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Hepatotoxicity and Nephrotoxicity of Widely Used Medicinal Herbs: A Critical Appraisal of Safety Evidence against the Assumption that "Natural" Means Safe

Niranjan Giri *and Umesh Maske

Master of Pharmacy (Pharmaceutics), Department of Pharmaceutics, Mangaldeep Institute of Pharmacy, Chhatrapati Sambhajinagar, Maharashtra, India

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***Corresponding Author:** Niranjan Giri

Email: niranjangiri009@gmail.com

ABSTRACT

Herbal medicines are used by a large share of the world's population. Many people believe these medicines are safe because they come from plants.. The published literature has not kept up with this belief. There are studies on the effectiveness of medicinal plants.. Data on safety especially for the liver and kidneys are not easy to find. They are spread out across case reports, pharmacovigilance systems and a few registry studies. These data are rarely gathered in a way.This narrative review looks at the evidence on liver and kidney damage linked to used herbal medicines. It tests the idea that "natural" means safe. The review includes literature from databases. The evidence was graded based on study type, causality assessment and biological plausibility.The review covers the patterns of liver injury caused by herbs. It discusses the ways herbs can harm the liver and kidneys. These include forming chemicals causing oxidative stress, damaging mitochondria, triggering immune reactions harming kidney tubules and damaging DNA. It also identifies herbs that have strong signals for harm. These include Aristolochia species, green tea extract, kava, turmeric, ashwagandha, Tinospora cordifolia, plants containing pyrrolizidine alkaloids and Garcinia cambogia.The review also looks at how problems like contamination, heavy metals and interactions with medicines make it harder to confirm cause and effect. Four key gaps stand out. First harms are often not reported in studies that look at effectiveness. Second many studies do not assess causality well. Third herbal products are not standardized. Fourth there is monitoring of kidney function.The review ends with advice for researchers, doctors and regulators. It stresses the need, for safety data better study methods and stronger oversight. The message is clear: just because something is natural does not mean it is safe.

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1. INTRODUCTION

I think Plants have provided medicines for long as written records exist and in many countries Plants still are the first choice for treatment. The World Health Organization reports that traditional and complementary medicine is practiced in every member state and a large share of people in low- and middle-income regions rely on Plants for their main care (WHO, 2019). In India, Ayurvedic, Siddha and Unani preparations are used with and sometimes instead of, standard treatment. The same pattern appears in Europe and North America where botanical supplements are sold over the counter and are often taken without advice. A belief runs through much of this use: what is natural cannot do harm. The belief is understandable. It is not supported by toxicology. Many of the poisons and drugs that doctors use are made from Plants and Plants create the chemicals that help them defend themselves not to help humans (Ernst, 1998). A herb that works enough to treat disease can also injure body tissue especially if taken in high amounts used for a long time or by someone who is sensitive. The liver and the kidney are the two organs most exposed to this danger. The liver takes in. Changes most plant chemicals that people swallow and while doing this the liver can produce harmful intermediates. The kidney removes these chemicals and their breakdown products and the kidneys tubular cells are exposed to high local amounts (Isnard Bagnis et al., 2004; Luyckx and Naicker, 2008). Both the liver and the kidney often fail without warning until damage is large. The evidence for safety is uneven. Effectiveness is studied in lab tests and small clinical trials. Those trials are often not set up or large enough to find rare side effects. Harms are reported thoroughly than benefits in randomised trials in general (Ioannidis et al., 2004) and herbal trials are no exception. Reviews of side effects of medicines repeatedly point out that most information comes from case reports that vary in quality (Posadzki et al., 2013). As a result doctors and patients often cannot tell a herbal poison from a contaminated or mixed product or from a cause that is not related to plants for liver or kidney injury. Several good reviews already cover liver damage (Stickel and Shouval 2015; Teschke et al. 2013; Philips et al. 2020; Patel-Rodrigues et al. 2024) and kidney damage, from Chinese herbal medicine (Yang et al. 2018). It is less common to find one review that looks at both the liver and the kidney together that rates how strong the evidence is of only listing plants and that asks directly why the safety information is so sparse. That is the purpose of this review.

