



Digital Evidence Chains for Phytopharmaceutical Claims: Connecting In Silico Evidence, Experimental Validation, Traditional Use, Safety Data, and Regulatory Logic

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ABSTRACT

Phytopharmaceutical claims often draw on heterogeneous evidence, including botanical identity, chemical characterization, computational prediction, experimental validation, traditional use, safety data, and regulatory reasoning. However, these evidence types do not support the same kinds of claims, and their overextension can lead to unsupported statements about efficacy, mechanism, safety, or regulatory relevance. This article proposes a digital evidence-chain framework for organizing phytopharmaceutical claim support through transparent links among evidence source, method, validation status, uncertainty, claim wording, expert interpretation, and decision boundary. The framework treats in silico prediction, network inference, molecular docking, and ADMET prediction as hypothesis-generating or plausibility-supporting evidence that requires experimental validation before stronger mechanistic or translational claims are made. It also treats traditional use as contextual evidence that may inform historical and ethnopharmacological interpretation but does not establish modern clinical effectiveness or universal safety alone. Safety data, pharmacovigilance signals, adverse-event evidence, herb–drug interaction evidence, and exposure plausibility are positioned as mandatory qualifiers for responsible claim support. Regulatory logic is framed as claim-specific reasoning rather than a universal evidence hierarchy. The proposed model contributes a structured approach for aligning evidence type, claim type, uncertainty, validation gaps, safety qualification, digital provenance, and expert review in phytopharmaceutical research.

Key Words: *Phytopharmaceuticals, Evidence chains, In silico evidence, Experimental validation, Traditional use, Safety data*

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INTRODUCTION

Phytopharmaceutical claims are evidence-dependent statements rather than simple descriptions of botanical origin, historical use, or pharmacological promise. Natural products remain important sources of therapeutic discovery, but their discovery relevance does not automatically justify strong claims about modern

phytopharmaceutical efficacy, mechanism, safety, or regulatory acceptability [1].

A claim that a product is pharmacologically plausible, traditionally used, experimentally active, clinically supported, or regulatory-relevant requires a different evidence basis in each case.

Modern natural-product research increasingly combines chemistry, biology, informatics, pharmacology, and

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translational reasoning, creating opportunities for more systematic evidence integration. At the same time, this diversity can fragment interpretation when computational predictions, biological assays, historical records, and safety observations are presented without clear boundaries between discovery, plausibility, validation, and claim support [2]. A digital evidence-chain approach is therefore needed to connect each evidence source to the claim it can responsibly support.

Clinical evidence for herbal and phytopharmaceutical interventions also depends on transparent reporting of the intervention itself. Reporting studies of Chinese herbal medicine formula trials show that trial interpretation requires sufficient detail about the herbal intervention, because weak intervention transparency can limit the ability to judge whether the evidence applies to a specific preparation or claim [3]. This reinforces the need for evidence chains that begin with product identity and preparation context rather than with outcomes alone.

Evidence-chain integrity should also begin before clinical results are available. Protocol-level reporting in traditional medicine trials is relevant because planned intervention details, outcomes, comparators, and methodological assumptions shape later claim interpretation [4]. The aim of this article is to propose an original digital evidence-chain framework for phytopharmaceutical claims that connects product identity, chemical characterization, in silico evidence, experimental validation, traditional use, safety data, evidence provenance, uncertainty, expert review, and regulatory decision boundaries.

Evidence chains in phytopharmaceutical research

A digital evidence chain in phytopharmaceutical research is a structured, traceable sequence linking a product-specific claim to the evidence used to support, limit, or reject that claim. Biomedical provenance research shows that evidence reuse and interpretation depend on knowing where data came from, how they were processed, and what transformations affected them [5]. In phytopharmaceutical research, this means that claims should be linked not only to citations but also to botanical identity, preparation context, chemical characterization, method metadata, validation status, and uncertainty.

Evidence chains differ from simple literature summaries because they preserve relationships among evidence source, method, interpretation, and claim boundary. Workflow provenance research in biomedical settings indicates that provenance should include processes and workflows, not merely final outputs [6]. For phytopharmaceutical claims, this distinction is crucial because a network prediction, docking result, extract assay, adverse-event report, or traditional-use record may become

misleading if detached from its method, assumptions, and context.

Digital evidence chains can also use structured representations to connect evidence entities that are often scattered across pharmacology, toxicology, clinical, and informatics sources. A knowledge graph developed for pharmacokinetic natural product–drug interactions illustrates how natural products, chemicals, enzymes, transporters, drugs, and interaction evidence can be represented as linked entities rather than isolated records [7]. In this article, such linking is interpreted as a support mechanism for transparent reasoning, not as proof that a relationship is clinically established.

