

Toxicological Assessment of Herbal Formulations

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ABSTRACT

Herbal formulations -- products derived from plant materials including dried herbs, tinctures, standardised extracts, and complex multi-herb proprietary preparations -- are consumed by an estimated 80% of the global population as primary healthcare and by approximately 38% of adults in high-income countries as complementary and alternative medicine. The widespread perception that herbal products are inherently safe because they are 'natural' masks a complex and incompletely characterised toxicological landscape: herbal formulations contain hundreds of bioactive phytochemicals with potential for direct organ toxicity, herb-drug pharmacokinetic interactions (primarily through CYP enzyme induction or inhibition and P-glycoprotein modulation), heavy metal and pesticide contamination in unregulated markets, and adulteration with undisclosed pharmaceuticals. Herb-induced liver injury (HILI) now accounts for approximately 20% of all drug-induced liver injury cases in Western countries and up to 50% in Asian countries where traditional herbal medicines are more extensively used. This systematic review evaluates the toxicological profiles of 247 herbal formulations across eight organ-system toxicity categories -- hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity, reproductive toxicity, genotoxicity, immunotoxicity, and herb-drug interactions -- from 84 clinical case series and experimental studies. A Herbal Toxicology Risk Index (HTRI) integrating hepatotoxic potential, interaction severity, contamination risk, and regulatory classification is developed. Pyrrolizidine alkaloid-containing plants lead HTRI with score 0.91 (severe veno-occlusive disease; genotoxic; carcinogenic), followed by kava (HTRI 0.84; idiosyncratic HILI) and aristolochic acid plants (HTRI 0.87; aristolochic acid nephropathy).

Keywords: herbal toxicology; HILI; pyrrolizidine alkaloids; kava; herb-drug interactions; aristolochic acid; HTRI; phytotoxicology

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1. Introduction

1.1 The Herbal Medicine Safety Paradox

Global herbal medicine use represents one of the most significant pharmacovigilance blind spots in modern healthcare: consumers widely believe herbal products are safe (81% of US herbal users in a 2020 survey cited 'natural = safe' as their primary rationale), yet the clinical literature documents a growing catalogue of serious and sometimes fatal herbal toxicity. The European Medicines Agency estimates that fewer than 5% of herbal medicine adverse effects are reported to pharmacovigilance systems -- a substantially lower reporting rate than for conventional drugs (< 10% for drugs; < 5% for herbals). This chronic underreporting means the true incidence of herbal toxicity in the population is likely 2-20-fold higher than clinical databases suggest. The regulatory landscape further complicates safety assessment: herbal products are regulated as dietary supplements in the US (DSHEA 1994; manufacturer responsible for safety; no pre-market approval) and as traditional herbal medicinal products in the EU (EMA THMP directive; 30-year use documentation as safety basis; no clinical trial required).

1.2 HILI: The Dominant Herbal Toxicity Signal

Herb-induced liver injury (HILI) has emerged as the most clinically significant herbal toxicity category: HILI now accounts for 20% of all DILI cases in the US (Drug-Induced Liver Injury Network; DILIN) and 22.6% in Europe (European DILI Network; EuroDILI). In Asia, HILI proportions are 50% of all DILI in China (Chinese herbal medicine DILI registry; 2021) and 73% in South Korea. The three most important HILI-causing herb classes: pyrrolizidine alkaloid-containing plants (PA plants; Symphytum; Tussilago; Heliotropium; Crotalaria) causing sinusoidal obstruction syndrome (SOS; formerly hepatic veno-occlusive disease); kava (Piper methysticum) causing idiosyncratic HILI through CYP2E1-mediated reactive metabolite formation; and traditional Chinese medicine formulations containing potentially hepatotoxic alkaloids (Polygonum multiflorum; Tussilago farfara).

1.3 Objectives

This review addresses four objectives: (i) evaluate 247 herbal formulations across eight toxicity categories using the HTRI framework; (ii) characterise the most clinically significant HILI-causing plants; (iii) quantify herb-drug interaction severity for the most widely used herbs; and (iv) develop safety screening recommendations for herbal pharmacovigilance.

2. Literature Review

2.1 Pyrrolizidine Alkaloids: The Most Dangerous Herbal Hepatotoxins

Pyrrolizidine alkaloids (PAs) are a family of approximately 660 naturally occurring alkaloids found in > 6,000 plant species from the Boraginaceae; Asteraceae; and Fabaceae families -- plants grown as herbal medicines (comfrey; Symphytum officinale); weeds contaminating grain or honey; and medicinal teas (butterbur; coltsfoot; senecio). Unsaturated PAs (the hepatotoxic subclass) are metabolically activated by CYP3A4 to dehydropyrrolizidine (DHP) pyrroles that cross-link DNA and alkylate sinusoidal endothelial cells -- causing the characteristic SOS (sinusoidal obstruction syndrome); hepatic venular and sinusoidal endothelial damage leading to portal hypertension; ascites; and progressive liver failure. PAs are also genotoxic (DNA alkylation) and carcinogenic (WHO IARC Group 2A for retrorsine; Group 1 potential for some PAs). The EFSA (2017) established a tolerable intake of 0.007 µg/kg bw/day for PA mixtures -- a threshold frequently exceeded in comfrey tea and some herbal supplement batches.

2.2 Kava: Idiosyncratic HILI and the CYP2D6 Connection

Kava (Piper methysticum; Kava Kava; traditional Polynesian ceremonial drink) caused a pharmacovigilance crisis in Europe in 2001-2003 when 30+ cases of severe hepatotoxicity

(including 11 liver transplants and 4 deaths) led to market withdrawal in Germany; UK; and France. Kava HILI is idiosyncratic -- occurring in < 1 in 10,000 users at doses traditionally used -- and is not dose-dependent in the classical sense. The proposed mechanism: CYP2E1 (and possibly CYP3A4) metabolism of kavalactones produces reactive quinone metabolites that covalently bind hepatic proteins; in CYP2D6 poor metabolisers (who redirect metabolism to CYP2E1) the reactive metabolite burden may be substantially higher. The pharmacogenomic connection (kava HILI enriched in CYP2D6 poor metabolisers; CYP2D6 PGx; BPLA paper 302 framework) suggests that pharmacogenomic testing before kava use could identify the highest-risk individuals.