2. REVIEW METHODOLOGY

This is a review that used a structured search, not a systematic review or a meta-analysis. PubMed, Scopus, Web of Science and Google Scholar were searched for articles published up to 2025 using combinations of the terms: "herb-induced liver injury" "herbal hepatotoxicity" "herbal nephrotoxicity" "aristolochic acid nephropathy" "dietary supplement liver injury" "Ayurvedic hepatotoxicity" "herbal contamination" "herb–drug interaction" and "pharmacovigilance herbal". The reference lists of reviews and clinical guidelines were also checked.Registry studies, consensus guidelines, systematic reviews, case series and mechanistic studies were given priority. Single case reports were used mainly to show a signal or to describe a situation. Articles were not included when the herbal exposure was not clear or when the report did not explain how other causes of injury were ruled out.Because herb-related case reports vary a lot in quality the evidence for each herb was graded by the authors in a way (Table 1). The grading looked at (a) whether causality was checked using a tool, like the Roussel Uclaf Causality Assessment Method (RUCAM) (Danan and Teschke 2016) (b) the number of independent reports and whether registry data are available (c) whether the product was chemically checked and (d) whether there is a biological reason to believe it could cause harm. This grading is a judgment made for this review is not a scale that has been tested.

3. WHY “NATURAL” DOES NOT MEAN “SAFE”

Three distinct ideas are often blurred in public discussion, and separating them clarifies the problem.

Origin is not safety. Arsenic, strychnine, digitalis glycosides and aristolochic acid are all natural. Toxicity depends on structure, dose, exposure duration and host factors, not on whether a compound was extracted from a plant or synthesised.

Long traditional use is not proof of safety. Traditional use shows that a preparation is not acutely and obviously lethal when made the way it was traditionally done. That doesn't mean it's safe from delayed or harm. Also it doesn't say anything about versions. In the past these preparations were often boiled, fermented or mixed with herbs. Each of those steps changes the chemical makeup. Today capsules and extracts focus on one part of the plant at much higher doses than what was used in traditional recipes. The kava story is an example. For generations people in Pacific communities drank liquid made from kava roots. Rarely had liver problems. Later organic-solvent extracts of kava were sold as supplements, in Europe and linked to serious liver issues. This led to rules and restrictions (Teschke et al. 2012).

Absence of reports is not absence of harm. Without systematic surveillance, uncommon harms are invisible. Idiosyncratic liver injury may occur in only a few per 10,000 or 100,000 exposed people, which no herbal efficacy trial is large enough to detect (Andrade et al., 2023).

4. EPIDEMIOLOGY OF HERB-INDUCED LIVER AND KIDNEY INJURY

4.1 Liver

The trustworthy information comes from studies that follow people over time. In the United States Drug-Induced Liver Injury Network (DILIN) dietary supplements made up about 9% of confirmed cases in the early group (Navarro et al., 2014) and the percentage went up from around 7% to 20% between the first and later groups (Navarro et al., 2017). Bodybuilding products and multi-ingredient supplements were a reason for the increase and cases linked to multi-ingredient products were often more serious.In mainland China a big countrywide study found that herbal and dietary supplements caused about a quarter of drug-induced liver injury cases (Shen et al. 2019). In India the data also shows the trend. Single-center studies show that traditional and alternative preparations play a role in drug-induced liver injury, including serious cases with acute-on-chronic liver failure (Devarbhavi et al., 2010; Philips et al. 2018). The Indian situation is tricky because of -herb mixtures with unknown ingredients and people using medicines on their own both of which make it hard to determine what caused the injury.These numbers need to be looked at. The way cases are defined the way products are checked and the way they are used in areas can be different so they can't be compared directly. They do show that liver injury, from herbs is an growing cause of liver disease and not something rare.

4.2 Kidney

I find that renal data are much weaker. There is no registry like DILIN for the kidney. Most of what we know comes from case series, clinic notes and a few population studies. In sub-Saharan Africa and South Asia reviews say that traditional medicines can cause kidney injury, in some hospitals (Luyckx and Naicker 2008; Jha, 2010). Chronic kidney injury is even harder to pin down because kidney disease grows slowly and doctors rarely ask about herb use. The well-known kidney disease caused by herbs is aristolochic acid nephropathy, which only came to light after a group of patients had fast-moving kidney failure in a Belgian slimming clinic in the early 1990s (Vanherweghem et al., 1993).

