular dynamics, and machine learning in phytopharmacology and natural product therapeutics. The review asks how existing review literature characterizes docking, dynamics, and machine-learning workflows; which natural product and therapeutic domains are most frequently discussed; where cross-method convergence appears useful; and which validation, reproducibility, reporting, and translational gaps limit the strength of computational evidence.

Umbrella review rationale

An umbrella review is appropriate when a field contains multiple review-level literatures that summarize related evidence but differ in scope, terminology, method emphasis, and interpretive standards. Computational phytopharmacology is such a field because molecular docking, molecular dynamics, network pharmacology, machine learning, ADMET modeling, and toxicity prediction are often reviewed separately, even when they are combined in practical natural product discovery workflows. Transparent reporting and credibility-aware interpretation are therefore necessary to avoid presenting a collection of review claims as if all were equally rigorous [5, 6].

The rationale for umbrella synthesis is also strengthened by the risk of evidence overlap. Reviews on medicinal plants, phytochemicals, Chinese medicine formulae, marine natural products, viral targets, cancer targets, inflammation, metabolic disease, and antimicrobial discovery may repeatedly cite similar primary docking or network-pharmacology studies. Without attention to overlap, an apparent consensus across reviews may reflect repeated reuse of the same computational studies rather than independent convergence across evidence streams [7].

A further reason for umbrella review logic is the need to separate computational plausibility from therapeutic evidence. Docking can suggest plausible ligand–target interactions, but docking scores do not confirm binding, pharmacological activity, safety, or efficacy. Molecular dynamics can examine whether predicted interactions remain stable under simulated conditions, but simulation stability does not establish biological effect. Machine learning can support prediction and prioritization across large chemical datasets, but predictive performance depends on training data, validation design, molecular representation, and applicability domain.

This umbrella review therefore treats review-level evidence as a structured interpretive layer rather than as direct proof of therapeutic activity. The synthesis focuses on what the review literature supports, what remains uncertain, and where computational claims require experimental confirmation. This design is intended to clarify how docking, molecular dynamics, and machine learning can contribute to natural product therapeutic prioritization while avoiding inflated conclusions about clinical or pharmacological efficacy.

Review-level evidence sources

The umbrella review scope covers peer-reviewed review-level evidence on computational phytopharmacology, natural product therapeutics, medicinal plant research, phytochemical screening, natural product databases, network pharmacology, docking, molecular dynamics, machine learning, ADMET prediction, toxicity prediction, QSAR, and virtual screening. Review-level sources were prioritized when they synthesized methodological applications, evidence patterns, therapeutic domains, validation gaps, or reproducibility concerns. Reviews of medicinal-plant network pharmacology were included because they often connect phytochemical identification, target prediction, pathway inference, and molecular docking within multi-target therapeutic hypotheses [8].

Evidence-source classification also considered the role of phytochemical and natural product databases. Computational review claims depend strongly on the

quality, coverage, curation, and standardization of compound structures and activity annotations. Review-level evidence on phytochemical structure and activity databases therefore supports the extraction of database-related limitations, including uneven compound coverage, inconsistent metadata, and variable suitability for docking, QSAR, machine learning, and target-prediction workflows [9].

Although review-level literature forms the main evidence base, selected primary database or methodological sources can be used narrowly when they clarify the infrastructure underlying computational phytopharmacology. Curated regional natural product databases, for example, are relevant because they expand searchable chemical space and affect the compounds available for virtual screening, docking, and machine-learning workflows [10]. Such sources are not treated as therapeutic evidence; they are used only to clarify evidence-source diversity and data-infrastructure relevance.

Eligibility assessment prioritized sources that allowed extraction of review type, natural product category, disease or therapeutic area, computational method, evidence scope, validation status, methodological limitation, overlap concern, translational relevance, and risk of overclaiming. In silico ADME reviews were included because developability prediction is frequently used to filter natural product candidates after docking, network pharmacology, or machine-learning prioritization, but ADME prediction remains dependent on model assumptions, compound representation, and applicability to natural product chemical space [11].

Table 1 summarises the umbrella review evidence-source framework used to classify review-level computational phytopharmacology evidence.

