Computational Safety Intelligence for Herbal Medicines: Predicting Toxicity, Herb–Drug Interactions, Dose Sensitivity, and Patient-Specific Risk

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ABSTRACT

Herbal medicines are widely used in clinical and community settings, yet their safety assessment remains challenging because herbal products may differ in botanical identity, preparation method, chemical composition, exposure profile, and patterns of concurrent use with conventional medicines. This original safety framework article proposes a computational safety intelligence approach for herbal medicines that integrates product identity, chemical characterization, toxicity prediction, herb–drug interaction mapping, dose and exposure interpretation, patient-specific vulnerability, evidence grading, validation planning, pharmacovigilance feedback, and clinical or regulatory decision boundaries. The framework distinguishes predicted toxicity alerts from experimentally observed toxicity, clinical adverse events, pharmacovigilance signals, mechanistic plausibility, exposure relevance, and regulatory actionability. Toxicity prediction is positioned as a prioritization tool for identifying toxicophore alerts, ADMET concerns, organ toxicity hypotheses, and validation needs. Herb–drug interaction assessment is framed through pharmacokinetic mechanisms, pharmacodynamic overlap, transporter and CYP involvement, polypharmacy context, and exposure plausibility. Dose sensitivity and patient-specific risk are treated as interpretation filters rather than universal risk thresholds. The proposed framework contributes a structured safety-intelligence model for supporting clinicians, toxicologists, pharmacologists, regulators, and researchers while emphasizing that computational predictions require cautious interpretation, rigorous validation, and qualified professional judgment.

Key Words: *Herbal medicines, Computational toxicology, Safety intelligence, Herb–drug interactions, Toxicity prediction, Dose sensitivity*

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INTRODUCTION

Herbal medicine safety is a persistent challenge for pharmacology, clinical care, toxicology, pharmacovigilance, and regulatory science because adverse-event evidence is distributed across spontaneous-report systems, case-based evidence, observational datasets, and heterogeneous product information rather than a single unified safety evidence stream [1, 2].

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This fragmentation matters because herbal products are not always chemically or biologically equivalent across manufacturers, preparations, extraction conditions, plant parts, or batches, and therefore safety interpretation requires more than a general claim about a botanical name. Spontaneous adverse-event reporting can support signal awareness for herbal medicine products, but such reports cannot by themselves establish incidence, causality, dose-response relationships, or individual patient risk [3]. A

computational safety framework must therefore avoid treating pharmacovigilance signals as definitive clinical proof while still using them as valuable indicators for prioritizing toxicological review, interaction assessment, mechanistic evaluation, and reporting improvements.

Herbal safety assessment also requires explicit attention to organ-specific signals, especially where suspected adverse drug reaction reports indicate recurring concern in clinically important domains such as hepatobiliary safety [4]. Such evidence should be interpreted through causality-aware logic because suspected reports may reflect product variability, co-medication, comorbidity, reporting bias, incomplete exposure information, or interactions rather than direct toxicity from a single constituent.

The aim of this article is to develop an original computational safety intelligence framework for herbal medicines. The framework is designed to separate predicted risk from validated safety evidence, distinguish mechanistic plausibility from clinical confirmation, incorporate exposure and dose sensitivity, account for patient-specific vulnerability, and define clinical and regulatory decision-support boundaries without implying that computational prediction can replace clinician, toxicologist, or regulator judgment.

Herbal medicine safety as a computational challenge

Computational safety assessment for herbal medicines must begin before toxicity modeling, because the primary object of analysis is often uncertain. Product identity, botanical authentication, plant part, preparation method, extraction context, processing conditions, and quality-control practices determine whether the chemical material being evaluated corresponds to the product actually used by patients or consumers [5]. Without this entry gate, downstream toxicity alerts and interaction predictions may be attached to an inadequately specified or compositionally different material.

Chemical characterization is the second computational challenge because herbal medicines may contain multiple known and unknown constituents, variable marker compounds, degradation products, contaminants, or preparation-dependent metabolites. Fingerprint-based standardization can help represent whole-profile variability and improve comparability across herbal materials, but it does not by itself establish clinical safety or identify all biologically relevant constituents [6]. Within a safety-intelligence framework, fingerprinting and chemical annotation should therefore function as compositional evidence layers rather than safety conclusions.

