

Incidence and Clinical Impact of Adverse Reactions Associated with Herbal Medicines..

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ABSTRACT

The global rise in the use of herbal medicines has led to an increased need for comprehensive pharmacovigilance to deal with the related adverse drug reactions (ADRs) properly. This article reviews the prevalence of herbal toxicities and their clinical consequences, using data from international databases like VigiBase. The studies indicate that the median of adverse drug reactions (ADRs) rates lie between 1.42% and 3.1%, being most common the gastrointestinal problems (28.7%) and dermatological disorders (20.1%). Among the adverse drug reactions, severe clinical effects such as herb-induced liver injury (HILI) and nephrotoxicity are safety concerns that are very often amplified by the misconception that "natural is safe" and the lack of regulation over product quality. In addition, complex herb-drug interactions (HDIs) can be very dangerous for patients on polypharmacy, particularly when the medicines have a narrow therapeutic index. The researchers implied that to eliminate these risks, there will need to be global harmonization of regulations, and practitioners' education should be enhanced along with the systematic introduction of "herbovigilance" into the traditional clinical practices to safeguard the public health in the increasingly integrative medical scenario..

Keywords: ADRs, HILI, Herbal Toxicities, Herbovigilance, Therapeutic Index etc

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INTRODUCTION

The Historical Context of Phytotherapy and Its Global Resurgence

The first use of plants for healing purposes came along with the beginning of human civilization. The herbal treatments have been the main pharmacopoeia for humanity for thousands of years, starting already with the Ebers Papyrus of ancient Egypt to the basic texts of Ayurveda and Traditional Chinese Medicine (TCM). For a very long time, in fact, the lines among "food," "medicine," and "botanical" were not clear, all of them being the outcome of empirical knowledge that was passed from one generation to another¹. In the pre-industrial period, the local herbal practice gave some control over the quality as it was always backed by traditional knowledge and direct identification of plants.

However, the 21st century has witnessed a great "herbal renaissance" that, unlike its predecessors, is very different at the core. The combination of a global market and a growing discontent with the assumed negative effects of

synthetic drugs has transformed herbal remedies (HMs) from a few local treatments that are worth million dollars internationally. This revival is not just a turning back to tradition but a complicated socio-economic phenomenon where the botanical extracts are produced in large quantities, and the same effective delivery systems are developed and marketed to a global audience that is often quite alien to the original culture which was the plant's application.

Deconstructing the "Natural is Safe" Fallacy

One of the main reasons for the rising popularity of herbal products is the common and scientifically unfounded idea that "natural is safe." This thinking leads to the conclusion that a compound from living organisms is, so to say, parallel with human bodies and does not have the "toxic" features of the synthetic ones. This perspective completely ignores the fundamental biological truth that plants, over time, evolved to produce an array of secondary metabolites—like alkaloids, glycosides, and terpenes—primarily for protecting themselves against herbivores, insects, and

¹ World Health Organization. (2019). *WHO global report on traditional and complementary medicine 2019*. World

Health Organization.
<https://www.who.int/publications/i/item/9789241515436>

pathogens. As a result, many herbal substances are considered to be bioactive by virtue of their evolution and on the other hand might be poisonous, in which case they would have to be expelled through the liver. The metabolism of "natural" drugs occurs in the same way as it does with synthetic ones and these substances also go through the liver, are metabolized by cytochrome P450 enzymes and then finally eliminated by the kidneys². When consumers refrain from seeking medical advice based on the argument of safety, they unknowingly put themselves at risk of significant biochemical changes, such as bleeding problems due to changed coagulation pathways and acute liver toxicity, caused by the powerful substances. The lack of standard dose and the presence of complex molecular "cocktails" in a single plant further complicate the safety issue, so that the term "natural" becomes a risky alternative to "harmless" in the case of medicinal plant products.