Table 1. Umbrella Review Evidence-Source Framework for Computational Phytopharmacology: Review Type, Natural Product Category, Therapeutic Area, Computational Method, Evidence Scope, Validation Status, Overlap Concern, Translational Relevance, and Risk of Overclaiming

Evidence-source dimension	Operational definition	Coding categories	Information extracted	Reason for inclusion	Risk of bias or limitation	Reporting safeguard
Review type	The evidence-synthesis design or article function used by the source.	Umbrella review; systematic review; scoping review; bibliometric review; integrative review; narrative review with structured synthesis; methodological review; primary study used only for method clarification.	Article type, synthesis style, methodological transparency, and relevance to review-level interpretation.	Distinguishes review-level evidence from primary computational studies and method-only sources.	Narrative reviews may vary in search transparency and selectivity.	Avoid treating all review types as equal in evidentiary strength.
Natural product category	The biological or chemical origin of the compounds discussed.	Medicinal plants; phytochemicals; marine natural products; microbial natural products; natural product-inspired scaffolds; natural-product databases; broad natural products.	Compound class, source domain, database or library type, and phytopharmacological relevance.	Ensures that sources are relevant to natural product therapeutics rather than general synthetic chemistry alone.	Some reviews mix natural and synthetic compounds without clear separation.	Attribute claims only to the natural product-relevant portion of the evidence.
Therapeutic or disease area	The pharmacological or disease domain addressed by the review.	Cancer; inflammation; infectious disease; viral disease; metabolic disease; neurodegenerative disease; antimicrobial discovery; antiviral discovery; broad drug discovery; not clearly reported.	Disease focus, therapeutic context, and claimed translational relevance.	Supports disease-area synthesis without inventing efficacy claims.	Disease emphasis may reflect publication trends rather than validated therapeutic strength.	Use cautious wording such as "discussed," "prioritized," or "hypothesized."

Computational method	The in silico approach reviewed or used for evidence interpretation.	Molecular docking; molecular dynamics; free-energy estimation; machine learning; deep learning; QSAR; ADMET prediction; toxicity prediction; virtual screening; network pharmacology; database mining.	Method type, workflow role, input requirements, output type, and interpretation limits.	Enables cross-method synthesis across docking, dynamics, and machine learning.	Method names may be used inconsistently across reviews.	Define methods by function rather than terminology alone.
Evidence scope	The breadth and target of the review's computational evidence.	Method-focused; disease-focused; compound-class-focused; database-focused; workflow-focused; translational-barrier-focused.	Main review objective, included evidence domains, and level of synthesis.	Helps determine whether a source supports a specific claim or only a broader background point.	Broad reviews can overgeneralize across heterogeneous evidence.	Link each citation to a precise manuscript claim.
Validation status	Whether computational claims were experimentally, externally, or prospectively validated.	Experimental validation reported; computational validation only; external model validation reported; validation limited; not clearly reported.	Type of validation, limits of confirmation, and translational interpretation.	Prevents computational prediction from being framed as pharmacological proof.	Reviews may report validation unevenly or incompletely.	State validation limitations explicitly and avoid efficacy language.
Overlap concern	The possibility that multiple reviews rely on the same primary computational studies or datasets.	Low; moderate; high; not clearly assessable.	Recurrent methods, disease areas, compound classes, datasets, and primary-study dependence.	Reduces false confidence caused by repeated citation of overlapping evidence.	Primary-study membership is often not extractable from narrative reviews.	Treat apparent consensus cautiously when overlap cannot be quantified.
Translational relevance	The degree to which evidence plausibly informs therapeutic prioritization or development.	High; moderate; low; methodological only; not clearly reported.	Link to prioritization, mechanism hypotheses, ADMET, toxicity, experimental follow-up, or development relevance.	Keeps synthesis focused on natural product therapeutics rather than computational performance alone.	Translational language may exceed the evidence base.	Distinguish prioritization from validation and therapeutic efficacy.
Risk of overclaiming	The likelihood that computational outputs could be interpreted beyond their evidentiary strength.	Low; moderate; high.	Claims involving docking scores, simulation stability, ML predictions, ADMET outputs, or clinical relevance.	Identifies where cautious interpretation is required.	Overclaiming risk varies by method and review quality.	Use qualified language and require experimental confirmation for therapeutic claims.