Natural product–drug interaction repository work further shows that claim-relevant evidence may span chemical characterization, pharmacokinetic mechanisms, clinical study data, and interaction interpretation [8]. This supports a broader evidence-chain principle: phytopharmaceutical claims should not be evaluated from a single evidence table alone. They should be examined through connected records that show whether the evidence is product-specific, chemically interpretable, mechanistically plausible, experimentally supported, safety-qualified, and appropriate for the proposed claim wording.

In silico and experimental evidence

In silico evidence is valuable in phytopharmaceutical research because it can help prioritize compounds, targets, pathways, and mechanisms for further investigation. Network pharmacology approaches for medicinal plants can support multi-target hypothesis generation by mapping relationships among constituents, targets, and disease-relevant pathways [9]. Within an evidence chain, such outputs should be categorized as mechanistic hypotheses or prioritization evidence unless they are supported by product-specific characterization and downstream validation.

The interpretive boundary of network pharmacology is especially important in natural-product research because predicted networks can be affected by database incompleteness, compound misidentification, target prediction uncertainty, pathway overrepresentation, and insufficient experimental follow-up. Recent critical discussion of network pharmacology in natural products emphasizes pitfalls that can arise when computational outputs are treated as confirmed mechanisms [10]. Therefore, the framework treats network-inferred evidence as useful but explicitly uncertainty-bearing.

Other computational approaches support different parts of the evidence chain. ADME prediction can contribute to exposure plausibility by estimating pharmacokinetic properties, drug-likeness, and medicinal chemistry characteristics, but it remains prediction-level evidence

requiring empirical confirmation [11]. Molecular docking can contribute to target-hypothesis development by modeling possible ligand–target binding, but docking evidence alone cannot establish biological activity, pathway modulation, therapeutic effect, or clinical relevance [12].

In silico ADME/Tox profiling of natural products can help identify early developability and toxicity concerns, especially when experimental resources are limited, but such predictions should be treated as screening evidence rather than definitive safety evidence [13]. Experimental

validation can strengthen a computational hypothesis when it tests relevant biological activity in defined systems, as shown by natural-product studies that combine multi-target screening with experimental validation [14]. Even then, experimental bioactivity supports biological plausibility or preclinical support only within the limits of the material, assay, model, exposure context, and validation design.

Table 1 summarises the roles and limitations of in silico and experimental evidence in phytopharmaceutical claim support.

Table 1. In Silico and Experimental Evidence for Phytopharmaceutical Claims: Computational Prediction, Network Inference, Molecular Docking, ADMET Prediction, In Vitro Validation, Preclinical Evidence, Mechanistic Plausibility, Interpretation Boundaries, and Validation Needs

Evidence type	Main purpose	Claim type supported	Evidence strength	Interpretation boundary	Validation requirement	Risk of overclaiming	Framework role
Target prediction	Prioritize possible molecular targets for constituents or extracts	Discovery hypothesis claim	Hypothesis-generating	Predicted target association is not target engagement	Requires experimental target or pathway validation	Presenting predicted targets as confirmed mechanisms	Early computational prioritization
Network pharmacology	Map possible multi-target and pathway relationships	Mechanistic plausibility claim	Plausibility-supporting when chemically and biologically contextualized	Network proximity does not establish causality	Requires pathway, target, or phenotypic validation	Treating network diagrams as mechanism proof	Mechanism-hypothesis organization
Molecular docking	Explore possible ligand–target binding interactions	Mechanistic plausibility claim	Screening-level structural hypothesis	Docking fit does not establish bioactivity or efficacy	Requires biochemical, cellular, or biophysical confirmation	Treating docking output as therapeutic evidence	Target-hypothesis refinement
ADME prediction	Estimate pharmacokinetic and developability plausibility	Discovery or exposure plausibility claim	Prediction-level evidence	Predicted absorption, distribution, metabolism, or excretion is not measured exposure	Requires empirical pharmacokinetic or exposure evidence where stronger claims are made	Treating predicted exposure as demonstrated bioavailability	Exposure plausibility screen
In silico toxicity prediction	Flag possible safety concerns or liabilities	Safety-screening claim	Early risk-screening evidence	Predicted toxicity does not prove harm or safety	Requires toxicological, clinical, or pharmacovigilance follow-up	Treating absence of predicted toxicity as proof of safety	Early safety triage
In vitro validation	Test biological activity in controlled experimental systems	Bioactivity claim	Experimentally supportive within assay limits	Cellular or biochemical activity does not establish clinical benefit	Requires reproducibility, relevant controls, and product characterization	Extrapolating assay activity to patient benefit	Biological plausibility support
Preclinical evidence	Examine pharmacological or toxicological effects in non-human systems	Preclinical support claim	Translationally informative but context-limited	Preclinical effect does not establish human effectiveness	Requires exposure relevance, model suitability, and later human evidence	Treating animal or model evidence as clinical proof	Translational bridge
Mechanistic assay evidence	Test a specific pathway, target,	Mechanistic plausibility or	Stronger than prediction when	Mechanistic signal remains model-dependent	Requires confirmation across relevant systems	Presenting one mechanism assay as full	Mechanism-validation checkpoint