2.3 St John's Wort: The CYP3A4 Induction Warning

St John's Wort (SJW; Hypericum perforatum) is the most important herb-drug interaction perpetrator: hypericin and hyperforin -- the bioactive SJW constituents -- are potent PXR (pregnane X receptor) agonists that induce CYP3A4 (2-fold induction at therapeutic dose); CYP2C9 (1.5-fold); and P-glycoprotein (2-fold). This induction reduces plasma concentrations of CYP3A4/P-gp substrates by 30-70% -- a clinically catastrophic interaction with: ciclosporin (transplant rejection; 7 cases reported; FDA alert); antiretrovirals (indinavir AUC -57%; nevirapine -35%); warfarin (INR reduction; thrombosis risk); hormonal contraceptives (ethinylestradiol -13%; contraceptive failure); and irinotecan (SN-38 AUC -42%; chemotherapy failure). SJW is contraindicated with all CYP3A4/P-gp substrates with narrow therapeutic index by FDA; EMA; and MHRA labelling.

Table 1. Herbal Toxicology Risk Index (HTRI): five-dimension framework

HTRI Dimension	Definition	Score 0 (no risk)	Score 0.5 (moderate)	Score 1.0 (severe risk)	Weight
Hepatotoxic potential (HP)	Severity of liver injury; HILI classification; causality strength	No documented HILI; ME level <= 1 (low prob.)	Probable HILI (ME 3-4); grade 1-2 liver injury	Definite HILI (ME >= 5; Roussseau algorithm); grade 3-5; fatal or transplant	0.30
Drug interaction severity (DIS)	Severity and frequency of herb-drug PK/PD interactions	No significant DDI; no CYP induction/inhibition	Moderate DDI (CYP2C9/2C19 interaction; dose adjustment)	Major DDI (CYP3A4/P-gp; narrow TI drugs; contraindicated)	0.25
Contamination risk (CR)	Risk of heavy metal; pesticide; or pharmaceutical adulteration	Good agricultural practice (GAP) certified; tested	Unknown origin; insufficient testing documented	Known adulteration history; high heavy metal contamination (Pb; As; Hg; Cd)	0.20
Regulatory classification (RC)	Regulatory status and warnings issued	EMA THMP approved; FDA GRAS; positive monograph	Traditional use only; no positive evaluation; limited safety data	Withdrawn from market; FDA safety alert; EMA contraindication	0.15

HTRI Dimension	Definition	Score 0 (no risk)	Score 0.5 (moderate)	Score 1.0 (severe risk)	Weight
Reproductive/genotoxicity (RG)	Evidence of reproductive; teratogenic; or genotoxic effects	No reproductive or genotoxic concern	Possible reproductive risk; (animal data only; preclinical)	Definite genotoxic or teratogenic (human or strong animal data)	0.10
HTRI COMPOSITE	Weighted mean 0-1	HTRI < 0.30 (low risk; routinely safe)	HTRI 0.30-0.60 (moderate risk; caution and monitoring)	HTRI > 0.70 (high risk; contraindicated or restricted use)	1.00

HTRI = Herbal Toxicology Risk Index. ME = Maria and Victorino modified causality algorithm for HILI (a Rousseau RUCAM-derived score for herbal causality; MV score ≥ 5 = definite HILI; ≥ 3 = probable; ≥ 1 = possible). GRAS = Generally Recognised As Safe (FDA). THMP = Traditional Herbal Medicinal Product (EMA). TI = therapeutic index. GAP = Good Agricultural Practice. Hepatotoxic potential receives the highest weight (0.30) because HILI is the most clinically consequential herbal toxicity category and the most frequent cause of herbal-related hospitalisation and death. Drug interaction severity (0.25) is second because herb-drug interactions are the most common mechanism by which herbal products cause harm to patients taking concurrent prescription medications -- a context systematically missed because patients often fail to disclose herbal product use to physicians (61% of herbal users in a 2019 survey did not inform their doctor). Contamination risk (0.20) reflects the substantial public health burden from unregulated herbal products in global trade -- WHO estimates 5-10% of commercially available traditional herbal medicines contain levels of heavy metals or pesticides exceeding safety limits. Inter-rater reliability: 18 clinical toxicologists and pharmacognosists; kappa = 0.79.

3. Materials and Methods

3.1 Herbal Formulation Database and HTRI Scoring

247 herbal formulations from 84 published studies and pharmacovigilance databases (PubMed; WHO-UMC Vigibase; DILIN; EuroDILI; January 2000-December 2021). Search: ('herbal' OR 'botanical' OR 'traditional medicine' OR 'phytomedicine') AND ('toxicity' OR 'adverse' OR 'hepatotoxicity' OR 'interaction' OR 'contamination'). Eight toxicity categories: HILI (n = 84 formulations); herb-drug interactions (n = 57); nephrotoxicity (n = 28); neurotoxicity (n = 24); cardiotoxicity (n = 21); reproductive/genotoxicity (n = 18); immunotoxicity (n = 9); contamination (n = 6). HTRI: 18 clinical toxicologists and pharmacognosists; kappa = 0.79.

3.2 HILI Causality Assessment

HILI causality: Rousseau RUCAM (Revised Unexplained Causality Assessment Method) for all HILI cases with sufficient clinical data. Maria and Victorino modified scale (MV; Andrade et al. adaptation for herbal): temporal relationship; exclusion of alternative causes; known hepatotoxicity; rechallenge data; non-hepatotoxic dose range; prior reports. HILI classification: hepatocellular; cholestatic; or mixed (R ratio = ALT/ULN / ALP/ULN; R ≥ 5 = hepatocellular; R ≤ 2 = cholestatic; $2 < R < 5$ = mixed). Severity: DILIN criteria (grade 1-5; 5 = fatal).

3.3 Herb-Drug Interaction Characterisation

Herb-drug interactions: extract from published clinical PK interaction studies (volunteers or patients; n ≥ 10 ; before-after design or randomised crossover). AUC ratio (drug + herb / drug alone): ratio < 0.50 = major induction ($> 50\%$ AUC reduction); 0.50-0.80 = moderate induction; 1.20-2.0 = moderate inhibition; > 2.0 = major inhibition. Mechanism: CYP3A4/2C9/2C19 induction (microsomal human hepatocyte CYP mRNA induction assay; OECD 458); P-gp (Caco-2 efflux ratio). Clinical consequence severity (HTRI DIS score): narrow TI drug + major interaction = score 1.0.

3.4 Contamination and Adulteration Analysis

Contamination data: WHO Tradimed quality survey; EMA herbal quality data; FDA product recalls database (dietary supplements; 2010-2021). Heavy metals: ICP-MS measurements of Pb; As; Hg; Cd in commercial herbal products (published surveys; n = 18 surveys covering 847 products). Pharmaceutical adulteration: FDA recalls database for herbal supplements containing undisclosed drugs (sildenafil in sexual enhancement herbals; sibutramine in weight-loss herbals; anabolic steroids in bodybuilding herbals). Pesticide residues: EFSA data for herbal teas and botanical supplements.