Molecular docking evidence

Review-level evidence presents molecular docking as one of the most common computational methods in natural product drug discovery because it can prioritize phytochemicals, natural product scaffolds, and medicinal plant constituents against selected protein targets. In phytopharmacology, docking is usually used to generate ligand–target hypotheses, rank candidate compounds, explore binding-site compatibility, and support virtual screening before experimental testing [12]. The review-level evidence supports docking as a triage tool, not as independent proof of biological activity.

Docking evidence is not limited to terrestrial medicinal plants. Marine natural product reviews also describe

docking as a practical strategy for exploring structurally diverse metabolites and identifying candidate target interactions in early-stage marine drug discovery [13]. However, the same interpretive caution applies across natural product sources: docking can suggest plausible molecular complementarity, but it does not demonstrate target engagement in biological systems, pharmacodynamic activity, bioavailability, safety, or therapeutic efficacy.

The strongest limitation identified across docking-focused evidence concerns the interpretation of docking scores and predicted binding poses. Scoring functions, protein preparation, protonation states, ligand conformations, water treatment, binding-site selection, and docking parameters can all affect the apparent ranking of natural product ligands. Methodological reviews of docking caution that estimated binding affinity should not be treated as factual evidence of binding strength without additional validation [14]. This limitation is especially important for natural products because stereochemistry, tautomeric state, glycosylation, flexibility, and structural annotation may complicate docking reliability.

Docking also appears frequently in combined network pharmacology workflows, where predicted compound–target networks are followed by docking to explore selected ligand–target pairs. Such workflows can support mechanism-oriented hypotheses in component-based traditional medicine and phytopharmacology, but they remain dependent on database quality, target prediction assumptions, pathway annotation, and experimental confirmation [15]. More broadly, phytochemical discovery increasingly blends traditional knowledge, computational triage, and modern pharmacological reasoning; nevertheless, docking-derived hypotheses should be positioned as prioritization evidence that requires reproducible methods and downstream validation [16].

Molecular dynamics evidence

Review-level evidence positions molecular dynamics as a complementary method that can extend docking-based hypotheses by examining whether predicted ligand–target interactions remain plausible under simulated molecular motion. In natural product and bioactive-compound research, molecular dynamics is most often used after docking to explore interaction stability, conformational behavior, binding persistence, and changes in the receptor–ligand environment over time [17, 18]. This role is valuable because docking is typically static, whereas molecular dynamics can model temporal behavior within defined simulation conditions.

Molecular dynamics evidence should still be interpreted as computational plausibility rather than direct pharmacological confirmation. Simulation outputs depend on force fields, parameterization, solvent models, protonation assumptions, system preparation, equilibration procedures, simulation length, and trajectory interpretation. Methodological reviews emphasize that molecular dynamics can be accessible and informative, but its outputs require careful interpretation because simulation design strongly influences the conclusions that can be drawn [19].

Binding free-energy calculations are often discussed as a way to strengthen post-docking interpretation by estimating energetic favorability more explicitly than docking scores alone. These approaches may help compare candidate ligands, refine hypotheses, and support prioritization within computational pipelines, but they remain sensitive to methodological choices and should not be treated as independent evidence of biological efficacy [20]. For natural products, the challenge may be intensified by compound flexibility, stereochemical complexity, uncertain ionization states, and limited experimental binding data for benchmarking.

Across the review-level evidence, molecular dynamics contributes most clearly when it is used to test the stability of a prior docking hypothesis rather than to generate an isolated claim of therapeutic promise. The strongest interpretation is therefore conditional: if a natural product ligand is docked into a biologically justified target, simulated with transparent parameters, and interpreted with appropriate caution, molecular dynamics can increase confidence in a mechanistic hypothesis. It cannot, however, confirm cellular activity, toxicity, pharmacokinetics, disease modification, or clinical relevance without experimental validation.