or biological process	bioactivity claim	experimentally grounded	when stronger claims are made	therapeutic explanation
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Traditional use and safety evidence

Traditional use evidence is an important component of phytopharmaceutical interpretation, but it must be documented with attention to context, preparation, plant part, cultural setting, indication wording, and source quality. Recommended ethnopharmacological field-study standards emphasize that traditional medicinal knowledge should be recorded and reported with methodological care rather than reduced to unverified claims of use [15]. In the proposed framework, traditional use supports historical and ethnopharmacological context, not independent proof of modern clinical effectiveness.

Historical records can also be organized more systematically when they are treated as evidence requiring collation, interpretation, and uncertainty assessment. A pragmatic historical assessment framework for traditional plant medicines shows that documented empirical use and safety information can be gathered in a structured way, while still requiring caution when translating historical evidence into contemporary claim support [16]. This distinction helps prevent traditional continuity from being overstated as universal efficacy or safety.

Product identity and chemical characterization are essential for connecting traditional-use evidence to modern pharmacological and toxicological evidence. Best-practice guidance for chemical characterization of extracts used in pharmacological and toxicological research stresses that extract identity and composition must be sufficiently described for research interpretation [17]. In evidence-chain terms, a traditional-use record becomes claim-relevant only when the plant identity, plant part, preparation, extraction context, and chemical comparability are made explicit enough to support responsible linkage.

Safety evidence requires its own evidence chain rather than being inferred from use history or computational prediction alone. Herbal pharmacovigilance literature highlights concerns about reporting, causality, product variability, and future surveillance needs in herbal medicine safety assessment [18]. Herb–drug interaction interpretation also requires causality assessment before patient-relevant risk claims are made [19]. Pharmacovigilance database studies can inform adverse-event signals associated with herbal medicines, but such signals require uncertainty-aware interpretation because reporting patterns, product identification, exposure context, and causality may be incomplete [20].

Regulatory logic and claim support

Regulatory logic in phytopharmaceutical research should be understood as claim-specific evidence reasoning rather than as a single universal hierarchy applied identically to every product, preparation, or statement. Critical analysis of plant-derived supplement quality, safety, efficacy, and regulatory needs shows that responsible interpretation requires coordinated attention to product quality, risk, evidence sufficiency, and the wording of claims [21]. In the proposed evidence-chain approach, regulatory relevance is therefore not treated as a final label but as an interpretive boundary that asks what kind of evidence is needed for a particular claim to be responsibly stated.

Traditional-use evidence is especially important for botanical and phytopharmaceutical claim discussions, but its regulatory and scientific role remains contested. Stakeholder arguments about botanical health claims indicate that traditional use may contribute contextual information while raising unresolved questions about whether such evidence is sufficient for substantiating health effects [22]. The framework therefore separates traditional-use contextual claims from bioactivity claims, clinical-support claims, and regulatory-relevant claims.

The complexity of using traditional-use data to support health effects also requires careful claim wording. Critical analysis of traditional-use evidence for botanical health claims shows that historical use does not automatically demonstrate modern health effects, particularly when product identity, preparation, exposure, population, and outcome context differ [23]. Within the framework, traditional use may support historical continuity or ethnopharmacological relevance, but it should not be converted into an efficacy or safety claim without additional evidence.

Claim support also depends on the jurisdictional and product-category context in which a claim is interpreted. Comparative analysis of health-claim requirements shows that substantiation expectations differ across regulatory settings and that claim wording must be aligned with the type and quality of evidence available [24]. Regulatory frameworks for traditional, complementary, and integrative medicines further indicate that evidence requirements are context-dependent and should not be treated as equivalent to automatic authorization or acceptance [25]. Thus, a digital evidence chain should distinguish evidence assessment, claim wording, safety qualification, expert review, and regulatory interpretation boundary.

Table 2 maps traditional use, safety evidence, and regulatory logic to responsible phytopharmaceutical claim support.