In silico ADME/Tox profiling of natural products can help identify physicochemical, pharmacokinetic, and toxicity-related concerns early in safety assessment, particularly when experimental evidence is incomplete [7]. However, predicted ADME/Tox profiles should be treated as prioritization signals that require domain-of-applicability checks, exposure-aware interpretation, and follow-up validation rather than as definitive evidence that a herbal product is safe or harmful.

The complexity of herbal products also creates a validation problem: structural alerts and computational predictions may be useful, but they are strongest when interpreted alongside experimental systems, toxicological assays, and transparent uncertainty statements. Integrating quantitative structure–toxicity relationship models with in vitro evidence can strengthen prioritization of natural-product safety concerns, while still requiring cautious translation from constituent-level predictions to product-level and patient-level safety interpretation [8].

Toxicity prediction and interaction mapping

Computational toxicity prediction for herbal medicines should be endpoint-specific rather than generic. Tools that predict multiple toxicity endpoints can identify hazards such as toxicophore alerts or organ-related concerns, while broader machine-learning toxicology research shows that prediction performance and interpretability vary by toxicity endpoint, chemical domain, input data quality, and validation setting [9, 10]. In this framework, such predictions are used to generate safety hypotheses and prioritize validation, not to confirm clinical toxicity.

ADMET prediction adds an exposure-aware layer to herbal safety intelligence because hazard signals are more interpretable when considered alongside absorption, distribution, metabolism, excretion, permeability, bioavailability, and metabolism-related properties. Computational ADMET resources can support early screening of chemical constituents for properties relevant to exposure plausibility and drug interaction potential [11]. Pharmacokinetic and drug-likeness descriptors can further help distinguish a theoretical structural concern from a constituent that may plausibly reach relevant systemic or local exposure under realistic use conditions [12].

Herb–drug interaction mapping requires attention to pharmacokinetic mechanisms, especially cytochrome P450 activity, metabolism, and transporter involvement. CYP activity prediction can help identify constituents that may warrant interaction review, particularly when a herbal product is used with drugs affected by the same metabolic pathways [13]. Such signals should be interpreted as mechanistic hypotheses because predicted enzyme involvement does not establish that a clinically meaningful interaction will occur.

Computational and data-mining approaches can connect phytoconstituents, toxicity alerts, CYP-related mechanisms, and potential herb–drug interactions, thereby

supporting prioritization of clinically relevant interaction hypotheses [14]. Pharmacodynamic interaction mapping is also needed when herbal constituents and medicines may have overlapping effects on physiological pathways, such as anticoagulant, sedative, immunomodulatory, cardiovascular, or QT-related effects; however, mechanistic overlap alone should not be presented as proof of patient harm.

Table 1 summarises computational safety domains relevant to toxicity prediction and herb–drug interaction mapping for herbal medicines.

Table 1. Computational Safety Domains for Herbal Medicines: Chemical Characterization, Toxicophore Alerts, ADMET Prediction, Organ Toxicity, CYP and Transporter Interactions, Pharmacodynamic Interactions, Evidence Strength, and Validation Needs