5. MECHANISMS OF HERBAL HEPATOTOXICITY AND NEPHROTOXICITY

The principal mechanisms are summarised in Figure 1. They are not mutually exclusive, and one herb can act through several.

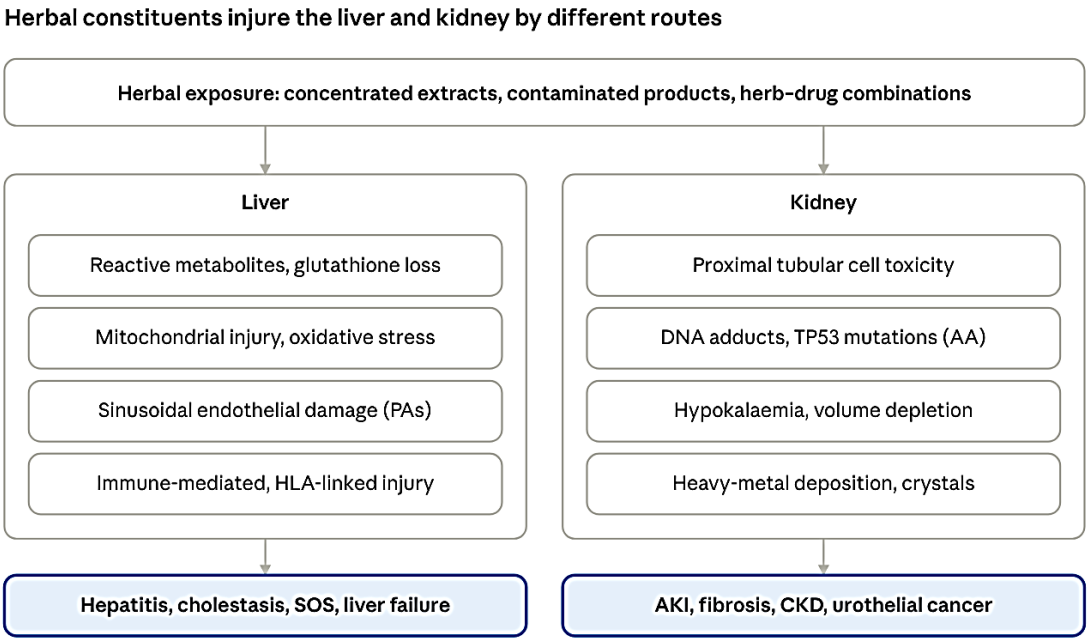


Figure 1. Principal pathways of herb-induced liver and kidney injury. PAs, pyrrolizidine alkaloids; AA, aristolochic acid; SOS, sinusoidal obstruction syndrome; AKI, acute kidney injury; CKD, chronic kidney disease.

5.1 Hepatic mechanisms

Reactive metabolite formation. Cytochrome P450 enzymes convert some phytochemicals into electrophilic metabolites that bind covalently to proteins and deplete glutathione. Pennyroyal oil, which contains pulegone, is a classic example. Its metabolite menthofuran causes centrilobular necrosis, and cases of fatal injury have been reported (Anderson et al., 1996). The furan-containing diterpenoids in germander (*Teucrium chamaedrys*) act in a similar way (Larrey et al., 1992).

Oxidative stress and mitochondrial injury. Drug-induced liver injury commonly involves mitochondrial dysfunction, loss of membrane potential and an increase in reactive oxygen species, leading to hepatocyte death (Jaeschke et al., 2012). Usnic acid, an uncoupler of oxidative phosphorylation found in lichen-based weight-loss products, was linked to acute liver failure (Favreau et al., 2002).

Pyrrolizidine alkaloid toxicity. Plants containing 1,2-unsaturated pyrrolizidine alkaloids, such as *Symphytum*, *Senecio* and *Crotalaria* species, are metabolised to pyrrolic derivatives that damage hepatic sinusoidal endothelial cells, producing sinusoidal obstruction syndrome (hepatic veno-occlusive disease) (Chen and Huo, 2010; Wiedenfeld, 2011).

