Herb–Drug Interaction Prediction in the AI Era: Pharmacokinetic Mechanisms, Pharmacodynamic Overlap, Patient Risk, and Clinical Safeguards

Thomas Dupont[1]*, Marie Leclerc[1], Julien Martin[2]

[1]Department of AI for Neuroprotective Flavonoids, Faculty of Pharmacy, Université Paris-Saclay, Paris, France.
[2]Department of Computational Toxicology and Ecopharmacology, Faculty of Pharmacy, University of Strasbourg, Strasbourg, France.

ABSTRACT

Herb–drug interactions represent a clinically important safety challenge because herbal product composition, patient disclosure, comedication patterns, pharmacological mechanisms, and evidence quality vary substantially across real-world use. This article develops an original AI-era risk prediction framework for herb–drug interactions that integrates pharmacokinetic mechanisms, pharmacodynamic overlap, patient-specific vulnerability, evidence confidence, uncertainty, and clinical safeguards. The framework separates predicted interaction signals from mechanistic plausibility, exposure relevance, patient-level risk, validation needs, and clinical decision boundaries. Pharmacokinetic interpretation focuses on CYP enzyme modulation, transporter effects, Phase II metabolism where supported, absorption and elimination considerations, exposure plausibility, therapeutic index, and dose-context caution. Pharmacodynamic interpretation addresses additive toxicity, opposing pharmacological effects, bleeding-related concern, sedation or central nervous system overlap, cardiovascular or QT-relevant concern, glycemic effects, blood-pressure effects, and organ vulnerability. Patient-risk interpretation incorporates older age, pregnancy and lactation where relevant, hepatic and renal function, comorbidities, polypharmacy, pharmacogenomic considerations where supported, self-medication disclosure, adherence context, and narrow therapeutic index medicines. The proposed framework positions AI as a tool for risk prioritization, evidence integration, literature triage, uncertainty communication, and safeguard planning. It does not present AI-assisted prediction as a substitute for clinician, pharmacist, toxicologist, pharmacologist, or regulatory judgment, and it does not provide patient-specific medical advice.

Key Words: *Herb–drug interactions, Artificial intelligence, Pharmacokinetics, Pharmacodynamics, Patient risk, Clinical safeguards*

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INTRODUCTION

Herb–drug interaction prediction requires a disciplined distinction between reported association, suspected mechanism, clinical causality, and patient-specific consequence. Causality assessment in herb–drug interaction cases remains challenging because product identity, constituent exposure, concomitant medicines, temporal relationships, dechallenge or rechallenge information, and alternative explanations are often incompletely described [1].

The clinical relevance of an herb–drug interaction signal depends on whether mechanistic evidence can be connected to plausible human exposure and meaningful pharmacological effect. A risk prediction framework therefore needs to integrate in vitro findings, pharmacokinetic reasoning, pharmacodynamic interpretation, and clinical-context review rather than treating all interaction reports as equivalent evidence [2].

Artificial intelligence can support herb–drug interaction assessment by improving literature triage, evidence extraction, pattern detection, and mechanistic hypothesis

Corresponding author: Thomas Dupont
Address: Department of AI for Neuroprotective Flavonoids, Faculty of Pharmacy, Université Paris-Saclay, Paris, France.
E-mail: ✉ thomas.dupont@universite-paris-saclay.fr
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generation, but computational outputs require pharmacological interpretation. AI-assisted prediction should therefore be framed as a risk-prioritization and evidence-integration process, not as an autonomous system for determining whether a patient should use an herbal product with a medicine [3].

Curated herb–drug interaction resources provide a foundation for structured evidence retrieval, but databases differ in scope, evidence grading, severity classification, and interaction interpretation. This article proposes an AI-era risk prediction framework that links curated evidence, pharmacokinetic mechanisms, pharmacodynamic overlap, patient vulnerability, clinical safeguards, validation planning, and explicit decision-support boundaries [4].

Herb–drug interactions as a clinical risk

The clinical risk of herb–drug interactions is shaped by incomplete and uneven evidence as much as by pharmacological plausibility. Intelligent literature-screening tools can help identify relevant herb–drug interaction publications, but literature triage remains a support function that requires expert assessment of mechanism, exposure context, evidence strength, and patient relevance [5].