Table 2. Traditional Use, Safety Evidence, and Regulatory Logic for Phytopharmaceutical Claim Support: Historical Context, Ethnopharmacological Evidence, Safety Data, Pharmacovigilance, Herb–Drug Interaction Evidence, Claim Wording, Evidence Sufficiency, and Decision Boundaries

Evidence or logic domain	Core question	Claim-support contribution	Evidence required	Safety requirement	Regulatory interpretation boundary	Uncertainty or limitation	Failure risk
Traditional use evidence	What has been historically or culturally used, and in what context?	Supports traditional-use contextual claims	Documented source, plant part, preparation, use context, and indication wording	Safety history must be interpreted separately from safety proof	Does not by itself establish modern health-effect substantiation	Context may differ from modern product and population	Treating historical use as efficacy proof
Ethnopharmacological evidence	Was the use recorded with adequate methodological and cultural context?	Supports historical plausibility and research prioritization	Field-study method, informant context, preparation details, and documentation quality	Risk information should be recorded where available	Supports context, not automatic regulatory acceptance	Reporting quality and cultural context may vary	Decontextualized or extractive interpretation
Chemical characterization	Is the studied product chemically interpretable and comparable?	Supports product-specific claim linkage	Botanical identity, extract profile, analytical method, and batch information	Toxicological interpretation requires product comparability	A claim cannot be responsibly transferred across chemically different preparations	Chemical profiles may vary by source and processing	Evidence applied to the wrong product
Safety data	What risks are known or plausible for the defined product and exposure?	Supports safety-qualified claims	Toxicology, contraindication, exposure, adverse-event, and interaction evidence	Risk must be product-, exposure-, and population-specific	Safety qualification is not universal safety certification	Evidence may be incomplete or population-limited	False reassurance about safety
Pharmacovigilance	Are there adverse-event signals requiring interpretation?	Supports risk monitoring and uncertainty qualification	Signal source, case detail, seriousness, duplicate review, and causality assessment	Signals require cautious interpretation and follow-up	Signal detection is not proof of causality or absence of risk	Underreporting and incomplete product identity are common limitations	Ignoring emerging risk signals
Herb–drug interaction evidence	Could the product alter exposure or response to a medicine?	Supports interaction warning or risk qualification	Interacting drug, product, mechanism, exposure, and causality evidence	Interaction risk must be assessed before patient-facing reassurance	Interaction evidence does not automatically define all clinical management	Case quality, exposure uncertainty, and confounding may limit certainty	Unsafe extrapolation to co-use contexts
Claim wording	Does the wording match the evidence type and evidence strength?	Converts evidence interpretation into responsible statements	Exact claim text, evidence chain, uncertainty statement, and validation gap	Safety qualifiers should accompany relevant claims	Claim wording must remain within scientific and regulatory boundaries	Ambiguous wording may imply stronger support than exists	Overstatement or implied authorization
Regulatory logic	What evidence is needed for the claim in its intended context?	Defines decision boundary and evidence	Product category, claim type, jurisdictional context, evidence package, and	Benefit-risk and safety context must be explicit	Regulatory relevance is not regulatory approval	Rules and expectations may vary by context	Treating scientific plausibility as authorization

sufficiency
question

expert
interpretation

Figure 1 illustrates how different evidence types support different levels of phytopharmaceutical claims, from discovery hypotheses to regulatory-relevant claim support.

