Digital Twins of Natural Product Pharmacology: Modeling Compound Exposure, Target Engagement, Pathway Response, Safety Risk, and Therapeutic Outcomes

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ABSTRACT

Natural product pharmacology presents a distinctive modeling challenge because botanical materials and derived preparations may contain multiple constituents with variable composition, uncertain bioavailability, overlapping targets, pathway-level effects, and context-dependent safety liabilities. This article proposes a conceptual digital twin framework that connects authenticated natural product identity with compound exposure, target engagement, pathway response, safety-risk interpretation, and bounded therapeutic outcome simulation. The framework begins with botanical provenance, phytochemical composition, chemical identity, and evidence quality before incorporating absorption, distribution, metabolism, excretion, physiologically based pharmacokinetic logic where supported, population variability, and pharmacokinetic–pharmacodynamic relationships. Target engagement is represented through graded confidence derived from binding, interaction, proteomic, functional, and attainable-exposure evidence rather than computational prediction alone. Pathway-response modeling integrates network and systems pharmacology with disease or phenotype context, while safety assessment incorporates ADMET evidence, toxicity findings, herb–drug interaction mechanisms, and pharmacovigilance signals. Virtual patient and virtual population logic may support scenario analysis and research prioritization, but simulated therapeutic outcomes remain hypotheses rather than demonstrations of efficacy, safety, clinical utility, or treatment benefit. Uncertainty quantification, expert review, internal and external validation planning, experimental confirmation, feedback updating, and a no-clinical-claim boundary are therefore treated as integral architectural components. The principal contribution is a staged and evidence-bounded digital twin architecture designed to strengthen mechanistic hypothesis generation and translational planning in natural product research without replacing experimental pharmacology, toxicology, clinical investigation, or accountable professional judgment.

Key Words: *Digital twins, Natural product pharmacology, Compound exposure, Target engagement, Pathway response, Safety risk*

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INTRODUCTION

Digital twins are emerging as computational representations that connect biological entities or processes with data, mechanistic assumptions, simulation, and iterative updating. In healthcare, however, the construction of a digital representation raises questions extending beyond technical accuracy, including whether the modeled

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entity adequately represents the person or biological system, how uncertainty is communicated, who remains accountable for interpretation, and how privacy, autonomy, and unequal data quality are managed [1]. These concerns are especially important in pharmacology because a simulated response may appear precise even when the underlying exposure, target, pathway, or safety evidence is incomplete. A digital twin should therefore be understood not merely as a detailed model, but as a purpose-defined and evidence-linked representation whose outputs remain constrained by its data provenance, biological assumptions, validation status, and intended context of use.

The attraction of digital twins for pharmacology lies in their potential to combine longitudinal molecular, physiological, clinical, and treatment-related evidence into an individualized representation that can be interrogated through alternative scenarios. Personalized digital twin concepts have consequently been proposed as mechanisms for integrating disease networks with repeated patient-specific measurements and for generating testable intervention hypotheses [2]. In natural product research, such an approach could be valuable because pharmacological interpretation often requires simultaneous consideration of botanical identity, composition, active and inactive constituents, metabolites, exposure variability, multiple candidate targets, interacting pathways, and safety liabilities. The value of the twin would not arise from reproducing all available data indiscriminately, but from organizing those data into a traceable chain from material identity to plausible biological response.

Digital twin scholarship also extends from individual-level models to virtual populations and population-health contexts, demonstrating that the meaning of a twin depends on its scale, data linkage, updating logic, and decision purpose. Health-oriented digital twins may integrate sensor, molecular, environmental, behavioral, and clinical data, yet their development remains inseparable from interoperability, governance, security, representativeness, and responsible interpretation [3]. Natural product pharmacology introduces additional heterogeneity because botanical source, harvesting, processing, extraction, formulation, storage, and batch composition can alter which compounds are present and which exposures are biologically plausible. A framework developed for a single chemically defined drug cannot therefore be transferred uncritically to a multicomponent natural product whose composition and interaction structure may vary.

Pharmacological virtual twins also depend on sufficiently detailed individual and model-system information, including physiology, biochemical function, disease state, organ function, concomitant treatment, and relevant sources of variability [4]. For natural products, this requirement must be expanded to include authenticated botanical provenance, quantitative phytochemical profiles, preparation characteristics, metabolite evidence, and mixture-specific interaction data. The objective of this article is therefore to propose a staged digital twin framework for natural product pharmacology that links compound identity and exposure with target engagement, pathway response, safety-risk interpretation, virtual-patient reasoning, and simulated therapeutic outcomes. The framework is intended to support research prioritization, mechanism exploration, experiment planning, and translational reasoning, while explicitly preventing unvalidated simulations from being interpreted as evidence of efficacy, safety, clinical benefit, or autonomous treatment guidance.

Digital twins in natural product pharmacology

In the present context, a digital twin of natural product pharmacology is defined as a purpose-specific, evidence-linked, and potentially updateable computational representation of a natural product, its constituent exposures, its biological interactions, and the response of a defined biological or patient context. Healthcare digital twins commonly combine heterogeneous data, computational models, bidirectional information flow, simulation, and updating, but their reliability is limited by interoperability, model transparency, privacy, security, and validation challenges [5]. The proposed natural product twin therefore differs from a static database record or one-time prediction because it includes explicit relationships among identity, exposure, target engagement, pathway effects, safety evidence, uncertainty, and feedback from new observations. Nevertheless, an updateable architecture alone does not make a model clinically credible; the quality of its representation depends on the adequacy of each component and the evidence connecting them.