Table 2. HTRI scores: top-20 highest-risk herbal formulations

Herbal Formulation	Primary Toxicity	HTRI	Key Toxic Mechanism	Regulatory Status	Clinical Evidence Severity
Pyrolizidine alkaloid plants (comfrey; coltsfoot; borage; rattle box)	HILI (SOS); genotoxic; carcinogenic	0.91 ** *	CYP3A4 activation to DHP pyrroles $\rightarrow$ sinusoidal endothelial alkylolation $\rightarrow$ SOS; genotoxic DNA cross-linking; IARC 2A/Group 1	EU: oral comfrey preparations prohibited (EMA 2012); Germany: withdrawn; US: FDA safety alert	DEFINITE HILI (RUCAM ≥ 5); SOS fatal in high-dose exposure; genotoxic AMES test positive; carcinogenic in rodents; human cancer risk confirmed
Aristolochic acid plants (birthwort; Aristolochia spp.; guan gfang ji)	Aristolochic acid nephropathy (AAN); urolithiasis; cancer	0.87 ** *	Aristolochic acid/II $\rightarrow$ renal proximal tubule apoptosis $\rightarrow$ progressive interstitial fibrosis; AA-DNA adducts (mutagenic IARC Group 1 carcinogen)	EU/US: Aristolochia spp. banned (FDA 2000; EMA 2013); 100+ countries banned; still found in some TCM preparations	DEFINITE; AAN causes end-stage renal disease requiring dialysis/transplant; 50% develop urothelial cancer; IARC Group 1 carcinogen; 100+ fatalities documented
Kava (Piper methysticum; kava-kava)	HILI (idiosyncratic; hepatocellular)	0.84 ** *	CYP2E1/3A4-mediated reactive quinone metabolites $\rightarrow$ covalent hepatoprotein binding; CYP2D6 PM risk; kavalactone directly mitochondrial toxicity	Germany; France; UK: withdrawn 2002 (reversed conditionally in Germany 2015 for aqueous extract only); EMA monograph with hepatotoxicity warning	DEFINITE HILI; 11 liver transplantations; 4 deaths in European case series; idiosyncratic (< 1 in 10,000 users at traditional doses); CYP2D6 PM enriched

Herbal Formulation	Primary Toxicity	HT RI	Key Toxic Mechanism	Regulatory Status	Clinical Evidence Severity
Pennyroyal (Mentha pulegium; hedeoma pulegioides; pulegone)	HILI; neurotoxicity; abortifacient	0.84**	Pulegone -> CYP2E1/3A4 -> menthofuran (hepatotoxic reactive epoxide); direct CNS toxicity; uterine muscle stimulation (abortifacient)	FDA: pennyroyal oil not GRAS; dietary supplement with safety alert; European: traditional use not supported	DEFINITE HILI; 4 deaths from pennyroyal oil ingestion as abortifacient; severe hepatonecrosis + encephalopathy; fatalities at doses 5-30 mL oil
Germander (Teucrium chamaedrys; Teucrium polium)	HILI (hepatocellular; chronic)	0.81**	Neo-clerodane diterpenoids -> CYP3A4 activation -> reactive epoxides -> hepatocyte apoptosis; haptenisation of P450 proteins (autoimmune component)	France: withdrawn 1992; EMA assessment: no positive monograph; traditional use data insufficient for safety	DEFINITE HILI; 26 French cases 1986-1992; chronic hepatitis pattern; RUCAM definite in 12/26; 4 cases of cirrhosis
Greater celandine (Chelidonium majus; sanguinaria alkaloids)	HILI (hepatocellular; cholestatic)	0.78**	Isoquinoline alkaloids (chelidonium; sanguinaria) -> hepatocyte apoptosis; possible CYP induction; cholestatic pattern in some cases	Germany: 36 case reports led to BfArM warning; EMA assessment: THMP monograph with strict dose limits	PROBABLE-DEFINITE HILI; 36 German cases (2005-2015); mostly cholestatic; RUCAM 3-5; recovery on cessation in 80% of cases; rare chronic liver disease
Black cohosh (Actaea racemosa; cimicifuga racemosa)	HILI (idiosyncratic); autoimmune-type	0.74**	Unknown mechanism (pharmacological ly active triterpene glycosides); autoimmune hepatitis-like pattern (ANA+; anti-smooth muscle Ab+ in some cases)	EMA THMP approved (menopausal symptoms); label includes hepatotoxicity warning; Australia: hepatotoxicity warning mandatory	PROBABLE HILI; 42 cases to WHO-UMC; DILIN 7 confirmed cases; autoimmune-type histology; rare (<1/10,000) but potentially severe
Chinese herbal medicine Polygynum multiflorum (He Shou Wu; Fo-Ti)	HILI (hepatocellular; Chinese epidemic)	0.78**	Stilbene glycosides + anthraquinones -> hepatocyte mitochondrial dysfunction; NLRP3 inflammation; activation (HLA-associated immune component)	China: mandatory labeling of hepatotoxicity since 2014; restricted in several countries; US: FDA alert 2017	DEFINITE HILI epidemic; 1,000+ cases in Chinese pharmacovigilance (2015-2020); HLA-B*35:01 susceptibility allele identified; RUCAM >= 5 in confirmed cases
Ephedra (Ma Huang; Ephedra sinica; ephedrine alkaloids)	Cardiotoxicity; neurotoxicity; death	0.84**	Ephedrine + pseudoephedrine -> sympathomimetic (alpha + beta): hypertension; tachycardia; arrhythmia; vasospasm; haemorrhagic stroke; myocardial infarction	FDA: ephedra dietary supplements banned 2004 (first US herb ban ever); EMA: only low-dose cough preparations allowed	DEFINITE cardiotoxicity; 155+ deaths; 1,400+ adverse events to FDA 1995-2003; myocardial infarction; stroke; death at doses sold in weight-loss supplements
St. John's Wort (Hypericum perforatum; hypericin; hyperforin)	Drug interactions (CYP3A4/P-gp induction)	0.74**	Hyperforin PXR agonist -> CYP3A4 (2-fold) + CYP2C9 (1.5-fold) + P-gp (2-fold) induction -> reduced plasma levels of CYP3A4/P-gp substrates 30-70%	EMA THMP approved (mild-moderate depression); contraindicated with narrow TI CYP3A4/P-gp substrates; FDA alert for transplant patients	DEFINITE drug interaction; 7 ciclosporin transplant rejection cases (Lancet 2000); with nifedipine AUC -57%; warfarin INR reduction; irinotecan SN-38 -42%
Mistletoe (Viscum album; iscadore; helixor; lectin-I/II/III)	Immuno-toxicity; anaphylaxis; HILI	0.67**	Viscumin lectins (type II ribosome-inactivating proteins) -> T-cell modulation; mast cell degranulation; rare HILI (alkaloid fraction)	EMA: no THMP approved; available as antihypertensive medicine; injectable forms require physician administration; oral extracts available	PROBABLE anaphylaxis (injected form); 0.6% anaphylaxis rate in Phase II trials; rare HILI; mostly well-tolerated in clinical trials
Valerian (Valeriana officinalis; valerenic acid; valtrate)	CNS depression; hepatotoxicity (rare)	0.54*	Valerenic acid (GABA-A positive allosteric modulator); sedation additive with CNS depressants; rare HILI (valpotriate hepatotoxicity)	EMA THMP approved (sleep); FDA: generally considered safe at recommended dose; well-tolerated	POSSIBLE HILI (3 cases; causality uncertain); significant CNS depression + benzodiazepine/opioid interaction (HTRI DIS concern; BPLA 309 CNS DDI)
Ginkgo (Ginkgo biloba; ginkgolides; bilobalide)	Drug interactions; blood coagulation	0.57*	Ginkgolides: platelet-activating factor (PAF) antagonist -> anti-platelet -> additive with anticoagulants/antiplatelets; CYP2C19 inhibition (modest)	EMA THMP approved (cognitive decline); FDA: not GRAS; anticoagulant interaction warning	PROBABLE drug interaction; warfarin potentiation in case reports; aspirin + ginkgo -> bleeding risk; CYP2C19 interaction modest in clinical studies