Machine learning evidence

Machine learning has become a major component of computational drug discovery because it can detect patterns across large molecular datasets, support prediction tasks, and prioritize compounds for downstream testing. In phytopharmacology and natural product therapeutics, machine learning is relevant to bioactivity prediction, target prediction, compound classification, QSAR modeling, ADMET prediction, toxicity screening, and virtual screening prioritization. Review-level evidence from drug discovery shows that machine learning can be useful across discovery and development workflows, but its reliability depends on data quality, validation design, and fit between the model domain and the prediction task [21].

Natural-compound bioactivity prediction illustrates both the promise and limits of machine learning. Model-based approaches can infer potential activity patterns from relationships among compounds, targets, and known drugs, thereby supporting prioritization of natural

compounds for further investigation [22]. However, these predictions should be treated as computational estimates, not as confirmed bioactivity. The strength of such evidence depends on chemical-structure standardization, training-set relevance, class balance, benchmark design, external validation, and prospective experimental testing.

Recent review-level evidence on artificial intelligence in natural product drug discovery describes applications across screening, molecular representation, generative design, dereplication, target inference, and compound prioritization [23]. These applications are especially attractive for natural products because the chemical space is large, structurally diverse, and incompletely explored. Nevertheless, AI-supported workflows remain constrained by incomplete databases, inconsistent metadata, limited negative data, uneven assay quality, and the risk that models trained on synthetic or drug-like chemical space may perform less reliably on complex phytochemicals.

Machine learning evidence in natural product development is therefore strongest when it is integrated with interpretable workflows, transparent validation, and experimental anchoring. Current landscape reviews emphasize that AI can support natural product discovery and development, but model outputs require biological interpretation and validation before they can inform therapeutic claims [24]. For an umbrella review, the key point is not whether machine learning is useful in principle, but whether review-level evidence shows reproducible, externally validated, and pharmacologically meaningful use in natural product therapeutic prioritization.

Cross-method evidence synthesis

Cross-method synthesis shows that molecular docking, molecular dynamics, and machine learning occupy different positions in computational phytopharmacology. Informatics-oriented natural product discovery links compound databases, chemical annotations, biological activity data, and computational tools into workflows that can support prioritization before experimental testing [25]. Within this logic, machine learning can screen broad chemical spaces, docking can propose ligand–target interactions, and molecular dynamics can examine whether selected interactions remain plausible under simulated conditions.

Natural product discovery benefits most when computational methods are integrated with experimental and pharmacological strategies rather than used as stand-alone evidence. Broad strategy reviews emphasize that natural product discovery involves compound sourcing, dereplication, structural elucidation, biological testing, mechanism investigation, optimization, safety assessment, and development planning [26]. Docking, dynamics, and machine learning can support several of these stages, but they do not replace the need for verified structures, validated targets, reproducible assays, and translationally relevant models.

The cross-method evidence also shows that apparent convergence can be useful but potentially misleading. When machine learning prioritizes a compound, docking supports a plausible target interaction, and molecular dynamics suggests interaction stability, the combined evidence may strengthen a hypothesis for experimental follow-up. However, convergence can create false confidence if all methods depend on the same uncertain structure, biased database, inappropriate target, weak scoring function, or unvalidated model. Contemporary natural product discovery strategies therefore require integrated workflows that connect computational ranking with experimental confirmation and development-oriented evaluation [27].

Multi-omics approaches offer an additional layer of evidence because they can support natural product isolation, biosynthetic interpretation, target-context mapping, and mechanism-oriented discovery. These approaches can complement docking, molecular dynamics, and machine learning by improving the biological and chemical context in which computational predictions are interpreted [28]. In umbrella synthesis terms, omics integration is not a replacement for validation; it is a way to improve the relevance of the questions being asked and the plausibility of the mechanisms being tested.

Network pharmacology provides another important bridge across methods because it is frequently used to connect phytochemicals, targets, pathways, and disease mechanisms in multi-component therapeutic hypotheses. Review-level evidence on Chinese medicine formulae indicates that network pharmacology can help frame multi-target mechanism hypotheses, but those hypotheses remain dependent on database assumptions and require experimental confirmation [29]. **Table 2** synthesizes review-level evidence across molecular docking, molecular dynamics, and machine learning in phytopharmacology and natural product therapeutics.