Safety domain	Core computational question	Typical input data	Potential safety signal	Main uncertainty	Validation requirement	Clinical interpretation boundary	Framework relevance
Chemical characterization	What constituents are known, measured, or plausibly present?	Botanical identity, plant part, extraction method, chromatographic profile, known and predicted constituents	Unresolved composition, unexpected constituent pattern, missing marker profile	Product-to-product variability and incomplete constituent annotation	Analytical confirmation and batch-aware documentation	Chemical presence does not equal clinical exposure or toxicity	Establishes the composition layer for all later safety reasoning
Toxicophore alerts	Do any constituents contain structural motifs associated with hazard?	Chemical structures, structural-alert rules, QSAR inputs	Reactive, genotoxic, hepatotoxic, cardiotoxic, or other structural concern	Applicability domain, false positives, missing metabolites	Orthogonal computational review and experimental toxicology where justified	A structural alert is a hypothesis, not a clinical toxicity diagnosis	Prioritizes constituents for deeper toxicological evaluation
ADMET prediction	Are predicted pharmacokinetic properties compatible with exposure?	Physicochemical descriptors, predicted absorption, metabolism, permeability, transporter features	High exposure plausibility, metabolic liability, transporter involvement	Model transferability to complex natural products and mixtures	In vitro ADME, PK evidence, or exposure-informed literature support	Poor predicted exposure does not prove safety; high predicted exposure does not prove harm	Separates theoretical hazard from exposure-relevant concern
Organ toxicity prediction	Which organ systems may require focused review?	Constituent structures, endpoint-specific models, toxicology databases	Hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity, reproductive/developmental or genotoxic concern where supported	Endpoint heterogeneity and limited herbal-product validation	Assay confirmation, animal or human safety evidence, pharmacovigilance follow-up	Predicted organ toxicity requires validation before clinical interpretation	Directs endpoint-specific safety triage
CYP interaction mapping	Could constituents alter metabolism of co-administered drugs?	Predicted CYP inhibition/induction, substrate profiles, drug pathway information	Plausible CYP-mediated herb–drug interaction	Concentration at enzyme site and product variability	In vitro enzyme data, PBPK modeling, clinical or real-world evidence	CYP prediction does not confirm clinically meaningful interaction	Supports pharmacokinetic interaction screening

Transporter interaction mapping	Could constituents affect transport-mediated drug disposition?	Transporter substrate/inhibitor predictions, ADME annotations, drug disposition data	Plausible transporter-mediated exposure change	Limited transporter-specific data for many constituents	Transporter assays, exposure modeling, clinical relevance review	Transporter signal alone cannot define interaction severity	Expands interaction mapping beyond CYP mechanisms
Pharmacodynamic interaction mapping	Could herbal and drug effects overlap biologically?	Target, pathway, pharmacology, adverse-effect, and indication data	Overlapping anticoagulant, sedative, immunologic, cardiovascular, or QT-related concern	Mechanistic overlap may not translate into clinical effect	Mechanistic validation, clinical observation, or case-supported review	Shared pathway activity does not prove patient harm	Captures non-PK interaction mechanisms
Evidence strength	How reliable is the signal?	Prediction, in vitro data, case reports, pharmacovigilance signals, clinical studies	Low-, moderate-, or higher-confidence safety hypothesis	Evidence type and relevance may be mismatched	Evidence grading and independent corroboration	Weak evidence must not be overstated	Prevents overinterpretation of computational outputs
Validation needs	What must be done before actionability?	Prediction confidence, endpoint seriousness, exposure plausibility, patient context	Need for assay, PBPK, real-world, or clinical follow-up	Resource limits and incomplete product information	Fit-for-purpose validation plan	Validation planning does not equal validation completed	Converts prediction into a research and review agenda

Dose sensitivity and patient-specific risk

Dose sensitivity is central to herbal medicine safety because interaction outcomes and toxicity concerns may depend on dose, duration, preparation type, constituent concentration, route of administration, and exposure context. Conflicting outcomes in herb–drug interaction studies can arise from these multifaceted variables, meaning that computational safety intelligence should avoid universal interaction claims when exposure conditions differ [15]. A predicted interaction is more informative when it is linked to whether a relevant constituent can plausibly reach concentrations compatible with the proposed mechanism.

Physiologically based pharmacokinetic modeling can support exposure-dependent interpretation of herb–drug interactions by testing whether a constituent, preparation, or dosing scenario is consistent with a plausible change in drug metabolism or exposure [16]. Such modeling is valuable because it connects mechanistic hypotheses to exposure plausibility, but it remains dependent on product composition, input assumptions, and the availability of suitable pharmacokinetic data.

Patient-specific risk is especially important in older adults, people with comorbidities, and individuals taking multiple medicines. Potential herb–drug interactions in community-dwelling older adults illustrate how age, polypharmacy, and medication complexity can increase the relevance of interaction screening while still requiring distinction between potential interactions and clinically confirmed harm [17]. Real-world evidence can add clinical context to herb–drug interaction evaluation, but observational data require careful interpretation because confounding, exposure misclassification, and incomplete product information may limit causal inference [18].