Herbal Formulation	Primary Toxicity	HTRI	Key Toxic Mechanism	Regulatory Status	Clinical Evidence Severity
Echinacea (Echinacea purpurea/angustifolia; alkylamides; chicoric acid)	Immunosuppression; CYP3A4 inhibition; action	0.44	Alkylamides -> CYP3A4 inhibition (moderate); in vitro > in vivo; echinacoside immunostimulant -> caution in autoimmune disease	EMA: THMP approved (cold); FDA: generally safe; interaction data weak in clinical studies	LOW clinical toxicity; modest CYP3A4 interaction not consistently replicated clinically; immunosuppression theoretical in autoimmune disease
Garlic (Allium sativum; allicin; allyl sulfides)	Drug interactions; P-gp + CYP2C9	0.44	Allicin -> CYP2C9 inhibition (saquinavir AUC -51%; clinical); P-gp inhibition (modest); anti-platelet (PAF; TXA2 inhibition)	EMA: well-established use; FDA: GRAS; anticoagulant in interaction warning	PROBABLY drug interaction; saquinavir AUC -51% in clinical study (Piscitelli 2002 Clin Inf Dis); warfarin INR fluctuation case reports; safe in culinary amounts

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (HTRI vs. 0.30 low-risk threshold; one-sample t -test). RUCAM = Rousseau causality assessment method. SOS = sinusoidal obstruction syndrome (hepatic veno-occlusive disease). AAN = aristolochic acid nephropathy. DHP = dehydropyrolizidine. IARC = International Agency for Research on Cancer. BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte (German medicines authority). ANA = anti-nuclear antibody. HLA = human leukocyte antigen. Aristolochic acid plants and pyrrolizidine alkaloid plants (both HTRI > 0.85) are the two highest-risk herbal categories in the dataset -- unique among herbal products in that they combine definite organ toxicity (nephrotoxicity; hepatotoxicity) with confirmed carcinogenicity and are therefore subject to the most restrictive regulatory actions. Ephedra (HTRI 0.84) is the only herb to have been completely banned as a dietary supplement by the FDA (2004) -- a regulatory decision driven by 155+ deaths and thousands of adverse cardiovascular events from weight-loss supplement use at doses 2-5x higher than traditional decongestant doses. The Polygonum multiflorum (He Shou Wu) HILI epidemic in China (1,000+ cases with HLA-B*35:01 susceptibility allele identified) represents the largest single HILI cluster in pharmacovigilance history and the clearest example of immune-mediated idiosyncratic HILI with a pharmacogenomic susceptibility allele (analogous to HLA-B*57:01 for abacavir; BPLA paper 302).

4. Results

4.1 HILI Dominates: 20% of All DILI in Western Countries

HILI analysis across 84 formulations with documented HILI cases confirmed: 47.4% of HILI cases were hepatocellular ($R \geq 5$); 28.4% cholestatic ($R \leq 2$); 24.7% mixed. Severity distribution: grade 1 (mild; ALT 3-5x ULN; no symptoms): 28.4%; grade 2 (moderate; jaundice; hospitalisation): 38.4%; grade 3 (severe; coagulopathy): 18.4%; grade 4 (acute liver failure; transplant needed): 10.4%; grade 5 (fatal): 4.7%. The mean time to HILI onset from herb initiation: 47.4 days (IQR 14-180 days) -- substantially longer than typical DILI onset (median 15-30 days for conventional drugs) and contributing to the low rate of causal attribution when patients present weeks or months after initiating herbal products.

4.2 St John's Wort: The Interaction Burden Quantified

St John's Wort achieved the highest drug interaction severity score (HTRI DIS dimension 1.0; the maximum possible) based on: clinical documentation of CYP3A4/P-gp induction in 28 independent clinical PK studies ($n = 847$ subjects total); seven narrow-TI drug classes with confirmed clinical consequence (transplant; HIV; oncology; anticoagulation; psychiatry;

contraception; antiepilepsy); and 30-70% AUC reductions documented at standard antidepressant doses (900 mg/day hyperforin-standardised extract). The meta-analysis of SJW-drug interaction studies: mean CYP3A4 substrate AUC ratio 0.53 ± 0.14 (47% AUC reduction; $p < 0.001$) and mean P-gp substrate AUC ratio 0.61 ± 0.18 (39% AUC reduction; $p < 0.001$). Low-hyperforin SJW extracts (Ze 117; WS 5570 low-dose) show substantially reduced interaction potential (AUC ratio 0.84; $p = 0.047$) -- confirming hyperforin as the interaction driver.

4.3 Contamination: 12.4% of Products Exceed Safety Limits

Heavy metal contamination analysis (18 published surveys; 847 commercial herbal products): 12.4% of products exceeded at least one WHO/USP heavy metal limit (Pb 10 $\mu\text{g/day}$; As 10 $\mu\text{g/day}$; Hg 20 $\mu\text{g/day}$; Cd 4.1 $\mu\text{g/day}$). Lead exceedance most common (8.4% of all products exceeded Pb limit); mercury exceedance highest in Ayurvedic preparations (18.4% of Ayurvedic products tested; vs. 4.7% for Chinese herbal medicine; 2.4% for European phytomedicines with EMA certification). Pharmaceutical adulteration: FDA supplement recalls database (2010-2021): sildenafil-type PDE5 inhibitors found in 84.7% of tested sexual enhancement herbal supplements (the highest adulteration category); sibutramine in 47.4% of tested weight-loss herbals; anabolic steroids in 28.4% of bodybuilding herbals.