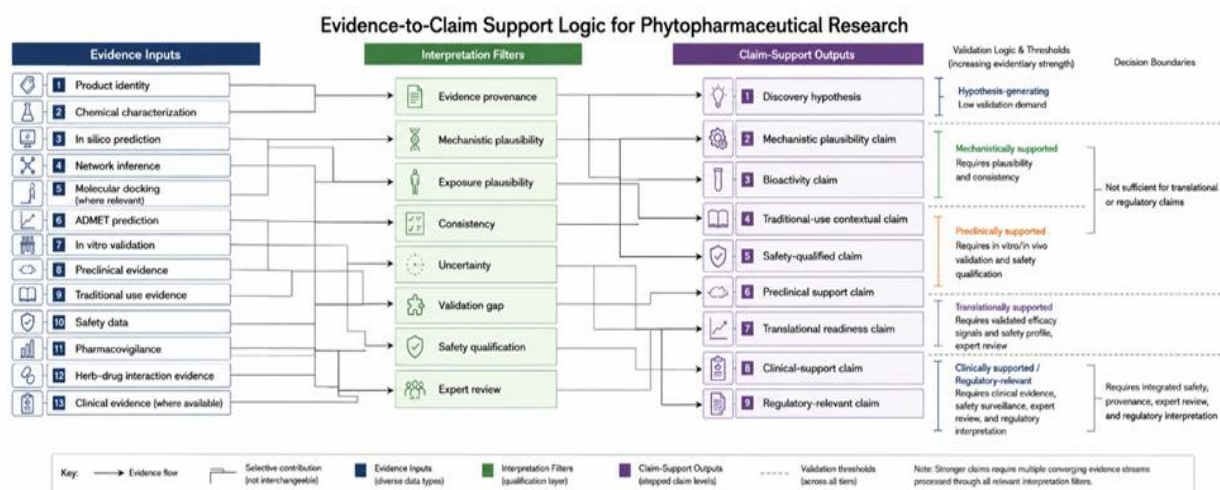


Figure 1. Evidence-to-Claim Support Logic for Phytopharmaceutical Research

Alt-text description

A claim-support logic diagram showing evidence types connected to claim levels. In silico evidence supports discovery hypotheses, experimental evidence supports biological plausibility, traditional use supports historical context, safety data qualify risk interpretation, clinical evidence supports stronger translational claims, and regulatory logic defines claim boundaries.

Proposed evidence framework

The proposed digital evidence-chain framework begins with phytopharmaceutical product identity and safety-relevant context. Natural product–drug interaction research recommendations show that interaction evidence requires structured attention to the product, exposure context, pharmacokinetic mechanism, and decision relevance [26]. In the framework proposed here, product identity, botanical authentication, plant part, preparation, extraction context, chemical characterization, and provenance form the entry gate before any mechanistic, safety, clinical, or regulatory-relevant claim is considered.

The second stage connects in silico prediction, experimental validation, exposure plausibility, and interaction logic. Modeling approaches for pharmacokinetic natural product–drug interactions show that decision-making can be supported when model assumptions, exposure considerations, uncertainty, and empirical evidence are made explicit [27]. Adaptation of drug–drug interaction study logic to natural product–drug interaction research further supports the need to connect

prediction, clinical pharmacokinetic design, and regulatory interpretation carefully rather than assuming that conventional frameworks can be transferred without qualification [28].

The third stage is digital provenance and auditability. A provenance-driven FAIR data pipeline demonstrates how scientific workflows can be made traceable through records of source data, transformation steps, quality-control actions, versioning, and workflow history [29]. In the proposed phytopharmaceutical framework, this logic is applied conceptually to evidence chains so that a claim can be traced backward to product identity, evidence source, method, validation status, uncertainty field, expert interpretation, and decision boundary.

The fourth stage separates evidence evaluation from decision interpretation. Evidence-to-decision frameworks show that evidence assessment should be linked to explicit judgments about benefits, harms, values, certainty, feasibility, and implementation rather than treated as a purely mechanical aggregation process [30]. For phytopharmaceutical claims, this means that a digital chain should not simply accumulate evidence; it should identify what the evidence can support, what remains uncertain, what validation is missing, and what claim wording would exceed the available support.

The final stage is expert-reviewed claim alignment. This is a proposed evidence-framework element that translates the preceding stages into transparent claim-support outputs: discovery hypothesis, mechanistic plausibility claim, bioactivity claim, traditional-use contextual claim, safety-

qualified claim, preclinical support claim, translational readiness claim, clinical-support claim, regulatory-relevant claim, or decision-support claim. Each output should include a validation gap, uncertainty statement, safety qualifier where relevant, and decision boundary indicating

that the framework supports responsible interpretation but does not provide medical advice, clinical authorization, or regulatory approval.

Table 3 presents the proposed digital evidence-chain framework for phytopharmaceutical claims.

Table 3. Proposed Digital Evidence-Chain Framework for Phytopharmaceutical Claims: Product Identity, In Silico Evidence, Experimental Validation, Traditional Use, Safety Data, Claim Logic, Regulatory Relevance, Digital Traceability, Expert Review, and Validation Gaps