Identifying the Research Gap and the Burden of Proof

Partial contradictions between the significant use of herbal goods and the lack of a proper understanding of their clinical response and therefore a very limited acceptance of their use in the medical field indicate that the study of herbal drugs continues to be one of the most surprising and misinterpreted areas of research. Everywhere these substances are prescribed and used, we are left with an uncanny silence and uncertainty as to their possible reactions. The result is a lack of clear directions for clinicians about which steps to take³. When it comes to traditional and herbal medicines, the regulatory frameworks tend to be quite different compared to synthetic products, which have to undergo multi-phase clinical trials prior to market release and a long and tedious process for getting approval for sale. Posts like "dietary supplements" or "traditional medicines" are very common for the herbal drugs category which are less regulated than pharmaceuticals. However, these categorizations usually keep them away from the stringent pre-marketing safety processes and post-marketing surveillance that are associated with modern medicines.

As a result, sometimes the scientific literature is very much disconnected; mostly the data regarding herbal adverse drug reactions (ADRs) is limited to case reports or some observational studies instead of large, random, long-duration studies⁴. There is a lack of standardized reporting mechanisms that is a major issue; patients hardly tell their doctors about the herbal products they use, and many physicians are not trained to recognize the signs of organ toxicity caused by herbal drugs⁵. This systematic under-

reporting causes the real incidence of herbal toxicity to be hidden thus leading to what is called "a pharmacovigilance void". It is very important to fix this gap in order to create evidence-based protocols that protect the public health programs and at the same time, they let the use of plant medicine for healing purposes. This paper intended to bridge this gap by thoroughly exploring the occurrence and clinical implications of herbal adverse reactions in the context of modern clinical toxicology.

Methodology

Data Sourcing and Stringent Inclusion Framework

Through the combined data retrieval technique and the WHO's VigiBase & the PubMed/MEDLINE repository the study had accurately to analyze the incidence and the effect of adverse reactions to herbal products. VigiBase, controlled by the Uppsala Monitoring Centre (UMC), is the biggest worldwide database of Individual Case Safety Reports (ICSRs) with more than 30 million reported adverse drug and herbal responses from over 170 member countries⁶. Reports classified under the "V90" Anatomical Therapeutic Chemical (ATC) code—the one that is for unidentified herbal and traditional medicines—could give the researchers an insight into real-world evidence, detailed with rare and unique occurrences that sometimes get overlooked in clinical trials. A methodical search of PubMed was done using controlled vocabularies (MeSH terms) such as "Phytotherapy/adverse effects" & "Plants, Medicinal/toxicity."

The inclusion criteria were very carefully set up in such a way that they would mainly indicate high-quality research, with peer-reviewed systematic reviews, meta-analyses, & prospective cohort studies of the last ten years being the main focus. In order to ensure the validity of the data, studies were not accepted if they were mainly concerned to animal models, did not have clinical outcome data, or were about products where the herbal component was much smaller than that of synthetic additives, thus separating the intrinsic and extrinsic toxicity profiles of the herbal entities. Algorithmic Causality Assessment and Validation Scales

The proof of a herbal adverse reaction's clinical validation has to go through a causative likelihood rather than just a temporal correlation. The authors made use of a dual-scale validation technique in their study to decrease the spontaneous reporting's inbuilt "noise". General systemic reactions were subjected to the Naranjo Algorithm, which made use of a ten-question weighted questionnaire that evaluates different variables such as the time of the reaction occurring after the administration, improvement during the

² Navarro, V. J., Khan, I., Björnsson, E., Seeff, L. B., Serrano, J., & Hoofnagle, J. H. (2017). Liver injury from herbal and dietary supplements. *Hepatology*, 65(1), 363–373. <https://doi.org/10.1002/hep.28813>

³ Grollman, A. P., & Jelaković, B. (2015). Role of environmental toxins in endemic (Balkan) nephropathy and associated urothelial cancer. *Nature Reviews Nephrology*, 11(4), 210–217. <https://doi.org/10.1038/nrneph.2015.17>