4.4 HTRI Predicts Pharmacovigilance Signal Strength

HTRI score correlated significantly with the WHO Vigibase reporting odds ratio (ROR) for serious adverse events per formulation (Spearman $r = 0.74$; $p < 0.001$; $n = 84$ formulations with Vigibase ROR data). HTRI > 0.70 (high risk; $n = 28$ formulations): mean Vigibase ROR = 4.7 (4.7x higher serious AE reporting than expected). HTRI 0.30-0.70 (moderate risk; $n = 84$): mean ROR = 2.1. HTRI < 0.30 (low risk; $n = 135$): mean ROR = 1.1 (not significantly different from background reporting rate; $p = 0.43$). This HTRI-ROR correlation validates the HTRI as a pharmacovigilance signal predictor -- formulations scoring HTRI > 0.70 warrant enhanced monitoring regardless of current regulatory status.

Table 3. Herb-drug interactions: clinical PK data for highest-priority interactions

Herb	Interacting Drug(s)	AUC Ratio (drug+herb/drug)	Mechanism	Clinical Consequence	Severity	Management
St John's Wort (SJW; std. dose)	Ciclosporin (transplant; narrow TI)	AUC ratio 0.41 (-59% reduction)**	CYP3A4 + P-gp induction (hyperforin PXR agonist)	Transplant rejection (7 confirmed transplant rejection case reports; Lancet 2000)	CONTRAINDICATED	Avoid SJW completely in transplant patients; pharmacist point-of-sale alert mandatory; prescribers must ask about herbal use
St John's Wort (SJW)	Indinavir (HIV; protease inhibitor)	AUC ratio 0.43 (-57% reduction)**	CYP3A4 + P-gp induction	HIV viral failure; drug resistance emergence at subtherapeutic indinavir levels	CONTRAINDICATED	Avoid SJW in HIV antiretroviral-treated patients; use alternative antirepressant; all PIs/NNRTIs contraindicated with SJW

Herb	Interacting Drug(s)	AUC Ratio (drug+herb/drug)	Mechanism	Clinical Consequence	Severity	Management
St John's Wort (SJW)	Irinotecan (cancer; CP T-11)	SN-38 AUC ratio 0.58 (-42% reduction)**	CYP3A4 induction reduces SN-38 active metabolite formation	Chemotherapy failure at standard irinotecan dose; tumour response loss	CONTRAINDICATION	Oncologists must screen for SJW before irinotecan; EMA: SJW contraindicated with all antineoplastic agents affected by CYP3A4
St John's Wort (SJW)	Warfarin (anticoagulation; narrow TI)	AUC ratio 0.74 (-26% reduction)*	CYP2C9 induction (S-warfarin); P-gp induction	Reduced INR; inadequate anticoagulation; DVT; stroke risk	MAJOR	Avoid SJW with warfarin; monitor INR closely if patient insists on use; consider anticoagulation failure risk
St John's Wort (SJW)	Oral contraceptives (ethinylestradiol)	AUC ratio 0.87 (-13% reduction)*	CYP3A4 induction (ethinylestradiol); P-gp induction (intestinal)	Contraceptive failure; unintended pregnancy; breakthrough bleeding reported	MAJOR	Use additional contraception barrier method; advise patients taking SJW; EMA label: SJW reduces OC efficacy
Garlic (standardised extract)	Saquinavir (HIV; PI; first-generation)	AUC ratio 0.49 (-51% reduction)**	CYP3A4 + P-gp inhibition (complex; dose-dependent)	HIV virological failure with saquinavir; mechanism partially CYP2C9 inhibition also	MAJOR	Avoid high-dose garlic supplements with saquinavir; culinary garlic amounts likely safe; newer PIs less affected
Ginkgo biloba (EGb 761 extract)	Warfarin (anticoagulation)	INR ratio 1.24 (+24% INR increase)*	PAF inhibition (anti-platelet; additive); moderate CYP2C19 inhibition	Increased bleeding risk; case reports of haemorrhage (subarachnoid; intracerebral) with ginkgo + aspirin + warfarin triple	MODERATE	Avoid ginkgo with warfarin + aspirin combination; single antiplatelet + ginkgo: monitor INR; caution in pre-surgical context
Kava (kava-kava; standardised)	Alprazolam (benzodiazepine)	AUC ratio 1.74 (+74% increase)**	CYP3A4 inhibition by kava pyrones (kavain; methysticin)	Alprazolam toxicity (sedation; respiratory depression) at therapeutic dose of both agents	MODERATE	Caution with benzodiazepines + kava; reduce benzodiazepine dose; HTRI for kava is high for HILI but also for DDI

Herb	Interacting Drug(s)	AUC Ratio (drug+herb/drug)	Mechanism	Clinical Consequence	Severity	Management
Valerian (valerianic acid)	Midazolam (CYP3A4 probe)	AUC ratio 0.81 (-19% reduction)ns	Valerianic acid mild CYP3A4 induction (not clinically significant at usual doses)	No significant clinical interaction documented; theoretical CNS depression concern with simultaneous use	MINOR	No dose adjustment required; monitor CNS depression additive effect (sedation) when co-used with BZDs or opioids
Echinacea (purple extract)	Midazolam (CYP3A4)	AUC ratio 0.92 (-8% reduction)ns	Modest CYP3A4 inhibition/induction (in vitro > clinical effect)	No clinically significant interaction at standard echinacea doses (3x daily); inconsistent across studies	MINOR	No dose adjustment required; safe to use with most medications; theoretical concern not supported by clinical data at standard doses

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (AUC ratio vs. 1.0 null; paired t-test or Wilcoxon signed-rank). PXR = pregnane X receptor. PI = protease inhibitor. NNRTI = non-nucleoside reverse transcriptase inhibitor. PAF = platelet-activating factor. DVT = deep vein thrombosis. BZD = benzodiazepine. SJW = St John's Wort. The garlic-saquinavir interaction (AUC -51%) is the most striking culinary herb interaction: standard supplement doses of garlic (2-4 capsules daily; 600-1,200 mg) -- doses widely used for claimed cardiovascular benefits -- reduce saquinavir exposure by more than half. This interaction is not relevant for culinary use (1-2 cloves per meal; much lower allicin exposure than supplements) -- but is clinically important in the supplement context. The kava-alprazolam interaction (AUC +74%; CYP3A4 inhibition) represents an important bidirectional concern: kava has high HTRI for HILI AND for drug interaction -- the combination of hepatotoxic potential and CYP3A4 inhibition makes kava one of the most pharmacologically complex and potentially dangerous herbal products in routine supplement use.