In primary healthcare, herb–drug interactions are complicated by self-medication, incomplete disclosure, variable product composition, and fragmented medication histories. These features mean that interaction prediction cannot begin only with molecular targets or enzyme labels; it must also capture what the patient is actually using, how it is prepared, and whether clinicians know about the exposure [6].

A patient-centered approach is essential because herb and prescription exposures intersect within individual histories of comorbidity, polypharmacy, organ function, adherence, and therapeutic vulnerability. Predicted interaction risk should therefore be interpreted through patient context and clinical review rather than presented as a direct instruction to continue, stop, substitute, or combine therapies [7].

Structured herb–drug interaction resources can support clinical risk awareness by organizing evidence across mechanisms, herbal products, medicines, and reported outcomes. However, such resources should be used as evidence-navigation aids, because database entries and predicted signals do not by themselves establish clinical actionability, regulatory actionability, or individualized medical advice [8].

Pharmacokinetic mechanisms

Pharmacokinetic herb–drug interaction prediction begins with mechanisms that can alter absorption, distribution, metabolism, or elimination. Relevant mechanisms include modulation of drug-metabolizing enzymes, effects on intestinal or hepatic transporters, changes in bioavailability, and pathway-specific exposure shifts, but the clinical relevance of these mechanisms depends on the affected drug, the herbal preparation, and the plausibility of exposure at real-use levels [9].

CYP enzymes and transporters are central to pharmacokinetic risk interpretation because many medicines depend on these pathways for clearance, distribution, or absorption. Nevertheless, an enzyme or transporter signal must be interpreted in relation to the drug's therapeutic index, the direction of the effect, the expected magnitude of exposure change, and whether the evidence comes from prediction, in vitro data, clinical pharmacokinetic study, or case-level observation [10].

Computational and experimental approaches can identify plausible CYP or P-glycoprotein interaction mechanisms, including constituent-level predictions and molecular docking signals. Such findings are useful for hypothesis generation, but they should not be treated as clinical confirmation unless they are linked to exposure-aware interpretation and appropriate validation [11]. Phase II metabolism, including UGT-mediated pathways, should also be included in the framework when the medicine and herbal constituents have evidence supporting this mechanism, rather than assuming that CYP pathways alone define pharmacokinetic risk [12].

Validation planning is essential because pharmacokinetic prediction requires methods capable of testing whether a mechanistic signal translates into meaningful human exposure change. Probe-based approaches can support evaluation of CYP and transporter functions [13]. High-risk comedication contexts also illustrate why exposure context matters: potent pharmacokinetic modifiers, vulnerable drug classes, and variable herbal preparations can shift the level of concern even when the same general mechanism is being considered [14]. Pharmacokinetic interpretation should therefore be integrated with pharmacodynamic overlap, patient vulnerability, and clinical safeguards before any risk signal is treated as clinically meaningful [15].

Table 1 summarises pharmacokinetic mechanisms relevant to AI-assisted herb–drug interaction prediction.

Table 1. Pharmacokinetic Mechanisms in Herb–Drug Interaction Prediction: CYP Enzymes, Transporters, Phase II Metabolism, Exposure Plausibility, Therapeutic Index, Evidence Strength, Interpretation Boundaries, and Validation Needs