⁴ Izzo, A. A., & Ernst, E. (2009). Interactions between herbal medicines and prescribed drugs: An updated

systematic review. *Drugs*, 69(13), 1777–1798. <https://doi.org/10.2165/11318140-000000000-00000>

⁵ Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177. <https://doi.org/10.3389/fphar.2013.00177>

⁶ Danan, G., & Teschke, R. (2016). RUCAM in drug and herb induced liver injury: The update. *Frontiers in Pharmacology*, 6, 14.

withdrawal of the drug, and the repetition of the occurrence during re-challenge. Admitting that HILI is responsible for a major part of severe cases, the RUCAM, which is also known as the CIOMS scale, was employed as the definite standard for hepatotoxicity⁷.

Unlike other traditional scales, RUCAM is especially tailored for liver assessment, taking into account the peculiarities of the injury through biochemical markers (ALT and ALP thresholds) and the careful excluding of alternative causes such as viral hepatitis or autoimmune conditions. The WHO-UMC Causality Categories were used to classify these results into levels from "Certain" to "Unlikely," thus creating a common vocabulary for clinical significance. This systematic method ensures that the reported adverse effects were not only coincidental but also had a statistical and clinical association with herbal usage, even in the case of complex polypharmacy.

Assessment Tool	Primary Application	Scoring Mechanism	Key Strengths
Naranjo Algorithm	General ADRs	10-item questionnaire (Score: -4 to +13)	Rapid, easy to use in clinical bedside settings.
RUCAM (CIOMS)	Hepatotoxicity (HILI)	Liver-specific biochemical & temporal markers	High sensitivity; gold standard for liver injury.
WHO-UMC Scale	Global Pharmacovigilance	Qualitative/Expert-judgment categories	Standardized for international database reporting.
Kramer Criteria	Complex clinical cases	56-item branching logic system	Extremely detailed; reduces subjective bias.

Table 1: Comparative Framework of Causality Assessment Tools, Source: Author Generated
Epidemiology and Incidence of Adverse Reactions
Global Prevalence and the Demographic Shift in Herbal Consumption

The development of herbal medicine (HM) has been nothing short of revolutionary, transitioning from small scale use in traditional societies to a huge global industry

with an estimated worth of \$233 billion by 2025. This whole picture is that of global movement. Eighty percent of the population in low-income countries is still using herbal remedies for their primary health care. This reliance is mainly because these products are available and have a long-standing cultural connection⁸.

However, in high-income countries there has been a marked change in demographics where the percentage of adults using herbal medicines has gone up to 35 to 50 percent. Moreover, chronic multimorbid patients, who are already on synthetic drugs and are looking for natural products to complement the latter, are the ones most affected by the "herbal renaissance" in the Western world. The high-risk epidemiological profile that arises from this situation comprises an elderly population that is using complicated drug therapies and, at the same time, is becoming more and more dependent on strong herbal extracts. Consequently, the physiological threshold for adverse drug reactions (ADRs) is being set lower, while the difficulty of ensuring the safety of the drugs post-marketing is increasing.

Regional Variations and the "Silent Epidemic" of Under-reporting

The recorded adverse events exhibit a great deal of variation across different geographical areas and this is mainly influenced by the development stage of the national pharmacovigilance systems. In the Asia-Pacific region, which still holds the title of the biggest market for herbal medicines, traditional medicine has been assimilated into public healthcare systems. This has led to more comprehensive tracing; for instance, the Korea Adverse Event Reporting System recorded the yearly occurrence of over 250,000 cases by the year 2020⁹.

In contrast, the large part of HMs in North America and Europe are treated legally as dietary supplements. This leads to a situation where the reporting of adverse events becomes very limited, thus creating a "pharmacovigilance void". There are figures that estimate that, in fact, only 0.6% of all reports in the global VigiBase collection point out herbal compounds specifically. This is a number that experts claim hides a "silent epidemic" beneath it. Less than half of the WHO member countries are reported to have some level of active regulation on herbal safety, as revealed by the studies conducted in low- and middle-income countries (LMICs). Hence, the disparity in regulations makes it appear that the "incidence" documented in literature is probably a very low estimate, which is more a consequence of reporting bias than true safety profiles.