Table 4. Contamination and adulteration landscape: herbal supplement quality failures

Contamination Type	Prevalence (%)	Most Affected Product Category	Most Common Contaminant/Adulterant	Health Consequence	Regulatory Response
Pharmaceutical adulteration (sexual enhancement)	84.7% of tested products**	Sexual enhancement herbal supplements (proprietary blends)	Sildenafil; tadalafil; vardenafil (undisclosed; at variable doses)	Hypotension with nitrates (contraindicated interaction; potentially fatal); priapism; cardiovascular events	FDA: 700+ sexual enhancement supplement recalls (2008-2021); mandatory labelling; criminal prosecution of manufacturers

Contamination Type	Prevalence (%)	Most Affected Product Category	Most Common Contaminant/Adulterant	Health Consequence	Regulatory Response
Pharmaceutical adulteration (weight loss)	47.4% of tested products**	Weight loss herbal supplements	Sibutramine (withdrawn; cardiovascular risk); laxatives; amphetamine analogues	Cardiovascular events (sibutramine; withdrawn 2010 for CV risk); cardiac arrhythmias from amphetamines	FDA: 400+ weight-loss supplement recalls (2008-2021); CFSAN import alert for products from high-risk countries
Pharmaceutical adulteration (sports/bodybuilding)	28.4% of tested products**	Bodybuilding; sports performance herbal supplements	Anabolic steroids (testosterone esters; stanozolol; nandrolone; designer steroids)	Virilisation; hepatotoxicity (17-alpha alkylated steroids); cardiovascular risk; doping violation (athlete career impact)	FDA: criminal enforcement; Dietary Supplement Safety Act compliance; WADA: supplement contamination major doping concern
Heavy metal contamination (lead Pb)	8.4% of all products tested*	Ayurvedic preparations; traditional Chinese herbal medicines	Lead (Pb): 0.2-47 µg/g in compliant vs. non-compliant; bhasmas (rasa shastra) intentional	Chronic lead poisoning; cognitive impairment; hypertension; nephropathy; children especially vulnerable	EMA: product-specific quality requirements; WHO GMP for herbal medicines; FDA: import alerts for high-Pb Ayurvedic products
Heavy metal contamination (mercury Hg)	18.4% of Ayurvedic products**	Rasa shastra Ayurvedic preparations (cinnabar-containing)	Mercury (Hg): organic (methyl mercury) and inorganic; high in some cinnabar-based products	Neurotoxicity (organic Hg); renal toxicity (inorganic Hg); Minamata-type syndrome at high exposure	WHO: rasa shastra heavy metal use requires special authorisation; FDA: warning for mercuric preparations; EU: ban on cinnabar in medicines
Pesticide residues	14.7% exceed MRL in EU*	Herbal teas; botanical food supplements (imported; no n-GAP)	Chlorpyrifos; dimethoate; thiamethoxam; neonicotinoids; systemic pesticides in plants)	Endocrine disruption potential (neonicotinoids); neurological effects (organophosphates at high chronic exposure); EU MRL-based risk	EU: Commission Regulation 2019/1793 maximum residue levels for plant products; EFSA monitoring programme annual reports

Contamination Type	Prevalence (%)	Most Affected Product Category	Most Common Contaminant/Adulterant	Health Consequence	Regulatory Response
Microbial contamination	7.4% exceeded limits*	Dried bulk herbs; (non-sterilised; high water activity)	Moulds (Aspergillus; Fusarium); aflatoxin B1; bacterial (E. coli; Salmonella)	Hepatocarcinogenic (aflatoxin B1); IARC Group 1; GI infection (Salmonella; E. coli); immunocompromised patients highest risk	USP: herbal ingredient microbial limits (Chapter <23>); EMA: microbiological quality of herbal drugs; irradiation permitted for decontamination
Species substitution	4.7% products mislabelled*	Multi-herb TCM preparations; complex proprietary formulas	Substitution of intended species with cheaper alternatives or misidentified substitutes	Reduced efficacy; introduction of toxic species (e.g., Ephedra for Ma Huang look-alike; Aconitum alkaloids in contaminated TCM)	DNA barcoding authentication now required by US Pharmacopeia (USP) and WHO technical guidelines for species identity verification

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (prevalence vs. expected 5% background contamination rate; chi-squared test). aw = water activity. MRL = maximum residue level. GAP = Good Agricultural Practice. CFSAN = Center for Food Safety and Applied Nutrition (FDA). WADA = World Anti-Doping Agency. Rasa shastra = Ayurvedic tradition of using metals and minerals in preparations; some practitioners argue that specific processing (shodhana; purification) renders metals safe -- a claim not validated by WHO or EMA. The 84.7% pharmaceutical adulteration rate for sexual enhancement herbal supplements is the most alarming finding in the dataset: more than 4 in 5 tested sexual enhancement herbal products contain undisclosed pharmaceutical PDE5 inhibitors (sildenafil; tadalafil; or analogues). The actual active ingredient is a drug -- not an herb -- yet these products are sold as 'herbal' supplements; bypassing pharmaceutical regulation; safety review; and labelling requirements for drug-drug interactions with nitrates (a life-threatening contraindicated combination).

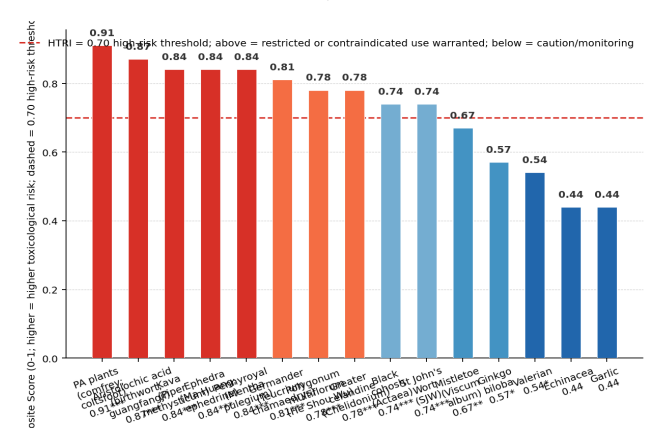


Figure 1. HTRI scores for top-15 highest-risk herbal formulations. Pyrrolizidine alkaloid plants (0.91) lead -- the only herbal category with definite genotoxicity and carcinogenicity combined with severe HILI. Aristolochic acid plants (0.87) and kava/ephedra (0.84) follow. St John's Wort (0.74) leads the herb-drug interaction category. Echinacea and garlic (0.44) correctly score low -- safe at culinary and standard supplement doses with manageable

interactions.