Pharmacokinetic mechanism	Core interaction question	Required evidence	Potential risk signal	Exposure interpretation need	Main uncertainty	Validation requirement	Framework role
CYP enzyme modulation	Could herbal constituents inhibit or induce a drug-metabolizing CYP pathway?	Drug metabolic pathway, herb constituent evidence, inhibition or induction data	Predicted or observed change in metabolic clearance	Determine whether constituent exposure is plausible at real-use levels	In vitro or predicted signal may not translate clinically	In vitro-to-in vivo assessment or clinical pharmacokinetic evaluation	Mechanistic plausibility screen
Transporter modulation	Could herbal constituents affect absorption, distribution, biliary transport, or renal transport?	Transporter substrate status, transporter inhibition or induction evidence	Potential change in absorption, tissue distribution, or elimination	Interpret by route, site of transporter expression, and drug dependence on transporter pathway	Transporter effects may be context-specific and bidirectional	Transporter-focused experimental or clinical evaluation	Exposure-pathway assessment
Phase II metabolism	Could UGT or other conjugation pathways be affected?	Evidence that the drug and herbal constituent involve relevant Phase II pathways	Possible altered conjugation and systemic exposure	Include only when pathway-specific evidence exists	Phase II evidence is often less complete than CYP evidence	Pathway-specific metabolism assessment	Non-CYP mechanism inclusion
Absorption-related effects	Could herbal preparation or constituents affect oral drug uptake?	Formulation, timing, intestinal enzyme or transporter evidence	Possible altered oral exposure	Consider preparation, route, timing, and bioavailability	Product variability and timing uncertainty	Human exposure or controlled interaction study where feasible	Exposure plausibility layer
Distribution relevance	Could protein binding or tissue distribution be relevant?	Drug distribution characteristics and supported displacement or transporter evidence	Possible shift in free or tissue exposure	Consider only when clinically meaningful and evidence-supported	Protein-binding signals can be overinterpreted	Drug-specific pharmacology review	Cautious secondary mechanism
Elimination pathway effects	Could renal, biliary, or metabolic elimination be affected?	Clearance pathway data and herb mechanism evidence	Potential accumulation or reduced exposure	Interpret with organ function and pathway dependence	Mechanism may be masked by multiple clearance routes	Clinical pharmacokinetic or mechanistic validation	Clearance-risk assessment
Therapeutic index sensitivity	Would a small exposure change matter clinically?	Drug therapeutic index, toxicity domain, monitoring context	Elevated concern for narrow therapeutic index medicines	Connect mechanism to consequence, not only exposure	Therapeutic index varies by drug and patient	Expert clinical pharmacology review	Risk-prioritization modifier
Evidence strength	What type of evidence supports the PK signal?	Prediction, in vitro, animal, clinical PK, case, pharmacovigilance, or database evidence	Low-, moderate-, or high-confidence concern	Interpret evidence hierarchy and consistency	Evidence sources may conflict	Transparent evidence grading	Confidence and uncertainty layer
Interpretation boundary	What should not be concluded from the PK signal?	Mechanism, exposure context, patient context, and validation status	Premature clinical inference	State that prediction does not prove clinical harm	Automation bias and false reassurance	Independent expert assessment before clinical use	Decision-support boundary

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Pharmacodynamic overlap

Pharmacodynamic overlap occurs when an herbal product and a medicine affect related physiological systems, therapeutic effects, toxicity domains, or opposing pharmacological pathways. Bleeding-related concern is a prominent example because anticoagulant or antiplatelet contexts may involve narrow clinical margins and outcome domains in which additive or opposing effects require careful interpretation [16].

Blood-pressure effects illustrate why pharmacodynamic overlap should be interpreted through patient context rather than treated as an automatic harm signal. Herbal products used alongside antihypertensive medicines may raise questions about additive, opposing, or unpredictable blood-pressure effects, but the relevance of such overlap depends on the medicine, the patient's cardiovascular status, and the quality of evidence [17]. Cardiovascular medicines also require combined pharmacokinetic and pharmacodynamic review because plant products may affect exposure pathways while also intersecting with cardiovascular pharmacology, including blood-pressure or rhythm-relevant domains where supported by evidence [18].

Sedation, analgesia, and other central nervous system effects create another domain in which additive pharmacology can become clinically important, particularly when CNS-active medicines are involved. Herbal products used for pain or neuroactive purposes may raise concerns about overlapping sedation, cognitive effects, or other pharmacological effects, but these concerns should be framed as risk hypotheses requiring context and evidence review [19]. Oncology settings require especially cautious interpretation because anticancer treatment may involve complex pharmacokinetic pathways, narrow therapeutic objectives, toxicity concerns, and high-consequence decisions that should trigger expert review rather than automated advice [20].

Pharmacovigilance evidence can help identify real-world patterns of reported herb–anticancer drug interactions, but signal detection does not by itself establish causality or patient-specific risk. In the proposed framework, pharmacodynamic overlap and pharmacovigilance signals are used to prioritize evidence review, validation planning, and safeguard design while preserving uncertainty about mechanism, exposure, confounding, and clinical consequence [21].

Patient risk and clinical safeguards

Patient-specific risk interpretation is necessary because the same predicted mechanism may have different implications across age, comorbidity, organ function, comedication burden, and therapeutic vulnerability. Older adults are a high-priority group for herb–drug interaction review because concurrent use of prescription medicines and herbal medicinal products is common in this population and may occur alongside multimorbidity and polypharmacy [22]. Medication review should therefore capture herbal products and supplements as part of a complete exposure history rather than treating them as separate from prescribed therapy [23].