Immune-mediated and idiosyncratic injury. Many cases of herbal liver injury are unpredictable, with a latency of weeks to months and features suggestive of hypersensitivity or autoimmunity. Genetic susceptibility is increasingly recognised: green tea extract and *Polygonum multiflorum* injury have both been associated with the HLA-B*35:01 allele (Hoofnagle et al., 2021). Autoimmune-like hepatitis has been described after the use of *Tinospora cordifolia* (Nagral et al., 2021).

Cholestatic injury. Some herbal products impair bile acid transport and secretion, giving a prolonged cholestatic picture, as described in several Ayurvedic and weight-loss product reports (Philips et al., 2020).

5.2 Renal mechanisms

Direct tubular toxicity. The proximal tubule is the main site of injury, because it takes up and concentrates xenobiotics. Aristolochic acids are transported into proximal tubular cells, where they cause cell death,

interstitial inflammation and progressive fibrosis (Debelle et al., 2008). Atractyloside, the toxin in *Callilepis laureola* (impila), inhibits the mitochondrial ADP/ATP carrier and produces both renal tubular and hepatic necrosis (Popat et al., 2001).

Genotoxicity and carcinogenicity. Aristolochic acid forms DNA adducts, and the characteristic A:T to T:A transversions in the *TP53* gene link exposure to upper urinary tract urothelial carcinoma (Grollman et al., 2007; Chen et al., 2012). This long-term cancer risk persists after kidney failure is established (Nortier et al., 2000).

Electrolyte and haemodynamic effects. Glycyrrhizin in liquorice inhibits 11β-hydroxysteroid dehydrogenase type 2, producing a syndrome of apparent mineralocorticoid excess with hypokalaemia and hypertension. Prolonged hypokalaemia can itself injure the kidney (Omar et al., 2012).

Crystal deposition, volume depletion and rhabdomyolysis. Some herbs and plant foods contribute to acute kidney injury by oxalate crystal formation, by intravascular volume depletion through purgative effects, or through myoglobin released from muscle injury (Luyckx and Naicker, 2008; Yang et al., 2018).

Heavy-metal nephrotoxicity. Lead, mercury, arsenic and cadmium in contaminated products damage the proximal tubule and the glomerulus (see Section 8) (Ernst, 2002).

6. HEPATOTOXICITY OF INDIVIDUAL HERBS: APPRAISAL OF THE EVIDENCE

Table 1 summarises the herbs with the most substantial published signal for liver injury and gives a qualitative assessment of evidence strength. A few merit further comment.

Green tea extract (*Camellia sinensis*). Brewed green tea has rarely been implicated, but concentrated extracts providing high doses of epigallocatechin gallate (EGCG) have been linked to hepatocellular injury, in some cases severe (Mazzanti et al., 2009). The European Food Safety Authority concluded that EGCG intake of 800 mg per day or more from supplements was associated with increased serum transaminases (EFSA Panel on Food Additives and Flavourings, 2018). The risk appears dose- and formulation-dependent, and is higher when concentrated extracts are taken on an empty stomach (Sarma et al., 2008).

Turmeric and curcumin (*Curcuma longa*). Turmeric has a long culinary history, and curcumin has been studied in many trials without major safety concerns, which is why recent liver injury reports surprised many clinicians. DILIN investigators described cases linked to turmeric supplements, a number of which involved formulations with enhanced bioavailability (for example, with piperine) and several of which carried HLA-B*35:01 (Halegoua-DeMarzio et al., 2023). The lesson is that a safe food spice cannot be assumed to be a safe concentrated supplement.

Ashwagandha (*Withania somnifera*). Ashwagandha is widely promoted as an adaptogen. A case series from Iceland and the DILIN registry documented cholestatic and mixed liver injury with a latency of a few weeks to months, with generally good recovery after withdrawal, although jaundice was prolonged in some patients (Björnsson et al., 2020).

Giloy or guduchi (*Tinospora cordifolia*). Use of this herb as an “immunity booster” increased sharply during the COVID-19 pandemic in India. Clinicians then reported cases of acute hepatitis, often resembling autoimmune hepatitis, some of which progressed to liver failure (Nagral et al., 2021; Philips et al., 2020).