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Table 2. Cross-Method Evidence Synthesis for Natural Product Therapeutics: Molecular Docking, Molecular Dynamics, Machine Learning, Network Pharmacology, ADMET Prediction, Validation Status, Translational Barriers, and Future Research Needs

Synthesis domain	Computational method involved	Natural product or phytochemical focus	Therapeutic or disease area	Review-level evidence pattern	Validation status	Main limitation	Translational implication	Future research priority
Ligand–target prioritization	Molecular docking; virtual screening	Phytochemicals, medicinal plant compounds, marine natural products, natural product scaffolds	Broad drug discovery, antimicrobial, antiviral, cancer, inflammation, metabolic and neurodegenerative contexts where reviewed	Docking is commonly used to rank candidate natural products and propose target interactions.	Usually computational; experimental confirmation often limited or unevenly reported.	Scoring uncertainty, protein preparation, ligand-state ambiguity, target-selection dependence.	Useful for triage, but not sufficient for binding or efficacy claims.	Standardized docking protocols and experimental binding validation.
Post-docking plausibility	Molecular dynamics; free-energy estimation	Docked natural products, bioactive peptides, phytochemical–target complexes	Mechanism-oriented drug discovery and target-stability assessment	Molecular dynamics is used to examine interaction stability, conformational behavior, and binding persistence.	Simulation-based; biological validation not implied.	Force-field dependence, simulation duration, parameterization, trajectory interpretation variability.	Can refine hypotheses before laboratory testing.	Transparent simulation reporting and benchmarked interpretation standards.
Bioactivity and target prediction	Machine learning; deep learning; QSAR; target prediction	Natural compounds, phytochemicals, natural product databases	Bioactivity screening and lead prioritization	Machine learning supports prediction across compound–target and compound–activity spaces.	Model validation varies; prospective experimental validation is often limited.	Dataset bias, imbalance, benchmark leakage, applicability-domain uncertainty, interpretability gaps.	Can prioritize candidates across large chemical spaces.	External validation, natural-product-specific benchmarks, and interpretable modeling.
ADMET and toxicity screening	ADMET prediction; toxicity prediction; machine learning	Phytochemicals and natural product-inspired compounds	Developability and safety triage	In silico filtering is used to flag absorption, metabolism, toxicity, and drug-likeness concerns.	Predictive; not a substitute for experimental safety testing.	Limited natural-product applicability, uncertain model domain, incomplete training data.	Helps deprioritize unsuitable candidates early.	Experimental ADMET confirmation and applicability-domain reporting.
Network-level mechanism hypotheses	Network pharmacology; docking; database mining	Medicinal plants, Chinese medicine formulae, multi-component phytochemical systems	Multi-target disease mechanisms	Network pharmacology maps compounds, targets, pathways, and disease associations, often followed by docking.	Hypothesis-generating; experimental mechanism confirmation required.	Database dependence, target-prediction uncertainty, pathway overinterpretation.	Useful for organizing complex phytopharmacological mechanisms.	Prospective testing of predicted compound–target–pathway relationships.
Cross-method	Docking; molecular dynamics;	Natural product candidates	Broad therapeutic prioritization	Convergent computational support may	Requires experimental validation	Shared biased inputs can	Supports rational selection of	Independent validation layers and

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convergence	machine learning; network pharmacology	prioritized by multiple computational streams		strengthen hypothesis generation when inputs and assumptions are independent.	before therapeutic interpretation.	create false confidence.	compounds for testing.	uncertainty-aware evidence grading.
Translational readiness	Integrated computational and experimental workflows	Natural product therapeutics and drug leads	Preclinical and development-oriented research	Computational methods can support prioritization, but translation requires pharmacological evidence.	Often incomplete at review level.	Limited prospective testing, poor reproducibility, weak assay linkage, clinical translation gaps.	Computational support should be framed as prioritization, not efficacy.	Reproducible pipelines linked to wet-lab, preclinical, and clinical evidence.

Figure 1 illustrates the umbrella evidence synthesis framework linking molecular docking, molecular dynamics, machine learning, validation gaps, and translational barriers in computational phytopharmacology.