A digital twin must also be distinguished from a virtual patient or virtual population. Virtual patients may be generated from mechanistic disease models to explore plausible biological trajectories or comparative intervention responses, and causal disease models may provide a foundation for in silico experiments [6]. Such entities become closer to digital twins when they are meaningfully connected to a specific biological system or individual, updated using relevant observations, and evaluated against a defined context of use. In natural product research, a virtual population might represent variability in physiology, metabolic capacity, co-medication exposure, or disease state, whereas a natural product digital twin would additionally require traceable representation of the administered material, constituent composition, and exposure-generating processes. A

synthetic cohort without product-specific evidence linkage should not be described as a validated natural product twin. Generative computational methods may expand the range of simulated patients, molecular states, or response scenarios used within digital twin research, particularly when empirical datasets are sparse. Generative artificial intelligence has been proposed as a means of augmenting digital twins in drug discovery and clinical-trial simulation, but its outputs can reproduce bias, generate biologically implausible states, or create false confidence when synthetic data are insufficiently constrained [7]. Within natural product pharmacology, generative methods could potentially assist sensitivity analysis or identify underexplored scenarios, yet they should not fabricate missing pharmacokinetic parameters, target relationships, safety evidence, or clinical outcomes. Any generated component would require provenance labeling, plausibility assessment, expert scrutiny, and separation from observed evidence.

The proposed framework therefore treats the digital twin as an integrated pharmacological architecture rather than a synonym for molecular docking, network visualization, machine-learning classification, PBPK simulation, or PK/PD modeling. Precision-pharmacology digital twins are most informative when they connect drug exposure with molecular action, physiological response, individual variability, and safety-relevant consequences [8]. A natural product twin must extend this logic to multicomponent composition, metabolite formation, competing or cooperative interactions, uncertain target assignments, pathway crosstalk, and herb–drug interaction risk. It may support hypothesis generation, scenario comparison, mechanism exploration, and prioritization of experiments, but it does not independently establish therapeutic efficacy, prove safety, replace experimental validation, or authorize clinical decision-making.

Compound exposure and target engagement

Compound exposure is the essential bridge between phytochemical composition and biological interpretation. Natural-product PBPK modeling can organize evidence concerning absorption, distribution, metabolism, excretion, metabolite formation, tissue exposure, and interaction mechanisms, provided that sufficient compound-specific and system-specific inputs are available [9]. The exposure layer should begin with authenticated botanical identity, preparation method, quantitative composition, chemical structure records, physicochemical characteristics, formulation properties, and bioavailability evidence. PBPK logic may be used where mechanistic parameters are adequate, while population pharmacokinetic modeling may be used where concentration–time data and covariate information permit estimation of typical exposure and interindividual variability. When neither approach is sufficiently supported, the framework should preserve exposure uncertainty rather than fill missing parameters through unsupported assumptions.

In vitro pharmacokinetic evidence may provide information on permeability, intestinal and hepatic metabolism, transporter effects, protein binding, enzyme inhibition, and enzyme induction for medicinal plants or their constituents, but translation from isolated assays to whole-body exposure remains uncertain [10]. Matrix effects, unidentified constituents, active metabolites, gastrointestinal transformation, microbiome-mediated metabolism, and batch variation may alter the relationship between an administered product and the compounds reaching systemic or local sites of action. Computational ADME models can help prioritize natural compounds or estimate properties such as tissue permeability, yet their interpretation requires attention to chemical-domain coverage, training-data relevance, and experimental confirmation [11]. The proposed framework therefore records both predicted and observed ADME evidence, assigns source-specific confidence, and prevents uncertain property estimates from being treated as measured human exposure.

Target engagement should be modeled only after exposure plausibility has been considered. Natural-product target identification may draw on biochemical affinity assays, activity-based profiling, proteomics, genetic perturbation, imaging, phenotypic screening, computational prediction, and complementary validation strategies [12]. Because each method captures a different aspect of the compound–target relationship, target confidence should reflect directness, replication, selectivity, biological context, attainable concentration, and consistency across independent evidence types. Cellular thermal shift assays and thermal proteome profiling may provide valuable evidence that a compound interacts with proteins in a biologically relevant environment, but a thermal-stability change does not by itself demonstrate causal mechanism or therapeutic benefit [13]. The target-engagement module should therefore distinguish predicted interaction, observed binding, intracellular engagement, functional modulation, and pathway-relevant causality.

Computational prediction can identify plausible natural-product targets and generate experimentally testable mechanism hypotheses, but such predictions remain dependent on reference data, chemical similarity, model assumptions, and disease context [14]. Network-level analysis can then position supported targets within disease modules and help evaluate pleiotropic or multi-target pharmacology, although network proximity or centrality should not be interpreted as evidence of clinical

effectiveness [15]. PK/PD linkage is consequently needed to connect time-varying exposure with target engagement and measurable biological response, while multi-compound exposure models should examine whether constituents compete for transport, metabolism, binding, or elimination. Within the proposed framework, only exposure-supported and confidence-weighted target relationships progress to pathway-response modeling. **Table 1** summarises compound exposure and target engagement modeling requirements for digital twins of natural product pharmacology.

Table 1. Compound Exposure and Target Engagement Modeling Requirements for Digital Twins of Natural Product Pharmacology: Phytochemical Identity, Bioavailability, Absorption, Distribution, Metabolism, Excretion, PBPK Logic, PK/PD Linkage, Target Confidence, Multi-Compound Exposure, and Validation Needs