Framework stage	Core evidence question	Required digital record	Evidence source	Claim-support function	Uncertainty field	Validation gate	Decision-support output	Failure risk
Product identity and context	What exactly is the phytopharmaceutical material?	Botanical name, authentication method, plant part, preparation, extraction context, batch details, and provenance	Botanical, analytical, manufacturing, or research records	Prevents evidence transfer across non-equivalent products	Identity confidence and product comparability	Botanical and product-description review	Product-specific evidence chain initiation	Misattributed evidence
Chemical characterization	Is the material chemically interpretable?	Analytical method, marker constituents, extract profile, batch comparability, and method metadata	Pharmacognosy, analytical chemistry, or quality-control evidence	Links chemistry to pharmacology and safety interpretation	Chemical variability and analytical completeness	Characterization adequacy review	Chemistry-supported claim boundary	Unreproducible or non-comparable claims
In silico evidence	What hypotheses are computationally plausible?	Input structures, database versions, models, parameters, output files, and assumptions	Target prediction, network pharmacology, docking, ADMET, or toxicity prediction	Supports discovery and mechanistic hypothesis generation	Model confidence, applicability domain, and database uncertainty	Experimental follow-up requirement	Prioritized hypothesis or validation plan	Computational overclaiming
Experimental validation	Has biological activity or mechanism been tested?	Assay system, material, concentration or exposure context, controls, outcomes, and reproducibility details	In vitro, biochemical, cellular, animal, or preclinical evidence	Supports bioactivity or mechanistic plausibility within model y limits	Assay relevance and reproducibility uncertainty	Product-specific and model-relevance review	Bioactivity or preclinical support statement	Assay-to-claim mismatch
Traditional use evidence	What historical or ethnopharmacological context exists?	Source, community or historical context, plant part, preparation, indication wording, and documentation method	Ethnopharmacological field studies or historical evidence	Supports contextual or research-prioritization claims	Contextual fit and documentation completeness	Source-quality and cultural-context review	Traditional-use contextual claim	Treating use history as proof
Safety evidence	What risks or safety uncertainties are known?	Toxicology, contraindications, adverse events, exposure context, interaction evidence, and patient-risk factors	Toxicological, pharmacovigilance, clinical, or interaction evidence	Qualifies safety-related wording and risk interpretation	Causality, exposure, and population uncertainty	Safety-review and risk-qualification gate	Safety-qualified claim or risk flag	False reassurance
Claim-support logic	What claim can the evidence responsibly support?	Exact claim wording, claim type, evidence chain version, rationale, and uncertainty statement	Integrated evidence-chain review	Aligns evidence type with claim type	Claim-strength uncertainty	Claim-evidence consistency review	Responsible claim wording	Overstatement

Regulatory relevance	What is the decision boundary for the intended claim context?	Product category, intended claim, jurisdictional context, evidence package, and review notes	Regulatory science and evidence-review literature	Defines boundary between scientific support and regulatory interpretation	Jurisdictional and category uncertainty	Expert and regulatory-logic review	Regulatory -relevant interpretation on boundary	Implied approval or legal overreach
Expert review and audit	Has the chain been critically examined?	Reviewer comments, conflict declarations, version history, decisions, and audit trail	Multidisciplinary review	Adds accountability and prevents opaque automation	Reviewer disagreement and unresolved gaps	Independent review and update gate	Reviewed evidence-chain output	Automation bias or hidden judgment

Figure 2 presents the proposed digital evidence-chain framework connecting phytopharmaceutical evidence sources, validation gates, claim logic, and regulatory decision boundaries.



Figure 2. Digital Evidence-Chain Framework for Phytopharmaceutical Claims

Alt-text description

A layered digital evidence-chain framework showing phytopharmaceutical product identity and chemical characterization feeding into in silico evidence, experimental validation, traditional use evidence, safety data, claim-support logic, expert review, digital traceability, and regulatory decision boundaries.

Practical implications

For phytopharmaceutical researchers, natural product pharmacologists, ethnopharmacologists, computational pharmacologists, safety scientists, evidence reviewers, and regulatory scientists, digital evidence chains can make claim development more transparent by requiring explicit links between evidence type, claim wording, safety qualification, and validation gap. Stakeholder use of evidence-to-decision frameworks shows that structured judgments can support practical decision processes when evidence interpretation is made explicit rather than hidden inside informal expert opinion [31]. In phytopharmaceutical research, this implies that evidence-

chain outputs should support deliberation, not replace expert judgment.

For digital decision-support platform designers, the framework provides a conceptual architecture for provenance-aware claim support. Clinical decision support literature emphasizes that digital systems can provide benefits but also carry risks related to implementation, usability, automation, and inappropriate reliance on system outputs [32]. Therefore, phytopharmaceutical evidence-chain platforms should include audit trails, uncertainty fields, safety alerts, claim-wording checks, expert-review workflows, and clear boundaries showing that decision support is not equivalent to clinical advice or regulatory authorization.

Future development should focus on standardized metadata for product identity, chemical characterization, traditional-use records, computational models, experimental validation, safety data, adverse-event evidence, interaction evidence, clinical evidence where available, and claim wording. Additional needs include claim-specific evidence grading, provenance-aware databases, validation-linked workflows, safety integration,

reproducibility checks, and expert-review interfaces. The most useful systems will likely be those that identify what evidence is present, what evidence is missing, what claims are supportable, what claims remain premature, and where further validation is needed.