Community settings may contain unrecognized potential herb–drug interactions because patients may use herbal products outside formal prescribing records and may not consistently disclose them during routine care [24]. Self-medication patterns, product uncertainty, and incomplete communication create a practical barrier for prediction systems: before a model can assess interaction risk, the exposure itself must be identified, documented, and interpreted in relation to patient context [25].

Clinical safeguards should also account for the difference between a pharmacovigilance signal, a suspected mechanism, and a clinically actionable interaction. Signal detection can support surveillance and prioritization, but spontaneous reports remain vulnerable to reporting bias, incomplete exposure details, confounding, and causality uncertainty [26]. Real-world evidence can inform safeguard planning by revealing patterns of use and possible interaction concerns, but it still requires careful interpretation before it is translated into clinical decision support [27].

In the proposed framework, patient-specific modifiers include older age, pregnancy and lactation where relevant, liver function, kidney function, comorbidities, polypharmacy, narrow therapeutic index medicines, pharmacogenomic considerations where supported, oncology or transplant contexts where supported, self-medication disclosure, adherence context, and the feasibility of monitoring. Safeguards include medication reconciliation, documentation of herbal exposure, clinician or pharmacist review, monitoring consideration, patient education boundaries, referral triggers, and explicit prevention of autonomous patient-specific advice.

Figure 1 illustrates how pharmacokinetic mechanisms, pharmacodynamic overlap, patient-specific risk factors, and clinical safeguards can be integrated into herb–drug interaction risk interpretation.

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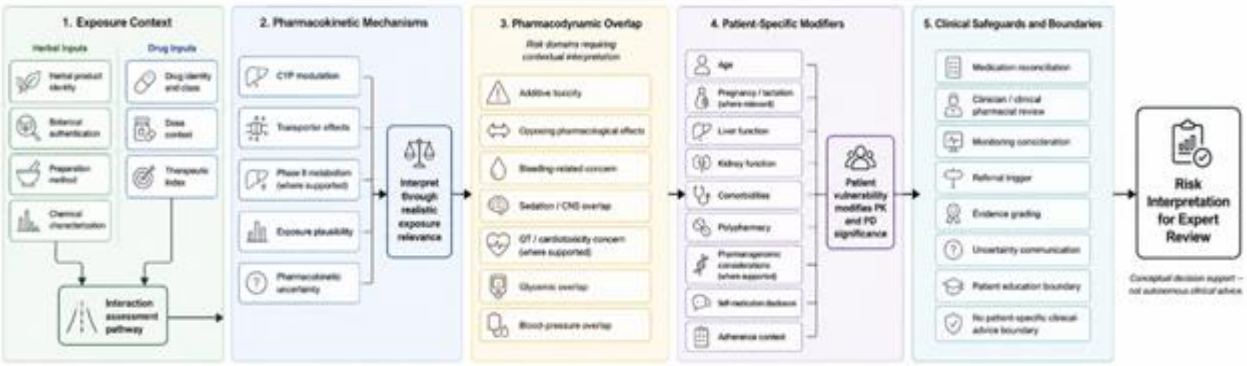

Figure 1. Patient-Centered Herb–Drug Interaction Risk Interpretation Pathway

The figure shows how herbal product identity, drug characteristics, pharmacokinetic mechanisms, pharmacodynamic overlap, patient-specific vulnerability, polypharmacy, evidence strength, uncertainty, and clinical safeguards can be connected to support risk interpretation. The pathway is conceptual and does not provide patient-specific medical advice.

Table 2 maps pharmacodynamic overlap, patient-specific risk modifiers, and clinical safeguards for herb–drug interaction prediction.