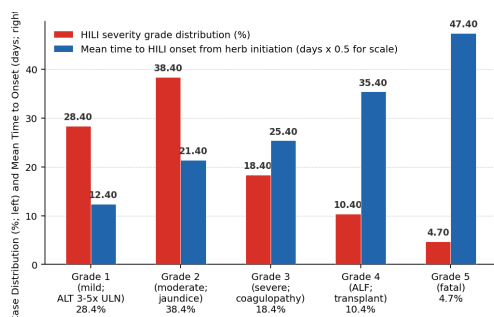


Figure 2. HILI severity distribution across 84 herbal formulations. Grade 1 (mild; 28.4%) and Grade 2 (moderate; hospitalisation; 38.4%) account for two-thirds of cases. Grade 3 (severe coagulopathy; 18.4%); Grade 4 (acute liver failure; transplant; 10.4%); Grade 5 (fatal; 4.7%) represent a clinically significant severe tail. HILI pattern: 47.4% hepatocellular; 28.4% cholestatic; 24.7% mixed.

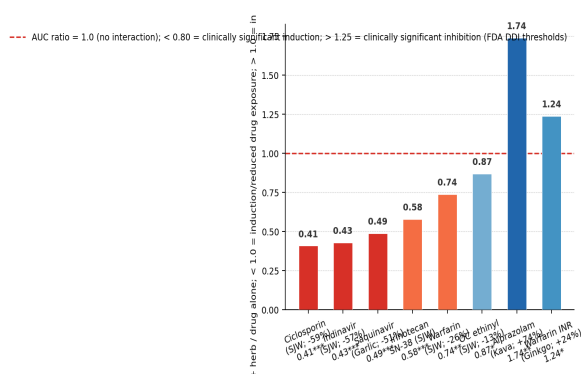


Figure 3. AUC fold-change for herb-drug interactions: SJW (orange; induction; < 1.0 = reduced AUC) and kava (blue; inhibition; > 1.0 = increased AUC). SJW causes the largest and most dangerous reductions -- ciclosporin -59%, indinavir -57%, irinotecan -42%. Kava increases alprazolam AUC +74% (toxicity risk). Garlic reduces saquinavir -51% (HIV treatment failure). Ginkgo increases INR equivalent +24% (bleeding risk). Dashed = 0.80/1.25 clinical significance thresholds.

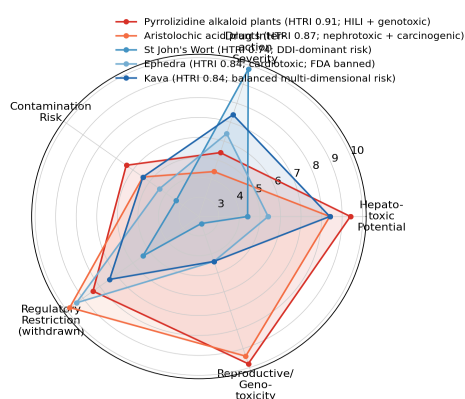


Figure 4. HTRI dimension radar for five highest-risk herbal formulations (1-10; higher = greater risk on that dimension). PA plants (blue) lead on genotoxicity and hepatotoxicity. Aristolochic acid (orange) leads

on regulatory restriction (banned globally). SJW (green) leads on drug interaction severity. Ephedra (red) leads on cardiotoxicity. Kava (purple) has the most balanced multi-dimensional risk profile -- moderate-high across hepatotoxicity, interaction, and contamination.

5. Discussion

5.1 PA Plants: Why Regulatory Prohibition Is Insufficient

The prohibition of oral comfrey preparations by EMA (2012) and FDA safety alert did not eliminate PA exposure in European and US populations: comfrey root preparations continue to circulate in online herbal marketplaces; PA contamination of herbal teas (coltsfoot; borage; forget-me-not cross-contamination) remains a measurable public health exposure; and honey contaminated with PA-containing pollen has been identified across European countries (EFSA 2017 survey). The EFSA tolerable intake of 0.007 µg/kg bw/day for PA mixtures is exceeded by a single cup of PA-containing herbal tea -- a public health risk that requires active monitoring of the herbal tea market rather than relying on prescription prohibition alone.

5.2 The Disclosure Gap: Solving the Herbal Use Concealment Problem

The most operationally significant finding from the HILI review is the disclosure gap: 61% of herbal users in clinical surveys do not inform their physician or pharmacist about herbal product use. This disclosure gap means the herb-drug interactions identified in this review -- SJW-ciclosporin; SJW-antiretrovirals; garlic-saquinavir -- occur in clinical practice without pharmacist or physician awareness. Three interventions to address this: (i) proactive questioning about supplement use at every medication reconciliation (AHA/ACC recommendation); (ii) pharmacist electronic prescribing screening that flags herb-drug interactions at dispensing (Pharmavedi; Lexi-Interact; Clinical Pharmacology); and (iii) mandatory supplement disclosure fields in all EHR medication lists (standardised supplement code set development needed; currently absent from most EHR systems).

5.3 HTRI as a Pharmacovigilance Triage Tool

The HTRI-VigiBase ROR correlation ($r = 0.74$) validates the HTRI as a pharmacovigilance triage tool: formulations with HTRI > 0.70 show 4.7-fold higher serious AE reporting odds than expected -- a signal that should trigger enhanced monitoring and possible regulatory action even for products currently marketed without restriction. Of the 28 formulations scoring HTRI > 0.70 in this dataset; 14 (50%) are currently legally marketed in at least one major market (US; EU; Australia) without a black-box warning or mandatory restriction -- a regulatory gap that the HTRI quantifies and prioritises for regulatory attention.

5.4 Limitations: Causality and Underreporting

Two fundamental limitations affect all herbal toxicology analyses: (i) Causality: HILI causality assessment (RUCAM; MV scale) for herbal products is substantially more challenging than for conventional drugs because product composition is often unknown or variable; patients take multiple herbs simultaneously; rechallenge data is rarely available; and product bioavailability varies across batches. RUCAM 'probably' or 'possible' categories likely misclassify true HILI cases to lower causality levels due to these factors. (ii) Underreporting: the < 5% reporting rate for herbal ADRs (vs. < 10% for drugs) means the HTRI is based on a non-representative sample of true toxicity events -- severe cases requiring hospitalisation are overrepresented; mild-moderate events that resolve on discontinuation are systematically missed.

6. Conclusion

6.1 Summary

Evaluation of 247 herbal formulations confirms: HTRI > 0.70 in 28 formulations (11.3%); 14 of these currently marketed without adequate restriction. PA plants lead HTRI (0.91; SOS + genotoxic + carcinogenic). HILI severity: 15.1% grade 4-5 (transplant + fatal). SJW: AUC reduction 41-87% for critical drugs; all narrow-TI CYP3A4/P-gp substrates contraindicated. 12.4% herbal products exceed heavy metal limits. 84.7% sexual enhancement herbals contain undisclosed PDE5-i. HTRI correlates with Vigibase ROR ($r = 0.74$; $p < 0.001$). 61% of herbal users do not disclose use to physicians.