Modeling component	Core pharmacology question	Required input data	Modeling function	Potential output	Uncertainty source	Validation requirement	Framework role
Phytochemical identity	Which chemical entities are demonstrably present in the modeled natural product?	Botanical authentication, analytical spectra, reference standards, stereochemical information, batch metadata	Resolve, standardize, and version constituent identities	Curated constituent inventory with identity-confidence labels	Misidentification, unresolved peaks, isomerism, degradation, contamination	Orthogonal analytical confirmation and authenticated reference materials	Establishes the admissible chemical entities for downstream modeling
Compound composition	What constituents and relative abundances characterize the preparation?	Quantitative chromatographic or spectroscopic data, extraction method, formulation and batch information	Represent composition and batch-to-batch variability	Quantitative compositional profile or constituent distributions	Matrix effects, extraction variability, incomplete detection and batch heterogeneity	Replicated profiling across representative preparations	Defines mixture-specific exposure inputs
Bioavailability evidence	Which constituents or metabolites can plausibly reach relevant sites?	Solubility, stability, permeability, formulation, food-effect, presystemic metabolism and in vivo evidence	Assign evidence-weighted bioavailability assumptions	Bioavailable constituent set with uncertainty descriptions	Sparse measurements, active metabolites, matrix and microbiome effects	Comparison of in vitro, preclinical and human observations where available	Prevents implausible targets from entering the model
Absorption modeling	How rapidly and extensively are constituents absorbed?	Dissolution, gastrointestinal stability, permeability, transporter and formulation evidence	Simulate or qualitatively represent gastrointestinal input	Absorption profiles and plausible absorbed fractions	Variable formulation, intestinal metabolism and transporter uncertainty	Comparison with observed concentration–time evidence	Initiates the exposure model
Distribution modeling	Which plasma, tissue or cellular compartments may be reached?	Protein binding, tissue partitioning, permeability, organ blood flow and	Estimate systemic and effect-site distribution	Plasma and tissue-exposure trajectories or bounded scenarios	Binding variability, uncertain partitioning and tissue-specific transport	Tissue measurements, imaging, biomarkers or validated surrogate evidence	Links systemic exposure to target-site plausibility

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		transporter data				where available	
Metabolism modeling	Which transformations generate active, inactive or potentially toxic metabolites?	Enzyme kinetics, metabolite identification, hepatic, intestinal and microbiome evidence	Simulate parent depletion and metabolite formation	Parent and metabolite exposure profiles	Enzyme polymorphism, inhibition, induction and unidentified pathways	Microsomal, cellular, organoid, preclinical or clinical metabolite comparison	Represents metabolite-mediated efficacy and safety hypotheses
Excretion modeling	How are constituents and metabolites eliminated or accumulated?	Renal, biliary, transporter, clearance and enterohepatic-cycling evidence	Estimate elimination and accumulation behavior	Clearance and persistence scenarios	Organ-function variability and incomplete mass-balance data	Excretion or mass-balance observations where available	Completes the ADME representation
Compound exposure	What concentration–time pattern is biologically plausible?	Integrated composition, ADME, formulation, administration and covariate data	Combine absorption, distribution, metabolism and excretion processes	Systemic or local exposure distributions with uncertainty	Parameter error, structural uncertainty and product variability	Internal model checks and comparison with independent pharmacokinetic observations	Provides the bridge from product composition to pharmacological action
PBPK logic where supported	Can physiology and compound properties mechanistically explain exposure?	Organ physiology, blood flows, physicochemical data, enzyme, transporter and tissue-partition information	Mechanistically scale exposure across tissues, conditions or populations	Organ-specific exposure and interaction scenarios	Missing parameters, uncertain scaling and mixture complexity	Fit-for-purpose qualification against independent datasets	Serves as a mechanistic exposure engine when evidence is adequate
Population pharmacokinetic modeling where supported	How does exposure vary among individuals?	Serial concentrations, exposure history, demographics, organ function, disease and co-medications	Estimate typical kinetics, variability and covariate relationships	Population distributions and individualized posterior exposure estimates	Sparse sampling, covariate imbalance and model misspecification	Diagnostic evaluation, resampling, external validation and prospective assessment	Supports virtual-population and patient-context modeling
Target annotation	Which biological entities are proposed as interacting partners?	Curated databases, literature evidence, assays, proteomic and computational results	Harmonize target names, isoforms, species and evidence provenance	Traceable target catalogue	Annotation errors, species mismatch and outdated database records	Manual curation and source verification	Provides standardized target candidates
Target engagement	Does an exposed	Binding, occupancy,	Integrate physical	Engagement-evidence	Assay artifacts,	Orthogonal engagement	Gates progression

	constituent interact with the proposed target in a relevant system?	CETSA, chemoproteomic, functional and exposure evidence	interaction with attainable concentration and biological context	tier or time-dependent engagement hypothesis	nonspecific effects and inadequate intracellular exposure	assays and relevant negative controls	from exposure to mechanism
Target confidence	How reliable is each compound–target relationship?	Replication, selectivity, genetic evidence, assay quality and prediction provenance	Weight evidence by directness, reproducibility and context	High, intermediate, low or unresolved confidence classification	Publication bias, database errors and indirect evidence	Independent replication and consistency across methods	Controls inclusion and weighting of targets in pathway models
Compound–target interaction	How do affinity, potency, kinetics and selectivity shape modulation?	Binding constants, residence time, concentration–response and selectivity evidence	Model occupancy or functional modulation where supported	Time-varying target-modulation hypotheses	Translation between assay systems and effect compartments	Quantitative testing in relevant biological systems	Supplies target-level input to pathway simulation
PK/PD linkage	How does exposure relate to engagement and biological response?	Exposure profiles, engagement biomarkers, response biomarkers and temporal data	Link concentration, engagement and response with delay or feedback where justified	Exposure–engagement–response relationships	Biomarker validity, hysteresis, tolerance and confounding	Prospective paired exposure and response measurement	Connects pharmacokinetics to biological effect
Multi-compound exposure interaction	Do constituents alter one another's absorption, metabolism, transport or elimination?	Mixture composition, shared enzymes or transporters, inhibition, induction and binding evidence	Represent competitive, inhibitory, inductive or formulation-mediated interactions	Mixture-specific exposure shifts and interaction hypotheses	High-dimensional constituent space and unidentified compounds	Focused interaction experiments and mixture-specific pharmacokinetic studies	Prevents independent-compound assumptions from distorting the twin

Pathway response and safety risk

Pathway-response modeling begins after compounds have been assigned plausible exposures and confidence-weighted targets. Systems pharmacology offers a means of organizing multicomponent natural products across compounds, targets, pathways, cells, organs, and disease phenotypes [16]. Network pharmacology can further represent formula–compound–target–pathway relationships and identify candidate biological modules, but its results are sensitive to database completeness, annotation quality, prediction bias, enrichment methods, and the frequent underrepresentation of pharmacokinetics [17]. A responsible twin should therefore treat network outputs as structured hypotheses rather than direct demonstrations of mechanism. Predicted targets with weak identity, exposure, or engagement evidence should receive reduced weight or remain outside dynamic pathway simulation until supporting evidence is obtained.