Certain treatment contexts demand heightened caution because the consequences of altered drug exposure or pharmacodynamic overlap may be clinically important. Interaction evidence involving Chinese herbal medicine and immunosuppressive drugs supports the need to flag high-risk co-use settings for expert review rather than to issue automatic conclusions [19]. Precision-oriented herbal safety further requires multivariable standardization that considers product characteristics, exposure context, and patient factors such as vulnerability, organ function, concurrent medicines, and clinically relevant variability [20].

Table 2 maps patient-specific factors that may modify herbal medicine safety, dose sensitivity, and herb–drug interaction risk.

Table 2. Patient-Specific Risk Modifiers for Herbal Medicine Safety: Age, Pregnancy and Lactation, Liver and Kidney Function, Comorbidities, Polypharmacy, Pharmacogenomic Variation, Frailty, Exposure Context, and Monitoring Needs

Risk modifier	Safety relevance	Potential mechanism	Computational representation	Clinical interpretation caution	Evidence needed	Failure risk if ignored	Framework implication
Age	May affect metabolism, renal clearance, polypharmacy burden, and vulnerability to adverse effects	Altered PK/PD, comorbidity accumulation, medication complexity	Age category, geriatric flag, medication-count context	Age alone should not be used as a deterministic risk label	Clinical context, medication review, organ-function information	Under-recognition of vulnerability or overgeneralized risk assignment	Include as a vulnerability modifier requiring professional interpretation
Pregnancy and lactation	May change safety priorities for mother, fetus, infant, or breastfeeding context	Altered physiology, fetal or infant exposure, limited safety evidence	Pregnancy/lactation flag where relevant and ethically appropriate	Computational systems should not provide pregnancy-specific advice without clinical expertise	Reproductive/developmental evidence, exposure data, professional evaluation	Inappropriate reassurance or unsupported alarm	Treat as high-caution context with validation and clinical referral boundaries
Liver function	Relevant to hepatotoxicity and metabolic interactions	Reduced metabolism, hepatic vulnerability, CYP-mediated interactions	Liver disease flag, hepatotoxicity alert, CYP pathway overlap	A liver-risk flag is not a diagnosis or causality assessment	Clinical history, liver-related evidence, exposure and PV review	Missed hepatobiliary risk or misattribution of causality	Connect organ toxicity prediction with patient vulnerability
Kidney function	Relevant to clearance, accumulation, and nephrotoxicity concerns	Reduced renal elimination, fluid/electrolyte vulnerability, renal adverse effects	Kidney-function flag, nephrotoxicity alert, renal clearance context	Predicted renal concern requires clinical and exposure validation	Renal function data, nephrotoxicity evidence, medication review	Failure to identify accumulation or renal-risk context	Add renal vulnerability to exposure and organ-toxicity modules
Comorbidities	May modify tolerability, pharmacodynamic sensitivity, or outcome seriousness	Disease–pathway overlap, altered physiology, contraindication-like context	Condition flags, pathway overlap, risk-domain annotation	Comorbidity flags require clinician interpretation and should not produce automated advice	Relevant clinical evidence and patient-specific evaluation	Mechanistic concerns may be missed in high-risk conditions	Use comorbidities as contextual filters, not standalone conclusions
Polypharmacy	Increases potential interaction pathways and interpretive uncertainty	Multiple CYP, transporter, and pharmacodynamic overlaps	Medication-count flag, interaction-network density, high-risk drug-class annotation	Network density does not equal clinical severity	Medication reconciliation, interaction evidence, exposure plausibility	Overlooking cumulative interaction burden or producing excessive false alarms	Prioritize expert review of plausible, serious, exposure-relevant interactions
Pharmacogenomic variation	May affect metabolism, response, or interaction susceptibility	Genotype-dependent enzyme or transporter function	PGx modifier only when evidence exists	Herbal extrapolation from drug PGx evidence	Evidence-graded PGx association and relevant pathway mapping	Unsupported personalization or missed variability	Include only as evidence-graded modifier