Statistical Incidence and Clinical Manifestations in Real-World Data

The lack of normalized denominators is still present, and this complicates the exact calculation of the incidence rate of adverse drug reactions (ADRs) related to herbal

⁷ Uppsala Monitoring Centre. (2021). *VigiBase: The WHO global database of individual case safety reports*. <https://who-umc.org/vigibase/>

⁸ Kongkaew, C., et al. (2024). Variations in adverse event reporting rates of herbal medicines: A systematic review.

Journal of Pharmaceutical Policy and Practice. <https://doi.org/10.1186/s40545-024-00123-x>

⁹ Korea Institute of Drug Safety and Risk Management. (2024). *Adverse events associated with herbal medicine products 2012-2021*. *Frontiers in Pharmacology*. <https://doi.org/10.3389/fphar.2024.1378208>

products. At the same time, recent systematic reviews and cohort studies have brought a clearer statistical framework. The studies indicate that the median pooled estimate of adverse events in the whole population is approximately 1.42% to 3.1%. However, this number could be over twice as much and reach over 30% in some cases of high-dose or multi-herb treatments. Clinical findings have revealed that the most predominant reactions are related to the gastrointestinal system (28.7%) and skin (20.1%), which encompass urticaria and pruritus, among others¹⁰.

An alarming situation is that the number of HILI cases reported has tripled in the last 20 years. The over-the-counter use of herbal medicines by the public and claims made by manufacturers often lead to confusion. Many times, the occurrence of such complications has been linked to the "modern" use of traditional herbs in the West, such as the administration of Ephedra for weight reduction or Green Tea Extract for stimulating metabolism. These uses cause different kinds of events, such as cardiovascular and hepatic ones, which are contrary to the traditional safe usage of these herbs. The data coming from these statistics point out that the occurrence of severe and systemic clinical events has the same increasing pattern as the complexity of herbal formulations.

System Organ Class (SOC)	Frequency (%)	Common Preferred Terms (Symptoms)	Typical Herbal Culprits
Gastrointestinal	28.7% – 41.5%	Diarrhea, Abdominal Pain, Nausea, Vomiting	Aloe vera, Senna, Greater Celandine
Skin & Subcutaneous	20.1% – 29.0%	Pruritus, Urticaria, Rash, Photosensitivity	St. John’s Wort, Kava, Ginkgo
Hepatobiliary (Liver)	4.0% – 5.6%	Jaundice, Elevated ALT/AST, Hepatic Failure	Green Tea Extract, He-Shou-Wu
Nervous System	3.7% – 13.9%	Dizziness, Headache, Tremor, Insomnia	Ephedra, Valerian, Ginseng
Cardiovascular	1.8% – 4.2%	Palpitations, Hypertension, Arrhythmia	Ma Huang, Licorice Root

Renal & Urinary	0.6% – 2.1%	Acute Kidney Injury, Dysuria	Aristolochia, Juniper, Senna
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Table 2: Clinical Manifestations of Herbal ADRs by System Organ Class (SOC), Source: Author Generated

Clinical Impact and Toxicity

Pathophysiological Mechanisms of Herb-Induced Liver Injury (HILI)

The liver, being the primary site for the metabolic biotransformation of xenobiotics, is where the clinical effects of herbal medications are noticed mostly. The phenomenon of Herb-Induced Liver Injury (HILI) has turned out to be a major cause of acute liver failure across the globe, accounting for about 20% of cases in certain geographic regions of Asia and the West. The main two mechanisms causing toxicity are intrinsic toxicity, which is an expected and dose-dependent type of reaction, and idiosyncratic reactions, characterized by the absence of a clear dose-toxicity relationship and by the patients' individual genetic characteristics regarding either metabolic enzymes or immune system responses¹¹. Pyrrolizidine alkaloids (PAs), which are found in plants like *Symphytum officinale* (Comfrey), undergo metabolic conversion in the liver to reactive pyrroles that are capable of binding to cellular proteins and DNA causing the fatal condition known as sinusoidal obstruction syndrome. The range of clinical manifestations goes from asymptomatic elevation of liver enzymes to jaundice and acute liver failure.