Table 2. Pharmacodynamic Overlap, Patient Risk, and Clinical Safeguards in Herb–Drug Interaction Prediction: Additive Toxicity, Opposing Effects, Narrow Therapeutic Index Drugs, Polypharmacy, Comorbidities, Organ Function, Medication Reconciliation, Expert Review, and Monitoring Boundaries

Risk domain	Core clinical question	Mechanistic concern	Patient-specific modifier	Potential safeguard	Evidence needed	Interpretation boundary	Framework implication
Bleeding-related overlap	Could herbal exposure intersect with anticoagulant or antiplatelet effect?	Additive bleeding concern or exposure-mediated change	Anticoagulant or antiplatelet use, narrow therapeutic index context	Expert review and monitoring consideration	Herb identity, medicine class, mechanism, clinical or case evidence	A bleeding-risk signal does not prove harm	High-priority pharmacodynamic review
Blood-pressure overlap	Could herbal and cardiovascular effects converge or oppose each other?	Additive, opposing, or unpredictable blood-pressure effect	Hypertension, cardiovascular comorbidity, multiple cardiovascular medicines	Medication reconciliation and clinician review	Drug class, herb pharmacology, patient cardiovascular context	No blood-pressure management advice is generated	Cardiovascular safeguard layer
CNS or sedation overlap	Could neuroactive effects add to medicine effects?	Sedation, cognitive impairment, analgesic or CNS pharmacology overlap	CNS-active medicines, frailty, fall-risk context	Review trigger and patient education boundary	Medicine class, herb pharmacology, evidence confidence	Overlap is a risk hypothesis, not clinical confirmation	CNS safety domain
QT or cardiotoxicity concern	Could cardiac electrophysiology or toxicity domains overlap?	Potential rhythm or cardiotoxicity concern where supported	Cardiac disease, QT-relevant medicines, electrolyte or comorbidity context	Specialist review trigger	Mechanistic or clinical evidence specific to the domain	No QT value or patient-level risk estimate is inferred	High-consequence signal escalation
Glycemic overlap	Could herbal and antidiabetic effects converge or oppose each other?	Additive or opposing glycemic effect	Diabetes, antidiabetic medicine use, comorbidity	Monitoring consideration and clinician review	Herb pharmacology, medicine class, patient context	No glycemic-treatment advice is produced	Metabolic safety domain

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Additive organ toxicity	Could herb and drug toxicities affect the same organ system?	Hepatic, renal, cardiovascular, CNS, or oncology toxicity overlap	Liver impairment, kidney impairment, comorbidities	Expert review and documentation	Toxicity evidence, organ function context, exposure history	Toxicity overlap requires validation and clinical interpretation	Vulnerability-sensitive safeguard
Opposing pharmacological effect	Could herbal exposure reduce or counter therapeutic intent?	Antagonistic or opposing effect domain	High-consequence therapy or narrow therapeutic objective	Referral trigger	Mechanistic plausibility and clinical evidence	Prediction does not establish loss of efficacy	Therapeutic-goal protection
Polypharmacy burden	Are multiple medicines and herbal products creating interaction complexity?	Networked PK and PD interactions	Multiple medicines, supplements, comorbidities	Full medication reconciliation	Complete medicine and supplement list	Model output supports triage only	Interaction-network prioritization
Older age	Does age increase sensitivity to interaction consequences?	Altered PK, PD sensitivity, comorbidity, polypharmacy	Older adult status	Medication review and exposure documentation	Age, medicines, herb use, comorbidities	Age alone is not an interaction diagnosis	Patient vulnerability layer
Pregnancy and lactation where relevant	Could maternal, fetal, or infant exposure make uncertainty unacceptable?	Exposure uncertainty, toxicity concern, insufficient evidence	Pregnancy or lactation context	Expert referral trigger	Exposure identity and safety evidence	No pregnancy or lactation advice is generated	Precautionary expert-review boundary
Pharmacogenomic variability where supported	Could genotype alter pathway relevance?	CYP, UGT, or transporter variability	Valid pharmacogenomic information where available	Specialist interpretation	Pathway-specific genotype evidence	No genotype is inferred without data	Conditional personalization layer
Medication reconciliation	Are all relevant exposures known?	Hidden herbal, supplement, or medicine exposure	Self-medication and incomplete disclosure	Document all exposures	Complete medication and herbal product history	Reconciliation is not a treatment recommendation	Foundational safeguard
Clinical pharmacist or clinician review	Does the risk signal require expert interpretation?	Complex PK, PD, evidence, or patient-context uncertainty	High-risk drug, vulnerable patient, severe toxicity domain	Expert-review trigger	Evidence summary, mechanism, patient context	AI does not replace professional judgment	Escalation safeguard
Monitoring consideration	Is a measurable safety or exposure domain relevant?	Possible PK change or PD effect	Narrow therapeutic index, organ vulnerability, high-risk context	Monitoring domain flag	Clinically meaningful endpoint and expert decision	No monitoring protocol is prescribed	Boundary-preserving safeguard
No clinical-advice boundary	What must the framework avoid?	Automation bias, false reassurance, unsafe self-management	Any patient-specific decision context	Boundary statement	Transparent uncertainty and evidence grade	No start, stop, substitution, or combination advice	Decision-support limit