	where supported			should be cautious			
Frailty	May increase vulnerability to adverse outcomes even at lower exposure	Reduced physiological reserve, sensitivity to CNS, cardiovascular, or renal effects	Frailty or vulnerability flag when available	Frailty cannot be inferred reliably from sparse data alone	Clinical assessment and medication-context review	Underestimation of harm in vulnerable users	Route to clinical review rather than automated risk scoring
Exposure context	Determines whether predicted hazard is plausible	Route, preparation, bioavailability, duration, accumulation, concentration	Route and preparation annotation, exposure plausibility filter	Lack of exposure data should be treated as uncertainty, not safety	Product composition, dose context, PK or bioavailability evidence	Toxicity alerts may be over- or underinterpreted	Make exposure plausibility a central interpretation filter
Monitoring needs	Helps define what follow-up evidence or review is required	Endpoint seriousness, co-medication risk, patient vulnerability	Validation-needed flag, PV-reporting relevance, clinical review boundary	Monitoring suggestions are not patient-specific medical advice in this framework	Clinician, toxicologist, or regulator review depending on context	Predictions may be used without safeguards	Translate signals into validation and decision-support boundaries

Safety intelligence requirements

Safety intelligence for herbal medicines requires structured information before computational prediction is attempted. A usable safety system must encode product identity, botanical authentication, plant part, preparation method, extraction context, chemical characterization, known constituents, predicted constituents, and evidence provenance. Standardized reporting and classification are essential because herbal and traditional medicine safety reports may otherwise be difficult to compare, code, retrieve, and interpret across pharmacovigilance systems [21].

A second requirement is scalable evidence ingestion for herb–drug interaction knowledge. Literature-screening tools can assist identification of relevant herb–drug interaction evidence, especially when interaction information is dispersed across case reports, pharmacokinetic studies, mechanistic studies, and narrative descriptions [22]. In a safety-intelligence framework, such tools should support evidence triage and expert review rather than replace critical appraisal, because extracted interaction statements still require interpretation of exposure, mechanism, product composition, and clinical relevance.

A third requirement is a computable knowledge structure that can connect natural products, constituents, drugs, enzymes, transporters, pathways, adverse-event signals, evidence records, and uncertainty annotations. Knowledge graph approaches can organize pharmacokinetic natural product–drug interaction evidence by linking entities and mechanistic relations while preserving evidence paths for review [23]. This structure is especially useful for herbal medicine safety because a single product may contain many constituents, and a single constituent may connect to multiple toxicity, ADMET, or interaction hypotheses.

A fourth requirement is boundary-aware artificial intelligence. AI tools can support assessment of drug–herb interactions when they are linked to mechanistic interpretation, explainability, evidence grading, and validation planning rather than treated as autonomous clinical decision-makers [24]. Herbal adverse-reaction signal evaluation also requires attention to the strength and type of supporting documents, because signals supported mainly by case reports, spontaneous reports, or incomplete documentation may be useful for prioritization but insufficient for definitive action [25]. **Figure 1** illustrates the computational safety intelligence pipeline linking herbal product identity, constituent characterization, toxicity prediction, interaction mapping, exposure plausibility, patient-specific risk, and validation requirements.