Pathway interpretation should prioritize causal and context-specific biology over simple connectivity. Mechanism-oriented network pharmacology seeks to identify disease-driving causal processes and intervention points rather than relying only on associations, highly connected nodes, or symptom-linked target lists [18]. The pathway layer of the proposed twin should consequently encode directionality, activation or inhibition, temporal relationships, feedback, compensatory responses, disease stage, tissue context, and phenotype-specific assumptions where evidence permits. Multi-compound effects may be represented as additive, antagonistic, potentiating, or

otherwise interactive, but synergy should not be inferred merely because several constituents affect the same assay or pathway. Quantitative synergy assessment requires explicit comparison against an appropriate additivity model, adequate concentration combinations, uncertainty estimates, and independent replication [19].

Safety modeling should be developed in parallel with pathway-response modeling rather than appended after a therapeutic hypothesis has already been favored. Cheminformatics can support natural-product property prediction, target inference, ADMET prioritization, and liability screening, yet its reliability is constrained by structural diversity, sparse annotations, uncertain compound identities, and limited applicability domains [20]. Empirical toxicity evidence, reactive-metabolite data, organ-specific hazards, transporter effects, and off-target activity should therefore be evaluated alongside computational outputs. Herb–drug interaction modeling requires particular caution because natural-product constituents may alter drug-metabolizing enzymes, transporters, protein binding, pharmacodynamic pathways, or overlapping toxicity mechanisms. In vitro hepatic models can help characterize inhibition, induction, metabolism, and transporter-mediated interactions, but translation to clinically meaningful interaction magnitude remains dependent on exposure plausibility, product composition, and corroborating evidence [21].

Pharmacovigilance evidence can provide an external feedback source for safety-risk hypotheses by identifying reported adverse events, interaction patterns, product-quality concerns, and underrecognized susceptible contexts. Herbal pharmacovigilance is nevertheless limited by underreporting, incomplete botanical and product identification, uncertain composition, co-exposures, variable causality assessment, and missing denominator information [22]. Within the proposed framework, safety signals should trigger structured review, targeted experiments, model revision, or scope restriction rather than automatic causal conclusions. Safety-risk outputs should be accompanied by uncertainty attribution and should never be interpreted as proof that a natural product is safe, unsafe, clinically beneficial, or suitable for a particular treatment decision. **Figure 1** illustrates how digital twins of natural product pharmacology can connect compound exposure, target engagement, pathway response, safety risk, uncertainty, and validation boundaries.

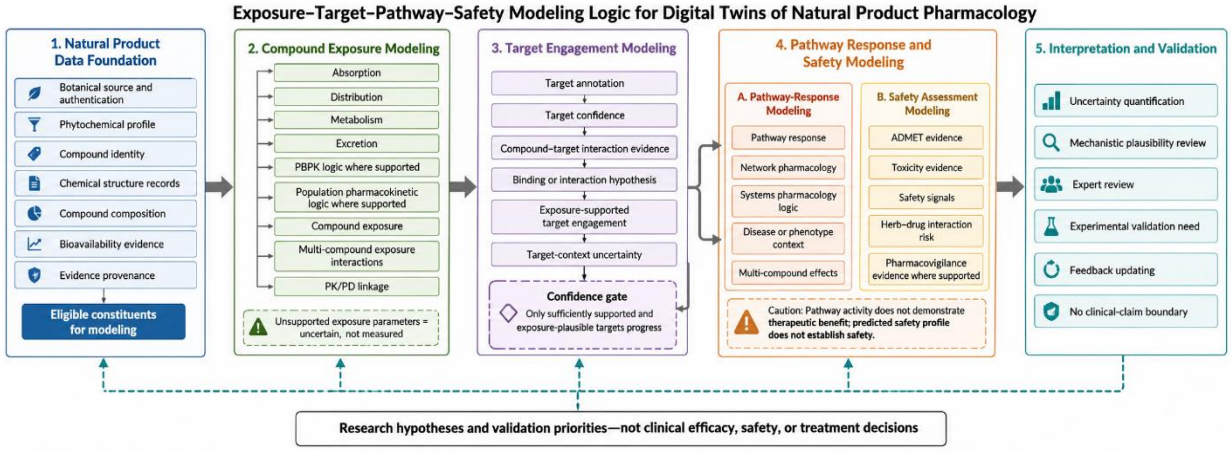

Figure 1. Exposure–Target–Pathway–Safety Modeling Logic for Digital Twins of Natural Product Pharmacology

Alt-text description

A conceptual modeling diagram showing natural product identity and compound exposure connected to target engagement, pathway response, safety risk, toxicity evidence, herb–drug interaction risk, uncertainty, expert review, and validation boundaries.

Therapeutic outcome simulation

Therapeutic outcome simulation should be positioned as the final hypothesis-generating layer of a natural product digital twin rather than as a direct predictor of clinical benefit. Mechanistic quantitative systems pharmacology models can generate virtual patients or virtual populations that represent variation in disease biology, pharmacological exposure, target modulation, and treatment response, but these simulated entities become credible digital twins only when they are connected to relevant observations, updated appropriately, and evaluated within a defined context of use [23]. In natural product pharmacology, outcome simulation would therefore begin with exposure-supported constituents, confidence-weighted target engagement, and biologically plausible pathway responses. The output should be expressed as a range of model-contingent response hypotheses rather than as a treatment recommendation, efficacy estimate, or individualized clinical prognosis.