Proposed risk prediction framework

The proposed framework begins with identity resolution before prediction. Herbal product identity, botanical authentication, plant part, preparation method, extraction context, chemical characterization, known constituents, predicted constituents, drug identity, drug class, dose context, therapeutic index, patient context, and medication list form the minimum input layer. Large language model approaches to herbal medicine–drug interaction prediction support the feasibility of AI-assisted information

integration, but the framework treats such outputs as prioritization signals requiring verification rather than autonomous clinical determinations [28].

The second framework layer maps interaction networks across medicines, herbal exposures, adverse-effect domains, and pharmacological mechanisms. Graph-based approaches to polypharmacy side-effect prediction show how complex interaction relationships can be represented computationally, which is relevant to herb–drug interaction risk triage when patients use multiple medicines and non-prescribed products [29]. In the proposed framework, network outputs are used to prioritize review of plausible interaction clusters, not to assign definitive patient-level harm.

The third layer evaluates pharmacological plausibility. Deep-learning interaction prediction across drug and food domains illustrates how computational methods can generate interaction hypotheses from structured features, but these hypotheses still require exposure interpretation, mechanism review, and validation before clinical inference [30]. For herb–drug interactions, this means that a predicted CYP, transporter, toxicity, or pharmacodynamic overlap signal should be filtered through preparation context, constituent plausibility, route of exposure, and drug vulnerability.

The fourth layer incorporates constituent-aware and explanation-oriented assessment. Substructure-based interaction models demonstrate that molecular features can contribute to interaction prediction, which supports the inclusion of chemical characterization and constituent-level reasoning in the framework [31]. Interpretable knowledge-subgraph learning further supports the need for transparent links between input evidence, predicted mechanisms, and output explanations, especially when risk signals may influence clinical review priorities [32].

The final layer defines safeguards, validation needs, and decision-support boundaries. Evidence grading should distinguish predicted signals, in vitro evidence, in vivo pharmacokinetic findings, pharmacodynamic overlap, case-report evidence, pharmacovigilance signals, clinical interaction evidence, patient-specific vulnerability, and regulatory actionability. The proposed framework is therefore a conceptual structure for risk prioritization, evidence integration, safeguard selection, expert-review triggering, pharmacovigilance feedback, and validation planning; it is not a clinically validated prediction system or a tool for autonomous patient-specific decisions.

Table 3 presents the proposed AI-era risk prediction framework for herb–drug interactions.

Table 3. Proposed Risk Prediction Framework for Herb–Drug Interactions in the AI Era: Herbal Product Identity, Chemical Characterization, Pharmacokinetic Mechanisms, Pharmacodynamic Overlap, Patient Vulnerability, Evidence Grading, Clinical Safeguards, Expert Review, Validation, and Decision Boundaries

Framework stage	Core purpose	Required input	Prediction or assessment logic	Potential risk signal	Clinical safeguard	Uncertainty source	Validation requirement	Failure risk	Decision-support boundary
Herbal product identity	Establish what exposure is being assessed	Botanical name, authentication, plant part, preparation, product details	Confirm identity before mechanism inference	Unclear or mixed herbal exposure	Exposure documentation	Mislabeling, variability, incomplete disclosure	Botanical or product verification where feasible	Wrong herb assessed	No risk interpretation without identifiable exposure
Chemical characterization	Link exposure to plausible constituents	Known and predicted constituents, chemical profile, extraction context	Map constituents to mechanisms and pharmacology	Constituent linked to CYP, transporter, toxicity, or PD domain	Chemistry-aware review	Unknown composition or batch variability	Analytical characterization or credible published evidence	Unsupported constituent inference	Predicted constituents are not confirmed exposure
Drug identity and therapeutic index	Determine drug vulnerability	Drug name, class, route, dose context, therapeutic index	Prioritize high-consequence medicines	Narrow therapeutic index or severe toxicity domain	Expert review trigger	Missing dose or clinical context	Drug-specific pharmacology review	Underprioritized high-risk medicine	No medication-change advice