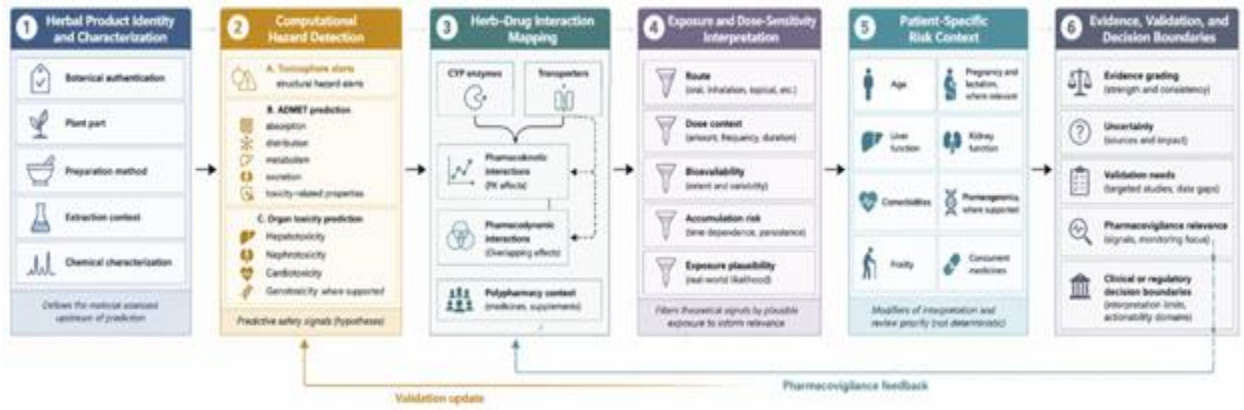

Figure 1. Computational Safety Intelligence Pipeline for Herbal Medicines

Alt-text description

A conceptual pipeline diagram showing herbal product identity, botanical authentication, chemical constituents, toxicophore alerts, ADMET prediction, organ toxicity prediction, CYP and transporter interaction mapping, pharmacodynamic interaction mapping, dose sensitivity, patient-specific risk factors, evidence grading, validation needs, and clinical or regulatory decision boundaries.

Proposed safety framework

The proposed computational safety intelligence framework is organized around ten linked stages: herbal product identity, chemical characterization, computational toxicity prediction, interaction mapping, dose and exposure plausibility, patient-specific risk stratification, evidence grading, validation planning, pharmacovigilance feedback, and clinical or regulatory actionability. Its design is grounded in the need for explainable safety prediction, transparent interaction reasoning, and evidence-graded patient-specific modifiers rather than opaque risk labels [26-28].

The first stage is product identity resolution. The framework requires explicit documentation of botanical authentication, plant part, preparation method, extraction context, and chemical characterization before toxicity or interaction prediction is interpreted. This stage functions as a safety gate because a prediction attached to an unresolved herbal identity may mislead downstream interpretation. The second stage is constituent-level and profile-level characterization, where known constituents, predicted constituents, analytical fingerprints, and uncertainty annotations define the chemical basis for hazard detection. The third stage is computational safety prediction. Toxicophore alerts, ADMET predictions, organ toxicity hypotheses, CYP and transporter interaction signals, and pharmacodynamic overlap are treated as structured safety signals. The framework does not assign clinical toxicity or interaction severity from these signals alone. Instead, each signal is routed through exposure plausibility, evidence strength, domain applicability, and validation need. This structure supports use of real-world data as a later evaluation layer while recognizing that real-world datasets require careful governance, bias assessment, and interpretation [29].

The fourth stage is dose, exposure, and patient-context interpretation. A hazard signal is evaluated in relation to route of administration, preparation concentration, bioavailability, metabolism, possible accumulation, concurrent medicines, organ function, age, pregnancy or lactation context where relevant, frailty, comorbidities, and pharmacogenomic considerations where supported. Machine-learning approaches to pharmacokinetic and pharmacodynamic modeling can contribute to dose-exposure interpretation when adequate data exist, but the framework does not invent thresholds or convert incomplete exposure information into deterministic patient advice [30].

The fifth stage is actionability. Signals are graded according to evidence type, mechanistic plausibility, exposure relevance, patient vulnerability, seriousness of potential outcome, validation status, and suitability for clinical or regulatory review. The output is not a patient-specific risk score; it is a structured decision-support map that identifies whether a concern should be treated as a predicted alert, mechanistic hypothesis, validation priority, pharmacovigilance signal, clinical review issue, or regulatory evidence gap.

Table 3 presents the proposed computational safety intelligence framework for herbal medicines.