Kava (*Piper methysticum*). Reports of severe liver injury, including transplantation, led several European countries to restrict kava products in the early 2000s. Whether the risk lies in the plant, in the extraction solvent, in poor-quality plant parts, or in drug interactions is still debated (Teschke et al., 2012).

Garcinia cambogia. Weight-loss products containing hydroxycitric acid have been linked to acute hepatitis and liver failure, although most products also contain other ingredients, which complicates attribution (Crescioli et al., 2018).

Black cohosh (*Actaea racemosa*). A causal link to liver injury remains controversial. When initially suspected cases were reassessed with structured causality criteria and product analysis, the evidence for causality was judged weak or doubtful in many of them (Teschke et al., 2011). This is a good example of why rigorous causality assessment matters in both directions: it prevents both false alarms and false reassurance.

Other herbs. Chaparral (*Larrea tridentata*) (Sheikh et al., 1997), germander (Larrey et al., 1992), noni juice (*Morinda citrifolia*) (Yüce et al., 2006) and pyrrolizidine-containing preparations (Chen and Huo, 2010) all have documented cases. Large compilations of case reports list many additional plants, although the quality of the reports varies widely (Teschke et al., 2012; Brown, 2017).

Table 1. Selected medicinal herbs associated with hepatotoxicity, with qualitative evidence grading

Herb (botanical name)	Suspected constituent	Pattern / mechanism	Evidence strength*	Key references
Green tea extract (*Camellia sinensis*)	EGCG and catechins	Hepatocellular; dose-dependent; HLA-B*35:01 association	Strong (registry, regulatory assessment)	Mazzanti et al., 2009; EFSA Panel, 2018; Hoofnagle et al., 2021
Turmeric / curcumin (*Curcuma longa*)	Curcuminoids (enhanced-absorption products)	Hepatocellular; immune-mediated	Moderate (case series, registry)	Halegoua-DeMarzio et al., 2023
Ashwagandha (*Withania somnifera*)	Withanolides (not confirmed)	Cholestatic or mixed; idiosyncratic	Moderate (case series)	Björnsson et al., 2020
Giloy (*Tinospora cordifolia*)	Not established	Hepatocellular; autoimmune-like	Moderate (case series)	Nagral et al., 2021
Kava (*Piper methysticum*)	Kavalactones	Hepatocellular; possible solvent or quality effect	Moderate to strong (regulatory action)	Teschke et al., 2012
Pyrrolizidine plants (*Symphytum*, *Senecio*)	1,2-unsaturated pyrrolizidine alkaloids	Sinusoidal obstruction syndrome	Strong (mechanistic and clinical)	Chen and Huo, 2010; Wiedenfeld, 2011
Germander (*Teucrium chamaedrys*)	Furano-diterpenoids	Hepatocellular; reactive metabolites	Moderate (case series)	Larrey et al., 1992
Pennyroyal oil (*Mentha pulegium*)	Pulegone / menthofuran	Centrilobular necrosis	Moderate (case reports, mechanism)	Anderson et al., 1996
Garcinia cambogia	Hydroxycitric acid (confounded)	Hepatocellular; acute liver failure	Limited to moderate (multi-ingredient	Crescioli et al., 2018

Herb (botanical name)	Suspected constituent	Pattern / mechanism	Evidence strength*	Key references
			products)	
Chaparral (*Larrea tridentata*)	Nordihydroguaiaretic acid	Hepatocellular and cholestatic	Moderate (case series)	Sheikh et al., 1997
Black cohosh (*Actaea racemosa*)	Unclear	Hepatocellular; causality disputed	Weak to doubtful after reassessment	Teschke et al., 2011

*Qualitative grading by the authors based on study design, structured causality assessment, number of independent reports and biological plausibility. It is not a validated scale.

7. NEPHROTOXICITY OF INDIVIDUAL HERBS: APPRAISAL OF THE EVIDENCE

Aristolochia species and aristolochic acid. This is the characterised herbal kidney toxin. Young women who visited a clinic got fast worsening kidney scarring after taking a weight-loss plan that mistakenly used Aristolochia fangchi instead of a Chinese herb because the names sounded alike (Vanherweghem et al., 1993). Some of those women later developed bladder cancer (Nortier et al., 2000). Aristolochic acid has also been linked to endemic kidney disease when wheat was contaminated with Aristolochia clematitis seeds (Grollman et al., 2007) and to the high rate of upper urinary tract cancer, in Taiwan (Chen et al., 2012). Even though the danger of acid has been known for thirty years products that contain aristolochic acid are still sold in some places and the problem is now seen as global (Debelle et al., 2008).