CYP interaction prediction	Identify enzyme-mediated plausibility	CYP substrate, inhibitor, inducer, constituent evidence	Screen inhibition or induction potential	Predicted metabolism change	Pharmacokinetic review	In vitro-to-clinical extrapolation	Mechanistic or clinical PK validation	Overcalling CYP signal	CYP prediction does not confirm clinical interaction
Transporter interaction prediction	Identify transporter-mediated plausibility	P-gp, OATP, BCRP, MRP, renal or hepatic transporter evidence	Assess pathway dependence and exposure relevance	Absorption, distribution, or elimination concern	Exposure review	Transporter site and direction uncertainty	Transporter probe or clinical evaluation	Missed non-CYP mechanism	Transporter signal is hypothesis-generating
Phase II metabolism assessment	Include supported conjugation mechanisms	UGT or other Phase II pathway evidence	Assess only where pathway evidence exists	Potential conjugation-mediated exposure change	Mechanism-specific review	Limited pathway evidence	Phase II metabolism validation	CYP-only framework bias	Unsupported Phase II claims avoided
Exposure plausibility	Filter mechanism by real-use context	Route, preparation, dose context, duration, bioavailability	Ask whether mechanism is reachable at plausible exposure	Mechanism plausible under exposure context	Exposure-aware caution	Product and use variability	Human exposure or PK evidence where possible	High-dose in vitro overinterpretation	No quantitative exposure values invented
Pharmacodynamic overlap	Identify shared or opposing effect domains	Drug pharmacology, herb pharmacology, toxicity domains	Map bleeding, CNS, cardiovascular, glycemic, BP, toxicity, or opposing effects	Additive toxicity or therapeutic opposition	Monitoring consideration or review	Mechanistic and clinical uncertainty	Clinical, pharmacovigilance, or mechanistic validation	Missing non-PK concern	Overlap does not prove harm
Patient vulnerability	Interpret risk through patient context	Age, organ function, comorbidity, pregnancy/lactation where relevant, pharmacogenomics where supported	Elevate review priority when vulnerability increases consequence	Vulnerable patient context	Clinician or pharmacist review	Missing patient details	Patient-specific clinical assessment	Automation bias	No individualized medical advice
Polypharmacy and self-medication	Capture cumulative and hidden exposures	Full medicine, supplement, and herbal product list	Identify networked and undisclosed risk	Multiple interacting exposures	Medication reconciliation	Incomplete disclosure	Reconciled exposure list	Hidden interaction pathways	Triage only
Evidence grading	Label confidence transparently	Prediction, in vitro, clinical PK, case, pharmacovigilance, database, clinical evidence	Grade by relevance, consistency, and causality	Low-confidence or conflicting signal	Evidence summary	Evidence heterogeneity	Independent evidence review	Weak evidence treated as strong	Evidence grade is not recommendation

Uncertainty communication	Prevent false certainty	Missing identity, exposure, mechanism, patient context, validation status	State what is unknown and why it matters	High uncertainty	Caution and referral threshold	Data gaps and conflicting evidence	Updated evidence assessment	False reassurance	Absence of prediction does not prove safety
Clinical safeguards	Define review and monitoring boundaries	Mechanism, evidence, patient risk, drug vulnerability	Select appropriate safeguard category	Review, monitoring consideration, referral, documentation	Safeguard planning	Context dependence	Clinician-led interpretation	Overstepping into advice	No start, stop, substitute, or combine instruction
Expert review trigger	Escalate high-consequence or uncertain signals	High-risk medicine, vulnerable patient, severe toxicity domain	Trigger pharmacist, physician, toxicologist, or specialist review	Serious or uncertain signal	Expert assessment	Specialty-specific complexity	Professional assessment	Delayed escalation	AI supports review, not replacement
Validation planning	Define how the signal should be tested	Mechanistic hypothesis, exposure scenario, endpoints	Identify appropriate validation pathway	Unvalidated prediction	Research or surveillance plan	Feasibility and evidence limitations	In vitro, clinical PK, PD, or pharmacovigilance validation	Premature deployment	Prediction is not confirmation
Pharmacovigilance feedback	Improve evidence over time	Reports, signal assessment, case detail, exposure documentation	Feed credible signals into evidence grading	Emerging safety pattern	Surveillance review	Reporting bias and confounding	Causality-aware signal assessment	Signal inflation	Signal does not equal causality
Decision-support boundary	Prevent autonomous clinical decisions	Intended use, user type, output format, governance rules	Restrict output to prioritization and evidence integration	Overconfident AI output	Boundary statement and audit trail	Automation bias	Governance and performance evaluation	Unsafe self-management	No patient-specific medical decision