CONCLUSION

This article proposed a digital evidence-chain framework for phytopharmaceutical claims that connects product identity, chemical characterization, in silico evidence, experimental validation, traditional use, safety data, digital provenance, claim-support logic, expert review, and regulatory boundaries. The central contribution is not a new clinical or regulatory grading system, but a structured way to align evidence type with claim type while preserving uncertainty, validation gaps, safety qualification, and decision boundaries. Evidence chains can support more responsible phytopharmaceutical research claims only when computational evidence, experimental evidence, traditional-use context, safety evidence, and regulatory interpretation are treated as complementary but non-interchangeable forms of support.

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REFERENCES

- [1] Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod.* 2020;83(3):770-803. doi:10.1021/acs.jnatprod.9b01285
- [2] Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, et al. Natural products for drug discovery in the 21st century: Innovations for novel drug discovery. *Int J Mol Sci.* 2018;19(6):1578. doi:10.3390/ijms19061578
- [3] Wang J, Shi D, Wang Y, Zhang X, Li H, Wang X, et al. Transparency and reporting characteristics of randomized controlled trials with Chinese herbal medicine formulas interventions. *Front Med.* 2024;18(4):757-61. doi:10.1007/s11684-024-1092-4
- [4] Zhang L, Li H, Hu L, Ou X, Tan H, Zhang X, et al. Reporting characteristics and quality of randomized controlled trial protocols in traditional Chinese medicine: A cross-sectional study. *Front Pharmacol.* 2024;15:1389808. doi:10.3389/fphar.2024.1389808
- [5] Johns M, Meurers T, Wirth FN, Haber AC, Müller A, Halilovic M, et al. Data provenance in biomedical research: Scoping review. *J Med Internet Res.* 2023;25:e42289. doi:10.2196/42289
- [6] Gierend K, Krüger F, Genehr S, Hartmann F, Siegel F, Waltemath D, et al. Provenance information for biomedical data and workflows: Scoping review. *J Med Internet Res.* 2024;26:e51297. doi:10.2196/51297
- [7] Taneja SB, Callahan TJ, Paine MF, Kane-Gill SL, Kilicoglu H, Joachimiak MP, et al. Developing a knowledge graph for pharmacokinetic natural product-drug interactions. *J Biomed Inform.* 2023;140:104341. doi:10.1016/j.jbi.2023.104341
- [8] Birer-Williams C, Gufford BT, Chou E, Alilio M, VanAlstine S, Morley RE, et al. A new data repository for pharmacokinetic natural product-drug interactions: From chemical characterization to clinical studies. *Drug Metab Dispos.* 2020;48(10):1104-12. doi:10.1124/dmd.120.000054
- [9] Noor F, Tahir Ul Qamar M, Ashfaq UA, Albutti A, Alwashmi ASS, Aljasir MA. Network pharmacology approach for medicinal plants: Review and assessment. *Pharmaceuticals (Basel).* 2022;15(5):572. doi:10.3390/ph15050572
- [10] Panossian A. Trends and pitfalls in the progress of network pharmacology research on natural products. *Pharmaceuticals (Basel).* 2025;18(4):538. doi:10.3390/ph18040538
- [11] Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 2017;7:42717. doi:10.1038/srep42717
- [12] Pinzi L, Rastelli G. Molecular docking: Shifting paradigms in drug discovery. *Int J Mol Sci.* 2019;20(18):4331. doi:10.3390/ijms20184331
- [13] Durán-Iturbide NA, Díaz-Eufracio BI, Medina-Franco JL. In silico ADME/Tox profiling of natural products: A focus on BIOFACQUIM. *ACS Omega.* 2020;5(26):16076-84. doi:10.1021/acsomega.0c01581
- [14] Deng YH, Wang NN, Zou ZX, Zhang L, Xu KP, Chen AF, et al. Multi-target screening and experimental validation of natural products from *Selaginella* plants against Alzheimer's disease. *Front Pharmacol.* 2017;8:539. doi:10.3389/fphar.2017.00539
- [15] Weckerle CS, de Boer HJ, Puri RK, van Andel T, Bussmann RW, Leonti M. Recommended standards for conducting and reporting ethnopharmacological field studies. *J Ethnopharmacol.* 2018;210:125-32. doi:10.1016/j.jep.2017.08.018