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Virtual patient logic may incorporate patient-context variables such as organ function, disease state, metabolic capacity, biomarker status, co-medication exposure, and other covariates that plausibly affect pharmacokinetics or pharmacodynamics. Multiscale digital twin studies demonstrate how physiological measurements, mechanistic models, and intervention effects can be combined to simulate personalized biological trajectories, although such models remain specific to their disease domain, available measurements, and calibration assumptions [24]. For natural products, personalization would additionally require product-specific composition, formulation, metabolite, and exposure information. A virtual patient should not be created by merely attaching demographic data to a generic pathway model; the individualized parameters must be traceable to evidence and accompanied by an explanation of which features remain inferred, missing, or uncertain.

Virtual populations may support comparison of response and safety hypotheses across plausible biological variability when sufficient mechanistic and population evidence exists. Quantitative systems pharmacology–based virtual twin approaches have been used to supplement limited therapeutic evidence in specific disease settings, illustrating how simulated populations can explore treatment-response heterogeneity while remaining dependent on the assumptions and calibration of the underlying model [25]. In natural product research, comparable methods could help prioritize which compositional, metabolic, interaction, or phenotype variables warrant experimental study. They should not be used to invent representative cohorts, assign unsupported outcome probabilities, or imply that simulated comparisons can replace controlled clinical investigation.

Credible therapeutic outcome simulation requires explicit verification, validation, and uncertainty quantification. Predictive biomedical models should be evaluated for code correctness, mathematical consistency, parameter plausibility, data fit, external performance, and suitability for their intended context of use [26]. Individualized pharmacological modeling further requires relevant covariates, qualified exposure–response relationships, prospective evaluation, workflow controls, and expert interpretation before outputs can support high-consequence decisions [27]. The proposed framework therefore separates simulated therapeutic outcomes from validated therapeutic outcomes and clinical outcomes. It also requires uncertainty intervals, sensitivity analysis, structural alternatives, experimental confirmation plans, and a no-clinical-claim boundary for every outcome-oriented output. **Table 2** maps pathway response, safety-risk, and therapeutic outcome simulation domains required for responsible digital twin interpretation.

Table 2. Pathway Response, Safety Risk, and Therapeutic Outcome Simulation in Digital Twins of Natural Product Pharmacology: Network Pharmacology, Systems Response, Multi-Compound Interaction, ADMET Evidence, Toxicity Signals, Herb–Drug Interaction Risk, Virtual Patient Logic, Uncertainty, and Decision Boundaries

Simulation domain	Core question	Evidence needed	Modeling logic	Potential simulation output	Risk of overinterpretation	Validation requirement	Decision boundary
Pathway response	How might exposure-supported target modulation propagate through biological pathways?	Target-engagement evidence, pathway topology, directionality, kinetics, feedback and biomarkers	Dynamic or causal propagation from engaged targets to downstream biological states	Time-dependent pathway-response hypotheses	Association or enrichment may be described as causal response	Perturbation experiments and pathway-level biomarker confirmation	Pathway response does not establish clinical outcome
Network pharmacology	Which targets and pathways may jointly contribute to a multicomponent effect?	Curated compound–target links, disease modules, confidence weights and exposure evidence	Evidence-weighted network construction and module prioritization	Candidate target–pathway modules	Database bias, degree effects and unvalidated predicted edges	Sensitivity testing and orthogonal biological validation	Network proximity alone cannot establish mechanism
Systems pharmacology	How do compounds,	PK, PD, pathway	Multiscale	System-level	Complexity may obscure	Modular calibration,	Systems simulation

	targets, pathways, cells, organs and feedback processes interact?	kinetics, physiological data, phenotype evidence and model assumptions	mechanistic integration	response trajectories	weak assumptions or non-identifiability	identifiability analysis and external testing	supports research hypotheses rather than clinical decisions
Disease or phenotype context	Is the proposed response relevant to the modeled biological state?	Disease mechanism, tissue context, stage, phenotype, comorbidities and biomarkers	Condition model structure and parameters on context-specific evidence	Context-specific pathway and response scenarios	Results may be generalized beyond the modeled condition	Independent disease datasets and subgroup evaluation	No transfer to other diseases or populations without revalidation
Multi-compound interaction	How do constituents combine at exposure, target or pathway levels?	Quantitative composition, individual and combined exposure, concentration–response and mechanistic evidence	Additive, antagonistic, potentiating or other interaction models	Combined-effect surfaces and interaction hypotheses	Coincident activity may be misclassified as interaction	Exposure-matched combination experiments and replication	Interaction remains hypothetical unless quantitatively supported
Synergy hypothesis where supported	Does a combination exceed an appropriate additive expectation?	Full concentration matrices, dose–response data and justified reference models	Comparison with explicit additivity models	Synergy estimates with uncertainty	Selective model choice or restricted concentrations may inflate synergy	Multiple reference models, confidence intervals and independent replication	No therapeutic-synergy claim from a single assay
ADMET evidence	What disposition or toxicity liabilities are plausible?	Physicochemical, absorption, metabolism, transporter, excretion and toxicity data	Integrate empirical findings with qualified predictive models	Liability flags and uncertainty ranges	Prediction may be described as observed safety or toxicity	Experimental confirmation and applicability-domain assessment	ADMET prediction supports prioritization only
Toxicity evidence	Which organs, mechanisms or exposure conditions may carry hazard?	Cytotoxicity, organ toxicity, reactive metabolites, repeat-exposure and mechanistic evidence	Exposure-aware hazard modeling	Toxicity hypotheses and candidate risk mechanisms	In vitro hazard may be translated directly to human risk	Relevant experimental, observational or validated alternative evidence	Toxicity modeling does not establish human risk magnitude
Safety-risk modeling	How do exposure, hazard and susceptibility combine?	Exposure distributions, toxicity findings, patient factors and	Probabilistic or rule-based integration of hazard	Ranked safety concerns with uncertainty	A low predicted risk may be presented as proof of safety	Calibration against known outcomes and stress testing	No declaration of safety without adequate validation