Figure 2 presents the proposed AI-era risk prediction framework for herb–drug interactions, linking mechanistic prediction, patient risk, evidence grading, safeguards, and validation boundaries.

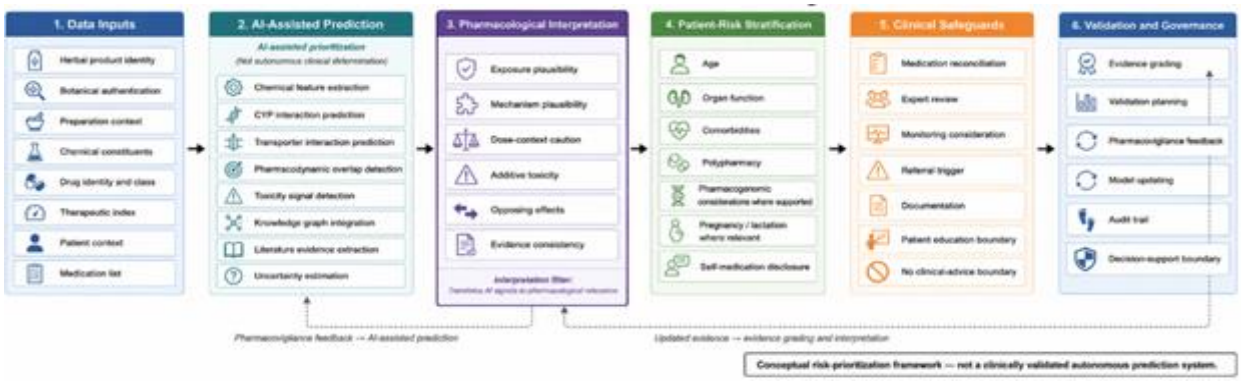

Figure 2. AI-Era Risk Prediction Framework for Herb–Drug Interactions

Alt-text description

A layered risk prediction framework showing herb and drug data entering AI-assisted mechanism prediction, pharmacokinetic and pharmacodynamic interaction assessment, patient risk stratification, evidence grading, clinical safeguards, expert review, validation planning, and decision boundaries.

Clinical implications

For clinicians, pharmacists, toxicologists, pharmacologists, and herbal medicine researchers, the framework offers a structured way to separate evidence retrieval from evidence interpretation. Explainable AI methods in interaction prediction are important because clinical users need to understand why a signal is generated, what evidence supports it, what is uncertain, and when expert review is needed [33].

For AI model developers and decision-support platform designers, the framework emphasizes that model architecture should be linked to pharmacological meaning, not only predictive performance. Machine-learning and graph-neural-network approaches can support interaction prediction, but clinical translation requires validation-aware design, careful output framing, and safeguards against automation bias [34].

For pharmacovigilance teams and translational safety researchers, the framework can support more consistent triage of predicted signals, case reports, database entries, literature evidence, and real-world safety patterns. Its clinical implication is not that AI can determine patient-level use of herbal products with medicines, but that AI-assisted tools can help organize evidence, communicate uncertainty, trigger expert review, and identify where validation is needed.

CONCLUSION

This article proposes an AI-era risk prediction framework for herb–drug interactions that integrates herbal product identity, chemical characterization, pharmacokinetic mechanisms, pharmacodynamic overlap, patient-specific vulnerability, evidence grading, uncertainty communication, clinical safeguards, expert review, validation planning, pharmacovigilance feedback, and decision-support boundaries. The central contribution is a structured approach for distinguishing predicted interaction signals from mechanistic plausibility, exposure relevance, patient vulnerability, evidence confidence, clinical safeguard needs, and validation requirements. Responsible herb–drug interaction prediction requires mechanistic evidence, exposure-aware interpretation, patient-context awareness, and clinical safeguards rather than reliance on computational outputs alone.

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