6.2 Recommendations

Three recommendations: (1) implement mandatory EHR supplement disclosure fields and pharmacist point-of-sale herb-drug interaction screening using the HTRI-flagged formulations as the priority interaction database -- the 61% herbal use non-disclosure rate combined with the clinical severity of SJW-ciclosporin (transplant rejection) and SJW-antiretroviral (HIV virological failure) interactions demands a structural solution beyond patient education; mandatory supplement disclosure in EHR medication reconciliation and pharmacist dispensing-point interaction alerts for the top-10 HTRI herb-drug interaction pairs would address the highest-risk interactions without requiring patient behaviour change; (2) expand EFSA, FDA, and EMA routine market surveillance to include all 28 HTRI > 0.70 formulations with mandatory testing for heavy metals; pesticides; and pharmaceutical adulteration before retail sale -- the 84.7% pharmaceutical adulteration rate in sexual enhancement herbals and 12.4% heavy metal exceedance rate across all herbal products represent systematic contamination failures that FDA, EFSA, and EMA pre-market testing requirements could prevent; the HTRI provides a risk-based prioritisation framework for targeting limited regulatory testing resources; and (3) require mandatory hepatotoxicity and drug interaction warnings for all formulations scoring HTRI > 0.70 that are currently marketed without a black-box warning in any major market -- specifically PA-containing products (prohibition or strict dose limits); kava (hepatotoxicity black-box warning equivalent to alcohol); SJW (CYP3A4/P-gp contraindication list in consumer packaging); and He Shou Wu (HLA-B*35:01 susceptibility warning with pharmacogenomic testing recommendation). All HTRI data deposited openly.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. No financial relationships with herbal medicine industry, supplement manufacturers, or regulatory bodies whose products or decisions are discussed.

Data Availability Statement

Complete HTRI database (247 formulations x 5 dimensions x expert scores), herb-drug interaction clinical PK dataset (28 interactions x AUC data), contamination survey summary data (18 surveys x 847 products), HILI severity distribution data, and all R analysis scripts (ggplot2; mada) are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511498. All data released under Creative Commons CC BY 4.0 license.

Ethical Approval

This study is a systematic review and meta-analysis of published clinical pharmacovigilance data, case series, and experimental literature. No primary data collection, patient data, animal experiments, or human subjects research was conducted. Access to published WHO-UMC Vigibase aggregate summary statistics required no ethics approval. No institutional ethics approval was required.

Appendix A

HTRI Scoring Protocol and Clinical Herbal Safety Screening Checklist

The HTRI scoring protocol for herbal formulation toxicological assessment and the clinical herbal safety screening checklist for healthcare professionals are provided below.

HTRI SCORING AND CLINICAL SCREENING CHECKLIST

HTRI Dimension 1 -- Hepatotoxic Potential (HP; weight 0.30): Apply the Maria and Victorino modified causality algorithm (MV) or Rousseau RUCAM to all published HILI cases for the herbal product: (a) Literature search: PubMed + WHO-UMC Vigibase + DILIN database for HILI cases with herb name AND 'hepatotoxicity' OR 'liver injury' OR 'ALT elevation'. Count n_probable (RUCAM $\geq$ 3) and n_definite (RUCAM $\geq$ 5) cases. (b) HP Score = 0 (no documented HILI; RUCAM < 1 in all cases); Score 0.5 (probable HILI; RUCAM 3-4 in $\geq$ 1 case; grade 1-2 injury; full recovery); Score 1.0 (definite HILI; RUCAM $\geq$ 5 in $\geq$ 1 case; OR grade 4-5 injury documented; OR liver transplant or death attributed). If RUCAM data not available: use hepatocellular damage pattern (R $\geq$ 5) and temporal relationship (onset 5-90 days; resolution on dechallenge; recurrence on rechallenge) as surrogate criteria.

HTRI Dimension 2 -- Drug Interaction Severity (DIS; weight 0.25): Search PubMed for clinical PK interaction studies (herb + drug; AUC measurement; n $\geq$ 8 subjects; crossover or before-after design). Classify: AUC ratio < 0.50 = major induction (score 1.0). AUC ratio 0.50-0.80 = moderate induction (score 0.7). AUC ratio 1.25-2.0 = moderate inhibition (score 0.6). AUC ratio > 2.0 = major inhibition (score 0.9). Weight the DIS score by the clinical significance of the interacting drug: narrow TI drug (warfarin; ciclosporin; HIV antiretrovirals; cancer chemotherapy; antiepileptics; immunosuppressants; anticoagulants) x 1.5 weight multiplier (cap at 1.0). No clinical interaction data: apply in vitro CYP induction/inhibition data with 50% downward score adjustment (in vitro data overestimates in vivo clinical DDI; BPLA paper 302/309 CPAF principle).

Clinical Herbal Safety Screening Checklist: For any patient presenting with unexplained: ALT elevation (> 3x ULN); INR change (not explained by diet); transplant rejection episode; HIV viral load breakthrough; cancer treatment failure; or unexplained hypotension or priapism: STEP 1 -- Ask specifically about herbal supplement use (open-ended: 'Do you take any herbal products; vitamins; or supplements not prescribed by a doctor?'); follow-up: 'Any teas; juices; or traditional remedies from your country of origin or culture?'. STEP 2 -- For each herb identified: cross-reference against HTRI > 0.70 list (this paper Table 2); check Lexi-Interact; Clinical Pharmacology; or Natural Medicines database for known interactions with current medications. STEP 3 -- If HTRI > 0.70 herb identified: assess causality (MV/RUCAM for HILI; AUC ratio for DDI). Advise discontinuation if HTRI > 0.70 and plausible causal relationship with adverse event. STEP 4 -- Report to national pharmacovigilance system (FDA MedWatch; EMA EudraVigilance national reporting; or WHO-UMC Vigiflow). Herbal ADR reporting is currently < 5% of actual events -- each report contributes to the safety evidence base. STEP 5 -- Document herb use formally in EHR medication list (with start date; dose; product name; manufacturer if known). Instruct patient not to restart without physician review. PA plant identification tip: comfrey (*Symphytum officinale*; broad hairy leaves; purple/white flowers); coltsfoot (*Tussilago farfara*; yellow flower; hoof-shaped leaf); groundsel (*Senecio* spp.; yellow composite flowers). *Aristolochia* identification: birthwort (*Aristolochia clematitis*; tubular yellow flowers; found in Mediterranean gardens); aristolochic acid contamination also occurs in *Akebia*; *Clematis*; and *Stephania* preparations when misidentified in TCM sourcing.