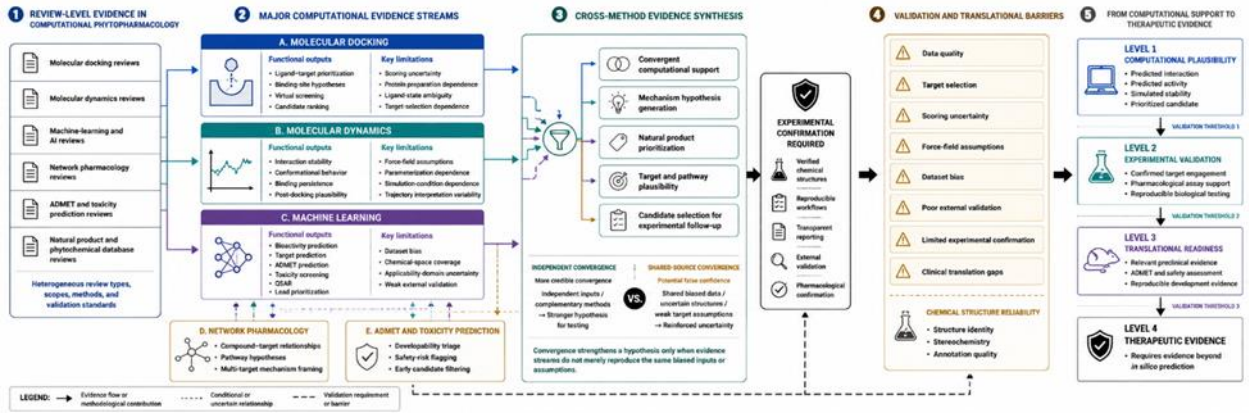

Figure 1. Umbrella Evidence Synthesis Framework for Computational Phytopharmacology and Natural Product Therapeutics

Alt-text description

A conceptual umbrella evidence synthesis framework showing review-level evidence sources feeding into three major computational method domains: molecular docking, molecular dynamics, and machine learning. These domains connect to natural product target prioritization, mechanism hypotheses, ADMET and toxicity screening, cross-method convergence, validation gaps, reproducibility concerns, experimental confirmation needs, translational barriers, and future research priorities.

Evidence gaps

One major evidence gap concerns the reliability of the chemical structures that enter computational workflows. Natural products can be structurally complex, stereochemically rich, and difficult to characterize, and incorrect structure assignments can undermine docking, molecular dynamics, QSAR, and machine-learning predictions before any biological interpretation begins. Reviews of structural reassignment highlight that computational natural product research must treat compound identity as a validation issue rather than as a fixed assumption [30].

A second gap concerns dataset bias and chemical-space coverage in machine learning. Natural products may be underrepresented, inconsistently annotated, or chemically distant from the compounds used to train general small-molecule models. Coverage bias can therefore affect prediction reliability, particularly when models are applied outside the chemical domains represented in training data [31]. This limitation has direct implications for phytochemical bioactivity prediction, ADMET modeling, toxicity screening, and virtual screening prioritization.

A third gap concerns applicability domains, external validation, and prospective experimental testing. Generative AI and predictive models can propose or

prioritize molecules, but model outputs are meaningful only within the boundaries of the data, assumptions, and validation contexts that support them [32]. Future computational phytopharmacology should therefore prioritize transparent reporting, verified structures, standardized docking and simulation protocols, natural-product-aware benchmarks, external validation, experimentally confirmed compound–target relationships, pharmacological assay integration, and cautious translation from computational plausibility to therapeutic evidence.

CONCLUSION

This umbrella review synthesizes review-level computational evidence on molecular docking, molecular dynamics, and machine learning in phytopharmacology and natural product therapeutics. The synthesis shows that docking can support ligand–target prioritization and binding-site hypotheses, molecular dynamics can examine interaction stability and conformational behavior, and machine learning can assist bioactivity, target, ADMET, toxicity, and prioritization tasks across complex natural product chemical spaces. However, these methods provide computational support rather than therapeutic confirmation. Stronger natural product therapeutic evidence requires reproducible workflows, verified compound identities, transparent reporting, external validation, experimental pharmacology, safety assessment, and translational evidence that moves beyond in silico plausibility.

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