Table 3. Proposed Computational Safety Intelligence Framework for Herbal Medicines: Product Identity, Chemical Characterization, Toxicity Prediction, Interaction Mapping, Dose Sensitivity, Patient-Specific Risk, Evidence Grading, Validation, Clinical Decision Boundaries, and Regulatory Actionability

Framework stage	Core safety question	Required evidence	Computational method or signal	High-risk indicator	Uncertainty source	Validation requirement	Clinical or regulatory implication
Product identity	Is the assessed material the same as the claimed herbal product?	Botanical authentication, plant part, preparation, extraction, batch context	Identity and metadata resolution	Unauthenticated material, ambiguous plant part, unknown preparation	Incomplete labeling, substitution, batch variability	Authentication and quality documentation	Unsafe to interpret predictions without identity resolution
Chemical characterization	What constituents are measured, known, or plausibly present?	Fingerprint profile, marker compounds, constituent annotation	Constituent mapping and profile comparison	Unexpected chemical profile or missing key markers	Unknown constituents and preparation-dependent variation	Analytical confirmation and reproducibility checks	Defines the chemical scope of safety assessment
Toxicity prediction	Which toxicity endpoints require attention?	Chemical structures, toxicity models, endpoint databases	Toxicophore, organ-toxicity, ADMET, genotoxicity or cardiotoxicity alerts where supported	Multiple convergent alerts or serious endpoint concern	Applicability-domain limits and incomplete endpoint evidence	Endpoint-specific experimental or literature validation	Prioritizes toxicological review without confirming clinical harm
Interaction mapping	Could the product affect drug exposure or response?	CYP, transporter, target, pathway, drug-mechanism data	PK and PD interaction hypotheses	Overlap with narrow-therapeutic-index medicines or high-risk pharmacology	Unknown constituent concentration and incomplete co-medication data	In vitro, PBPK, clinical, real-world, or expert-review evidence	Supports interaction triage and clinical review boundaries
Dose and exposure plausibility	Is predicted hazard compatible with plausible exposure?	Route, preparation, duration, bioavailability, metabolism, accumulation information	Exposure plausibility filter	Concentrated preparation, prolonged use, plausible systemic exposure	Missing dose, poor constituent quantification, variable formulation	PK, bioavailability, or exposure-informed evidence	Prevents overinterpretation of non-exposure-relevant alerts
Patient-specific risk	Which user factors may modify concern?	Age, organ function, pregnancy/lactation context, comorbidities, polypharmacy, frailty, PGx where supported	Vulnerability flags and contextual modifiers	Organ impairment, polypharmacy, high-risk medicines, vulnerable physiological state	Sparse patient data and ethically sensitive modifiers	Qualified clinical evaluation and evidence-graded interpretation	Routes signals to professional review rather than automated advice
Evidence grading	How strong and relevant is the supporting evidence?	Prediction, assay, animal, case report, pharmacovigilance, clinical, or real-world evidence	Evidence-level annotation	Serious signal with convergent evidence	Heterogeneous evidence and reporting bias	Independent corroboration and transparent grading	Avoids conflating prediction with validated risk
Validation planning	What evidence is needed before stronger interpretation?	Signal seriousness, mechanism, exposure plausibility, evidence gaps	Validation-needed flag	Serious endpoint with plausible exposure but limited validation	Resource constraints and incomplete product data	Fit-for-purpose assay, modeling, observational, or clinical follow-up	Converts prediction into research and safety-monitoring agenda

Clinical decision boundary	What can the system responsibly support?	Evidence grade, patient context, clinical seriousness, uncertainty statement	Decision-support category	High uncertainty in vulnerable or polymedicated context	Incomplete patient history and lack of validated calculator	Clinician or toxicologist review	Supports professional judgment without issuing medical advice
Regulatory actionability	Is the concern relevant to reporting, labeling, surveillance, or research prioritization?	Pharmacovigilance reports, evidence documentation, seriousness, reproducibility	Regulatory-relevance flag	Repeated serious signal or evidence gap affecting public safety interpretation	Underreporting and incomplete causality data	Regulatory-grade evidence review and surveillance feedback	Supports safety communication and monitoring without inventing decisions

Figure 2 presents the proposed safety framework for predicting and interpreting herbal medicine toxicity, herb–drug interactions, dose sensitivity, and patient-specific risk.