Callilepis laureola (impila). This southern African herb contains atractyloside. Poisoning produces hepatic and renal tubular necrosis, with high mortality, and it is a reminder that a single plant can injure both organs at once (Popat et al., 2001).

Liquorice (*Glycyrrhiza glabra*). Chronic high intake of glycyrrhizin-containing products leads to hypokalaemia, hypertension and, in severe cases, rhabdomyolysis and renal impairment (Omar et al., 2012). The risk is mainly with excess consumption of confectionery, tonics and supplements, and not with occasional use.

Other plants and preparations. Reviews of Chinese herbal medicine identify several additional agents linked to acute kidney injury or interstitial nephritis, as well as contamination with heavy metals and undeclared pharmaceuticals (Shaw, 2010; Yang et al., 2018). Ayurvedic *rasa shastra* preparations, which deliberately incorporate processed metals, are a particular concern for both renal and hepatic safety (Saper et al., 2008). Evidence for many suspected nephrotoxic herbs, however, rests on isolated reports, and renal biopsy data are often missing.

Table 2. Selected herbs and herbal products associated with nephrotoxicity

Herb / product	Toxic agent	Renal lesion / mechanism	Evidence strength*	Key references
Aristolochia species	Aristolochic acids I and II	Proximal tubular injury, interstitial fibrosis, DNA adducts, urothelial carcinoma	Strong (clinical, epidemiological, mechanistic)	Vanherweghem et al., 1993; Nortier et al., 2000; Debelle et al., 2008
Callilepis laureola	Atractyloside	Tubular necrosis; mitochondrial ADP/ATP carrier inhibition	Moderate (case series)	Popat et al., 2001
Liquorice	Glycyrrhizin	Hypokalaemia,	Moderate to strong	Omar et al., 2012

Herb / product	Toxic agent	Renal lesion / mechanism	Evidence strength*	Key references
(*Glycyrrhiza glabra*)		hypertension, secondary renal injury	(clinical, mechanistic)	
Metal-containing Ayurvedic preparations	Lead, mercury, arsenic	Tubular and glomerular toxicity	Moderate (product analysis; limited clinical linkage)	Saper et al., 2008; Ernst, 2002
Various Chinese herbal products	Variable, including adulterants	Acute kidney injury, interstitial nephritis	Variable; often weak	Shaw, 2010; Yang et al., 2018

*Qualitative grading by the authors; not a validated scale.

8. CONTAMINATION, ADULTERATION AND PRODUCT QUALITY

In cases the problem is not the herb that the label claims but what else the herb product contains. I have read a study of medicines sold online that found about one in five products contained detectable lead, mercury or arsenic and some exceeded daily intake limits (Saper et al., 2008). Heavy metals themselves are known to be toxins for the liver and kidneys (Ernst, 2002).Adding to this risk are adulteration, with drugs, microbial contamination, mycotoxins and pesticide residues (Posadzki et al., 2013; WHO, 2007). Species substitution is another problem. DNA barcoding of supplements sold in North America showed that most contained plant material not declared on the label and that fillers and substitutes were common (Newmaster et al., 2013). When a product is mislabelled, any case report that follows is attributed to the plant, which corrupts the whole safety literature.The practical consequence is that a published case of "herb X hepatotoxicity" cannot be trusted unless the herb product was chemically authenticated and tested for contaminants. Few reports meet this standard.