		co-medications	and exposure				
Herb–drug interaction risk	Could constituents alter drug exposure or pharmacological effects?	Enzyme, transporter, receptor, physiological and clinical interaction evidence	Mechanistic PK or PD interaction scenarios	Direction and plausible range of interaction hypotheses	Screening signals may be interpreted as clinically established interactions	Translational studies and real-world or clinical corroboration	No dosing or treatment-management recommendation
Pharmacovigilance signal integration where supported	Do real-world safety reports alter prior risk hypotheses?	Product identity, adverse-event reports, co-exposures, chronology and causality information	Structured or probabilistic updating of safety hypotheses	Updated signal priority	Disproportionality or case accumulation may be mistaken for causality	Case review, confounding assessment and independent data sources	Signal detection initiates investigation rather than causal determination
Therapeutic outcome simulation	What response is plausible under explicit mechanisms and assumptions?	Validated exposure–response relationships, phenotype models, endpoints and uncertainty distributions	Propagate mechanistic states to predefined research outcomes	Scenario distributions for simulated therapeutic outcomes	Simulated endpoints may be described as clinical benefit	External outcome validation and prospective evaluation	A simulated outcome is not a validated therapeutic or clinical outcome
Virtual patient logic	How might an individual biological context alter response?	Patient-specific covariates, biomarkers, organ function, history and co-exposures	Personalize model parameters or posterior distributions	Individualized scenario range	Incomplete data may produce false precision	Repeated measurements and prospective individual-level assessment	Not autonomous clinical decision support
Virtual population comparison	How might response vary across a plausible population?	Population distributions, covariate relationships, mechanistic constraints and calibration targets	Generate and qualify biologically plausible virtual subjects	Population response and uncertainty distributions	Synthetic populations may be assumed to represent real populations	Distributional checks, external comparison and representativeness assessment	No population-level clinical conclusion without empirical confirmation
Uncertainty quantification	How reliable and variable are the simulated outputs?	Parameter distributions, structural alternatives, measurement error and data-quality ratings	Propagate aleatory and epistemic uncertainty	Prediction intervals, sensitivity rankings and uncertainty attribution	Narrow intervals may conceal structural uncertainty	Calibration, empirical coverage testing and sensitivity analysis	Decision use is restricted when uncertainty exceeds predefined limits
Experimental confirmation need	Which assumptions require laboratory or observational testing?	Sensitivity analysis, model discrepancies, missing evidence and	Rank experiments by expected information value	Validation and experiment-prioritization plan	Simulation may be used to avoid necessary experiments	Predefined criteria and independent replication	Modeling complements rather than replaces experimentation

		translational priorities					
No clinical-claim boundary	Which conclusions are prohibited at the current evidence stage?	Intended use, validation status, audience and governance assessment	Apply explicit restrictions to output language and decision use	Research-only interpretation statement	Research simulation may be presented as medical advice	Expert review and claim audit	No efficacy, safety, dosing, utility or adoption claim without corresponding evidence

Proposed digital twin framework

The proposed framework begins with a declared research purpose and context of use. Drug-development digital twin architectures should specify what the twin is intended to represent, which decisions it may inform, what data are required, how the component models interact, and how credibility will be evaluated [28]. For natural product pharmacology, the initial context might involve mechanism exploration, exposure prioritization, target-confidence assessment, interaction-risk evaluation, or experiment planning. It should not begin with a claim that the twin will optimize therapy or predict patient benefit. The natural product data foundation records botanical source, authentication, preparation, quantitative composition, chemical identities, analytical uncertainty, bioactivity evidence, safety information, provenance, and version history.

The second and third stages comprise phytochemical identity resolution and compound exposure modeling. Medical digital twins depend on the integration of mechanistic models with specific biological data and iterative comparison between predicted and observed system behavior [29]. Accordingly, the exposure module should accept only constituents whose identity and composition are sufficiently documented for the intended analysis. It can then integrate bioavailability evidence, absorption, distribution, metabolism, excretion, PBPK logic where supported, population pharmacokinetics where supported, active or toxic metabolites, and multi-compound exposure interactions. When exposure information is inadequate, the framework should output an evidence gap or bounded scenario rather than a falsely precise concentration estimate.

The fourth and fifth stages address target engagement and pathway response. Roadmaps for complex biological twins emphasize modular and multiscale development, common standards, transparent interfaces, benchmark problems, and interdisciplinary validation [30]. The target module therefore separates predicted interactions from measured binding, intracellular engagement, functional modulation, and causal evidence. Only confidence-weighted targets proceed to pathway modeling. The pathway module integrates causal network structure, systems pharmacology, tissue and phenotype context, feedback, temporal behavior, and multi-compound effects. Each module remains independently reviewable so that an error in chemical identity, exposure, target annotation, or network structure can be localized rather than concealed within an opaque end-to-end score.

The sixth stage combines safety-risk interpretation and bounded therapeutic outcome simulation, while the seventh introduces uncertainty, expert review, validation planning, and decision controls. Computational performance alone is insufficient for translation because implementation, regulation, equity, accountability, privacy, workflow integration, and potential clinical harm also influence digital twin credibility [31]. Safety interpretation therefore integrates ADMET evidence, toxicity findings, off-target activity, herb–drug interaction mechanisms, and pharmacovigilance signals. Therapeutic outcome simulation may compare mechanistically plausible response scenarios, but every output must disclose parameter uncertainty, structural uncertainty, evidence quality, applicability limits, and prohibited clinical interpretations. Pharmacologists, pharmacometricians, toxicologists, analytical scientists, natural product specialists, clinicians, and data-governance experts should review the model according to the context of use.

The final stage is feedback updating under version control. Patient digital twins should be distinguished from static records, generic simulations, synthetic patients, and population-level prediction models by their specific representation, meaningful linkage to observations, and capacity for justified updating [32]. In the proposed framework, new analytical results, exposure measurements, target-engagement experiments, pathway biomarkers, safety signals, literature findings, and validation outcomes can revise the relevant modules. Every material change should create an auditable model version and trigger regression testing or revalidation proportionate to its effect. The framework remains conceptual: it defines components, information flow, credibility requirements, and decision boundaries but does

not claim that a complete natural product digital twin has been implemented or validated. **Table 3** presents the proposed digital twin framework for natural product pharmacology.