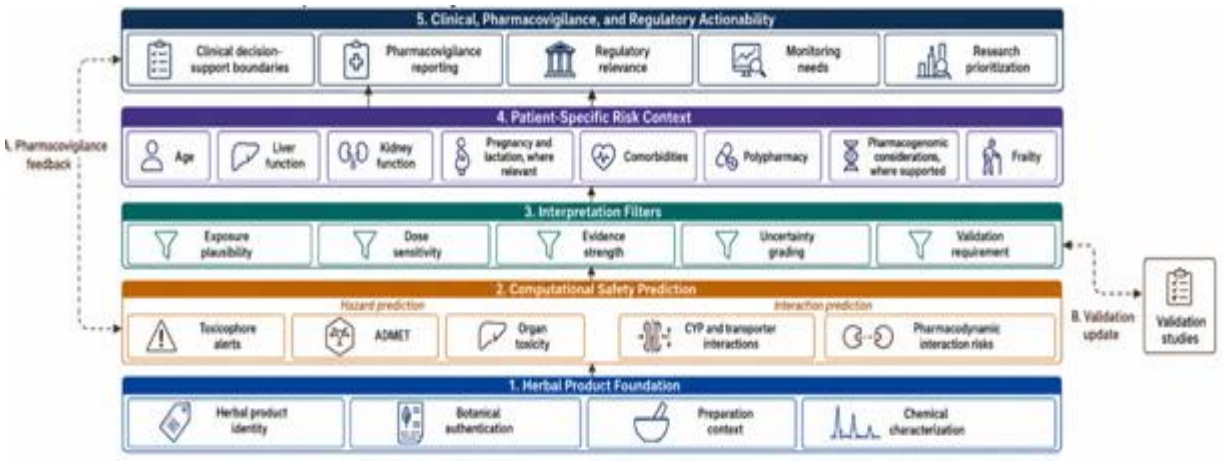

Figure 2. Computational Safety Framework for Herbal Medicine Risk Assessment

Alt-text description

A layered safety framework diagram showing herbal identity and chemical characterization as the foundation. Above this are layers for toxicity prediction, herb–drug interaction mapping, dose sensitivity, patient-specific risk factors, evidence grading, validation, pharmacovigilance feedback, clinical decision boundaries, and regulatory implications.

Clinical and regulatory implications

For clinical pharmacology and integrative medicine, the main implication is that computational safety intelligence should function as structured decision support, not as automated medical advice. Stakeholder perspectives in herbal pharmacovigilance indicate the importance of better reporting practices, coordination, and globally applicable recommendations for improving herbal safety monitoring [31]. A computational framework can help clinicians and toxicologists identify plausible concerns, but decisions about individual patients require qualified professional evaluation, medication reconciliation, clinical history, and context-specific judgment.

For pharmacovigilance and regulatory science, the framework emphasizes that global adverse drug reaction databases can support surveillance and signal detection while remaining limited by suspected-report causality, underreporting, variable documentation, and incomplete product or exposure information [32]. Computational tools can improve organization of evidence, identify repeated patterns, and prioritize review, but they should not convert spontaneous-report signals into regulatory conclusions without formal assessment.

Future development should focus on validated models, exposure-aware herbal constituent datasets, standardized product annotation, transparent interaction databases, pharmacovigilance feedback loops, and evidence frameworks that distinguish prediction, mechanism, case evidence, real-world association, and regulatory actionability. The value of safety intelligence will depend less on producing a single risk label and more on making uncertainty visible, identifying validation needs, and supporting safer interpretation of herbal medicine use in complex clinical and public-health contexts.

CONCLUSION

This article proposed a computational safety intelligence framework for herbal medicines that integrates product identity, chemical characterization, toxicity prediction, herb–drug interaction mapping, dose sensitivity, patient-specific risk, evidence grading, validation planning, pharmacovigilance feedback, and clinical or regulatory decision boundaries. The framework positions computational methods as tools for structured risk prioritization and hypothesis generation rather than as substitutes for toxicological validation, clinical judgment, or regulatory review. Its central contribution is a safety logic that separates predicted hazard from observed toxicity, plausible mechanism from confirmed clinical interaction, and evidence gaps from actionability. Computational safety tools are most useful when interpreted cautiously, validated rigorously, and embedded within clinical and regulatory safeguards.

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