Table 3. Quality problems that confound herbal safety evidence

Problem	Example	Consequence for safety assessment	Key references
Heavy-metal contamination	Lead, mercury, arsenic in Ayurvedic products	Hepatic and renal injury attributed to the herb rather than the metal	Saper et al., 2008; Ernst, 2002
Species substitution and mislabelling	Undeclared plants and fillers in supplements	Wrong plant implicated in case reports	Newmaster et al., 2013
Adulteration with pharmaceuticals	Undeclared synthetic drugs	Drug toxicity misattributed to the herb	Posadzki et al., 2013
Microbial and chemical contaminants	Mycotoxins, pesticides	Additional hepatotoxic exposure	WHO, 2007
Non-standardised extracts	Variable marker content between batches	Dose cannot be reconstructed or compared	Ekor, 2014

9. HERB–DRUG INTERACTIONS

Patients rarely take herbs by themselves. Many people use them with prescription medicines and some herbs can either increase or decrease the activity of cytochrome P450 enzymes and transporters which changes how much of a drug is in the body (Izzo and Ernst, 2009). This situation has two effects. First a herb can make the liver or kidney damage caused by a regular medicine worse for example by increasing the amount of a drug that has a range between a helpful dose and a harmful dose. Second when someone is taking medicines at the same time it is hard to tell which one caused any harm. A case where ashwagandha was linked to harm in a person also taking propranolol and alprazolam shows this problem clearly (Philips et al. 2020). Collecting information, about all the medicines being taken along with herbs is very important. This is rarely done properly.

10. DIAGNOSTIC AND CAUSALITY CHALLENGES

Diagnosing herbal liver injury is a diagnosis of exclusion. Viral hepatitis, alcohol, autoimmune and metabolic liver disease, biliary obstruction and other drugs must be excluded. International guidelines recommend a structured approach and the use of causality tools such as RUCAM (Danan and Teschke, 2016; EASL, 2019; Chalasani et al., 2021). Even so, applying RUCAM to herbal products is difficult, because the exposure is often poorly documented and the product cannot be re-tested. Teschke and Eickhoff (2015) argue that many published cases fail minimum quality criteria, including adequate exclusion of alternative causes and product analysis.

For the kidney, no equivalent, widely accepted causality instrument exists, and renal biopsy is not routinely performed. Early renal injury is often missed because serum creatinine rises late, and herbal exposure is not a routine question in a nephrology history. A suggested approach to evaluating suspected herbal injury is shown in Figure 2.

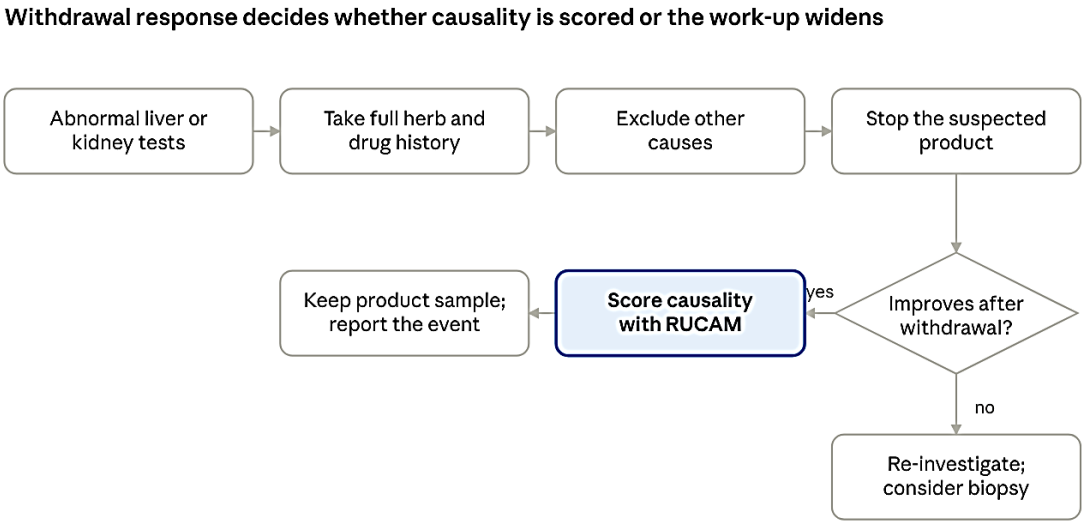


Figure 2. Suggested approach to evaluating suspected herb-induced liver or kidney injury. RUCAM, Roussel Uclaf Causality Assessment Method. Evaluation of suspected herbal injury · 6 steps, 1 decision

11. REPORTING GAPS, PHARMACOVIGILANCE AND REGULATION

The central point of this review is that herbal safety evidence is incomplete in a structural way. Four gaps stand out.