Table 3. Proposed Digital Twin Framework for Natural Product Pharmacology: Data Foundation, Phytochemical Identity, Compound Exposure, Target Engagement, Pathway Response, Safety Risk, Therapeutic Outcome Simulation, Expert Review, Validation Planning, Feedback Updating, and Translational Boundaries

Framework stage	Core purpose	Required input	Modeling or interpretive function	Potential output	Validation need	Failure risk	Feedback mechanism	Translational boundary
Natural product data foundation	Establish traceable product identity and evidence provenance	Botanical identity, origin, preparation, formulation, batch, analytical and literature metadata	Harmonize product, batch, constituent and evidence records	Versioned natural product evidence object	Authentication, provenance and data-quality audit	Wrong species, adulteration, batch mismatch or undocumented processing	Update when new sourcing, analytical or quality evidence emerges	No pharmacological inference from an unauthenticated or inadequately characterized material
Phytochemical identity resolution	Define the chemical entities eligible for modeling	Structures, stereochemistry, metabolites, quantitative profiles and analytical confidence	Resolve identities, duplicates, ambiguity and confidence	Curated phytochemical profile	Orthogonal analytical confirmation and reference standards	Ambiguous, duplicated or incorrectly assigned compounds	Reconcile new spectra, standards and metabolite evidence	Unresolved constituents remain explicitly unknown
Compound exposure modeling	Estimate biologically plausible concentrations over time	Composition, formulation, ADME, administration, physiology and covariates	Simulate or bound systemic, tissue and metabolite exposure	Exposure distributions with uncertainty	Observed pharmacokinetic comparison and external evaluation	Implausible exposure assumptions and inadequate mixture representation	Recalibrate with new concentration and biomarker evidence	No target or outcome inference without plausible exposure
Target engagement modeling	Determine whether exposed constituents interact with proposed targets	Binding, occupancy, CETSA, chemoproteomic, functional and exposure evidence	Weight target evidence and model engagement where justified	Target-confidence profile and engagement hypotheses	Orthogonal assays, relevant controls and replication	Equating prediction or binding with causal therapeutic action	Update with engagement and perturbation experiments	Target engagement does not establish therapeutic efficacy
Pathway-response modeling	Represent propagation from target modulation to biological systems	Supported targets, causal topology, kinetics, feedback and phenotype context	Simulate dynamic or qualitative pathway responses	Pathway-response hypotheses and sensitive mechanisms	Perturbation studies and biomarker confirmation	Associational networks presented as causal or generalizable	Compare predicted states with experimental responses	Pathway response does not establish clinical outcome
Safety-risk modeling	Identify exposure-dependent	ADMET, toxicology, off-target, herb–drug	Integrate hazard, exposure, interaction	Prioritized safety hypotheses	Calibration against known safety	Predicted low risk described	Update with experiments, case	No declaration of safety or clinical

	hazards and interactions	interaction, susceptibility and pharmacovigilance evidence	and uncertainty		evidence and targeted experiments	as proof of safety	assessment and real-world signals	management recommendation
Therapeutic outcome simulation	Explore bounded response scenarios	Qualified PK/PD, pathway, phenotype and endpoint models	Propagate mechanistic states to predefined research outcomes	Simulated therapeutic outcome distributions	Independent and prospective endpoint validation	False precision and clinical overclaiming	Compare simulations with subsequent observations	Simulation is not validated clinical benefit
Virtual patient or virtual population logic	Represent individual or population heterogeneity	Covariates, biomarkers, physiology, organ function, co-medications and population distributions	Personalize parameters or generate qualified virtual populations	Individual or population scenario distributions	Predictive checks, representativeness analysis and prospective testing	Bias, poor transportability and biologically implausible synthetic subjects	Update using longitudinal and population evidence	Not autonomous personalized therapy or a substitute for trials
Uncertainty quantification	Make data, parameter and structural uncertainty explicit	Measurement error, parameter distributions, structural alternatives and evidence-quality ratings	Sensitivity analysis, probabilistic propagation and model comparison	Intervals, uncertainty maps and influential assumptions	Calibration and empirical coverage assessment	Hidden structural uncertainty and overconfident outputs	Revise uncertainty as evidence and model structure change	Decision use restricted when uncertainty is excessive
Expert review	Assess pharmacological, toxicological and translational plausibility	Model documentation, assumptions, outputs, discrepancies and uncertainty	Multidisciplinary structured review	Accept, revise, restrict or reject recommendation for research use	Predefined review criteria and documented accountability	Automation bias or undocumented subjective judgment	Reviewer findings become traceable model-change requests	The model does not replace accountable experts
Validation planning	Match credibility evidence to the intended context of use	Intended use, model-risk assessment, datasets and acceptance criteria	Plan verification, calibration, internal, external and experimental tests	Prospective validation plan	Independent datasets and predefined performance or plausibility criteria	Circular validation, data leakage or post hoc acceptance criteria	Failed tests trigger revision, scope reduction or rejection	Claims cannot exceed the validated context
Feedback updating	Maintain correspondence with new evidence	New analytical, experimental, pharmacokinetic, safety and outcome data	Bayesian updating, recalibration, discrepancy analysis and version control	Updated model version and audit trail	Regression testing and proportionate revalidation	Model drift, unstable updating or loss of reproducibility	Closed evidence–model–experiment feedback loop	Each version retains a separately documented scope
No clinical-	Prevent unsupporte	Validation status,	Enforce output	Research-only	Claim audit and	Simulatio n	Boundar y	Clinical adoption or

claim boundary	d efficacy, safety or treatment conclusions	intended audience, context of use and governance assessment	labels, prohibited claims and decision restrictions	interpretation statement	accountable approval	presented as medical advice or validated clinical evidence	reviewed only after new validation evidence	regulatory acceptance requires separate evidence and authorization

Figure 2 presents the proposed digital twin framework for natural product pharmacology, integrating compound exposure, target engagement, pathway response, safety risk, therapeutic outcome simulation, expert review, validation planning, and feedback updating.