- [16] Clair S, Kirk R, Coulter ID, Saller R. A pragmatic historical assessment tool: A new systematic framework for the collation and evaluation of documented empirical effectiveness and safety of traditional plant medicines in the European Materia Medica. *Complement Med Res.* 2023;30(4):340-53. doi:10.1159/000531021
- [17] Heinrich M, Jalil B, Abdel-Tawab M, Echeverria J, Kulić Ž, McGaw LJ, et al. Best practice in the chemical characterisation of extracts used in pharmacological and toxicological research—The ConPhyMP—Guidelines. *Front Pharmacol.* 2022;13:953205. doi:10.3389/fphar.2022.953205
- [18] Choudhury A, Singh PA, Bajwa N, Dash S, Bisht P. Pharmacovigilance of herbal medicines: Concerns and future prospects. *J Ethnopharmacol.* 2023;309:116383. doi:10.1016/j.jep.2023.116383
- [19] Awortwe C, Makiwane M, Reuter H, Muller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb–drug interactions in patients. *Br J Clin Pharmacol.* 2018;84(4):679-93. doi:10.1111/bcp.13490
- [20] Kongkaew C, Phan DTA, Janusorn P, Mongkhon P. Estimating adverse events associated with herbal medicines using pharmacovigilance databases: Systematic review and meta-analysis. *JMIR Public Health Surveill.* 2024;10:e63808. doi:10.2196/63808
- [21] Abdel-Tawab M. Do we need plant food supplements? A critical examination of quality, safety, efficacy, and necessity for a new regulatory framework. *Planta Med.* 2018;84(6-07):372-93. doi:10.1055/s-0043-123764
- [22] Lenssen KGM, Bast A, de Boer A. Should botanical health claims be substantiated with evidence on traditional use? Reviewing the stakeholders' arguments. *PharmaNutrition.* 2020;14:100232. doi:10.1016/j.phanu.2020.100232
- [23] Lenssen KGM, Bast A, de Boer A. The complexity of proving health effects with data on 'traditional use': A critical perspective on supporting botanical health claims. *Trends Food Sci Technol.* 2022;120:338-43. doi:10.1016/j.tifs.2021.12.030
- [24] Kušar A, Žmitek K, Lähteenmäki L, Raats MM, Pravst I. Comparison of requirements for using health claims on foods in the European Union, the USA, Canada, and Australia/New Zealand. *Compr Rev Food Sci Food Saf.* 2021;20(2):1307-32. doi:10.1111/1541-4337.12716
- [25] Chen Q, Cheng HJ, Bian ZX, Lyu AP, Yang Y, Chan KW. Regulatory frameworks and evidence requirements for traditional, complementary and integrative medicines. *Bull World Health Organ.* 2025;103(11):696-707C. doi:10.2471/BLT.25.293437
- [26] Paine MF, Shen DD, McCune JS. Recommended approaches for pharmacokinetic natural product-drug interaction research: A NaPDI Center commentary. *Drug Metab Dispos.* 2018;46(7):1041-5. doi:10.1124/dmd.117.079962
- [27] Cox EJ, Tian DD, Clarke JD, Rettie AE, Unadkat JD, Thummel KE, et al. Modeling pharmacokinetic natural product–drug interactions for decision-making: A NaPDI Center recommended approach. *Pharmacol Rev.* 2021;73(2):847-59. doi:10.1124/pharmrev.120.000106
- [28] Cox EJ, Rettie AE, Unadkat JD, Thummel KE, McCune JS, Paine MF. Adapting regulatory drug-drug interaction guidance to design clinical pharmacokinetic natural product-drug interaction studies: A NaPDI Center recommended approach. *Clin Transl Sci.* 2022;15(2):322-9. doi:10.1111/cts.13172
- [29] Mitchell SN, Lahiff A, Cummings N, Hollocombe J, Boskamp B, Field R, et al. FAIR data pipeline: Provenance-driven data management for traceable scientific workflows. *Philos Trans A Math Phys Eng Sci.* 2022;380(2233):20210300. doi:10.1098/rsta.2021.0300
- [30] Schünemann HJ, Wiercioch W, Brozek J, Etzeandía-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol.* 2017;81:101-10. doi:10.1016/j.jclinepi.2016.09.009
- [31] Dahm P, Oxman AD, Djulbegovic B, Guyatt GH, Murad MH, Amato L, et al. Stakeholders apply the GRADE evidence-to-decision framework to facilitate coverage decisions. *J Clin Epidemiol.* 2017;86:129-39. doi:10.1016/j.jclinepi.2017.02.019
- [32] Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: Benefits, risks, and strategies for success. *NPJ Digit Med.* 2020;3:17. doi:10.1038/s41746-020-0221-y