1. **Harms are under-reported in efficacy studies.** Trials of herbal products are usually designed around efficacy outcomes, with small samples and short follow-up. Reporting of harms in trials is generally weaker than reporting of benefits (Ioannidis et al., 2004), and liver and kidney function are not always monitored.

2. **Spontaneous reporting is weak.** Patients rarely tell clinicians about herbal use, and clinicians rarely report suspected herbal reactions. Many countries lack pharmacovigilance systems that can capture herbal adverse events (Ekor, 2014). The WHO has issued guidance on integrating herbal safety monitoring into national systems (WHO, 2004), but implementation is uneven.
3. **Case reports are heterogeneous.** Many do not identify the plant by botanical name, verify the product, record the dose and duration, or exclude other causes (Teschke and Eickhoff, 2015).
4. **Renal surveillance is almost absent.** Hepatic registries exist for drug-induced liver injury, but there is nothing comparable for herb-induced kidney injury.

Regulation differs widely between countries. In some jurisdictions herbal products are classified as food supplements, with lighter requirements for safety evidence than for medicines, and in others they are regulated as traditional medicines. This inconsistency allows products with a documented signal to remain on the market in one country while restricted in another, as happened with kava (Teschke et al., 2012).

12. RESEARCH GAPS AND FUTURE DIRECTIONS

Based on the evidence reviewed, the following gaps deserve priority:

1. Prospective, multi-centre registries of herb-induced liver and kidney injury that require chemical verification of the implicated product.
2. Standardised case-report templates that capture botanical identity, extract type, dose, duration, concomitant drugs and exclusion of alternative causes.
3. Inclusion of liver and kidney biomarkers, and pre-specified harm reporting, in clinical trials of herbal products.
4. Pharmacogenetic work, building on the HLA-B*35:01 finding, to identify susceptible individuals (Hoofnagle et al., 2021).
5. Dose–response and formulation studies for concentrated extracts, comparing them with traditional preparations.
6. Better methods for the early detection of herbal nephrotoxicity, including tubular injury biomarkers.
7. Analytical authentication, using chemical fingerprinting and DNA barcoding, as a routine requirement for products used in safety studies (Newmaster et al., 2013).

Table 4. Summary of evidence gaps and proposed responses

Gap	Why it matters	Proposed response
Harms under-reported in trials	Rare events are never detected	Pre-specified safety outcomes; liver and kidney monitoring
Weak spontaneous reporting	Signals are noticed late	Herbal modules in national pharmacovigilance systems
Unverified products in case reports	Wrong plant may be blamed	Mandatory chemical and DNA authentication
Weak causality assessment	False alarms and false reassurance	Routine use of RUCAM-type tools; standardised templates
No renal registry	Kidney harm remains invisible	Establish herbal nephrotoxicity registries; add herb history to renal work-up

Gap	Why it matters	Proposed response
Inconsistent regulation	Same product treated differently across borders	Harmonised minimum safety and quality requirements

14. LIMITATIONS OF THIS REVIEW

This is a narrative review, and although the search was structured, it was not exhaustive, and some relevant reports may have been missed. The evidence grading is qualitative and reflects the authors' judgment. Most evidence comes from case reports and series, which cannot establish incidence or confirm causation. Publication bias may also over-represent striking cases. For all these reasons the summary of evidence should be read as a guide to the strength of signals, not as a measure of risk.

15. CONCLUSION

I feel the evidence reviewed here does not support the idea that natural productsre safe. Several used herbs, such as green tea extract, turmeric supplements, ashwagandha, Tinospora cordifolia, kava for the liver and Aristolochia species for the kidney have credible and sometimes well-documented risks. Equally some suspected connections, such as that with cohosh are weaker than first thought and careful assessment of cause and effect is required in both directions. The deeper problem lies in the safety evidence itself: harms are under-reported products are unverified, cause and effect is assessed and kidney injury is barely monitored. Closing these gaps will require registries, standardised reporting, product authentication and stronger monitoring of drug safety. Until then patients and clinicians should treat products with the same caution, as any other pharmacologically active substance.

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