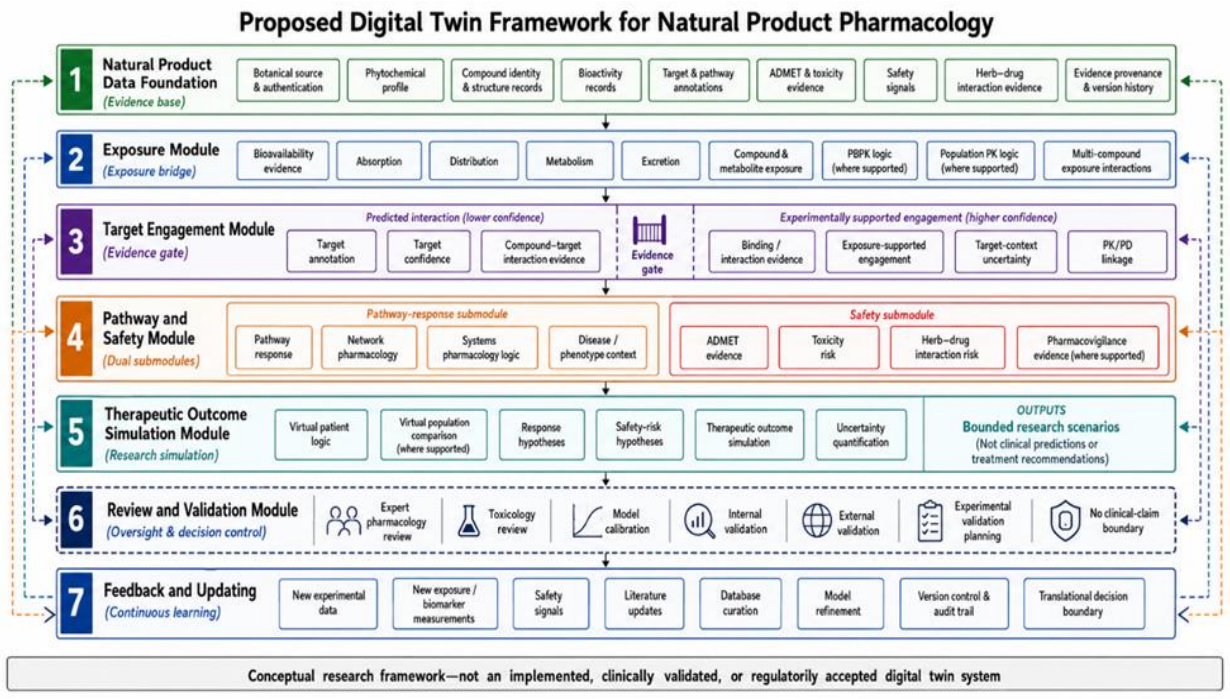

Figure 2. Proposed Digital Twin Framework for Natural Product Pharmacology

Alt-text description

A conceptual digital twin framework showing natural product data inputs flowing into exposure modeling, target engagement, pathway response, safety-risk modeling, therapeutic outcome simulation, uncertainty assessment, expert review, validation planning, translational boundaries, and feedback loops.

Translational implications

The proposed framework may support natural product and phytopharmaceutical development by clarifying which evidence is needed before chemical composition, exposure, target, pathway, safety, or response claims can be connected. Translation of health digital twins requires fit-for-purpose data, interoperable infrastructure, governance, qualified computational components, external validation, accountable review, and integration into well-defined research or healthcare workflows [33]. In early natural product research, the framework could identify whether analytical characterization is sufficient, whether predicted targets are reachable at plausible exposures, whether pathway hypotheses are mechanistically coherent, and which experiments would most reduce uncertainty. It may thereby improve prioritization without assigning unsupported efficacy or commercial-development status to a candidate.

Safety assessment and herb–drug interaction research may particularly benefit from a modular twin structure. Exposure models can identify which constituents or metabolites warrant enzyme, transporter, organ-toxicity, or pharmacodynamic-interaction testing, while pharmacovigilance signals can be used to update prior risk hypotheses. Systems pharmacology models can then connect exposure-dependent target effects with disease and toxicity pathways, allowing researchers to compare competing mechanisms and design discriminating experiments. These functions remain investigational because the health digital twin literature is heterogeneous,

and many described systems lack the dynamic linkage, validation evidence, external evaluation, or clinical integration required for adoption [34].

Responsible development should therefore use digital twin outputs to guide research prioritization, model refinement, validation planning, and transparent discussion of uncertainty. Experimental pharmacology remains necessary to confirm compound identity, exposure, target engagement, mechanism, interaction, and toxicity, while clinical research remains necessary to determine therapeutic benefit, real-world safety, and clinical utility. Expert review should remain accountable for determining whether a model is biologically plausible, whether its context of use is appropriate, and whether its outputs can support a particular research decision. The proposed architecture is not intended to recommend natural products, alter treatment, replace trials, or support autonomous therapeutic decisions.

CONCLUSION

This article proposes a conceptual digital twin framework for natural product pharmacology that connects authenticated natural product data with phytochemical identity, compound exposure, target engagement, pathway response, safety-risk interpretation, therapeutic outcome simulation, uncertainty quantification, expert review, validation planning, and feedback updating. Its central premise is that a useful natural product twin must preserve an auditable evidence chain from the administered material to each simulated biological consequence. Exposure plausibility must precede target interpretation, target confidence must constrain pathway modeling, and pathway or safety simulations must remain distinct from validated clinical outcomes. Virtual patient and virtual population methods may strengthen scenario exploration, but they cannot compensate for missing chemical, pharmacokinetic, mechanistic, toxicological, or clinical evidence. By embedding validation gates, explicit decision boundaries, and a no-clinical-claim rule into the architecture, the framework positions digital twins as tools for hypothesis generation and translational planning rather than as substitutes for experiments, professional judgment, clinical investigation, or regulatory evaluation.

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