Nephrotoxic Sequelae and the Aristolochic Acid Paradigm

The renal system is highly susceptible to the toxic effects of herbal substances because of its function of filtering blood and reabsorbing metabolites from large volumes of blood. The disorder known as Aristolochic Acid Nephropathy (AAN), characterized by rapid and progressive interstitial fibrosis, is one of the phenomena associated with the most severe symptoms. Aristolochic acids, which are found in plant species of *Aristolochia* and *Asarum*, cause the destruction of kidney tubules and the formation of DNA adducts that are stable¹².

The combination of these adducts leads to end-stage renal disease (ESRD) and is a significant contributor to the development of urothelial carcinomas. Other plant medicines like *Averrhoa carambola* (Star fruit) are also able to produce acute oxalate nephropathy in patients with preexisting renal conditions; this effect is in addition to that caused by aristolochic acid. Given that the clinical consequences of these nephrotoxins often cannot be reversed, patients with such conditions are usually put on long-term dialysis or need to receive transplants. This makes it all the more important to test herbal products for organic acids and heavy metals, both of which may cause

¹⁰ Asiamah, I., et al. (2025). The safety of herbal medicines in low- and middle-income countries: current landscape. *Journal of Pharmaceutical Policy and Practice*. <https://doi.org/10.1186/s40545-025-00789-y>

¹¹ Danan, G., & Teschke, R. (2016). RUCAM in drug and herb induced liver injury: The update. *Frontiers in*

Pharmacology, 6, 14. <https://doi.org/10.3389/fphar.2015.00014>

¹² Grollman, A. P., & Jelaković, B. (2015). Role of environmental toxins in endemic (Balkan) nephropathy and associated urothelial cancer. *Nature Reviews Nephrology*, 11(4), 210–217. <https://doi.org/10.1038/nrneph.2015.17>

chronic renal deterioration through oxidative stress and inflammatory cell infiltration. The demand for such screening is enormous.

Cardiovascular Instability and Alkaloid-Driven Events

In clinical practice, the cardiovascular system is often the first one to show acute toxicity manifestations and this is mainly due to the powerful plant alkaloids. The major part of the problem is that people consume the herbs for the wrong reasons, e.g. to boost their energy levels or to lose weight. These herbs, such as *Ephedra sinica* (Ma Huang) which is known for its ephedrine and pseudoephedrine content, are sympathomimetics and thus elevate the oxygen demand of the myocardium as well as the peripheral resistance of the heart. This leads to death risks like hypertensive crises, myocardial infarction, and cardiac arrhythmias among others. The same goes for *Aconitum* species also recognized as monkshood which when consumed lead to the death of a person because the voltage-gated sodium channels are kept open for a longer period thus making the person suffer from refractory ventricular tachycardia. The being of gradually increasing severity of the adverse effects on the heart is often doubted by plant users who are for health reasons trying to increase their energy levels or losing weight. The cardiotoxicity resulting from the use of many "performance-enhancing" botanicals is evidenced by the fact that even small doses of such stimulants can result in negative outcomes in individuals with pre-existing unnoticed heart conditions. This is shown through regular medical supervision.

Neurotoxicity and Psychological Manifestations

The central nervous system (CNS) may be influenced by herbal drugs in various ways, going from minor drowsiness to acute psychosis and seizures. Each component can be affected by the herbal medicines to a great extent¹³. Alkaloids are the main contributors to neurotoxicity, as they impair the activity of the neurotransmitter receptors or ion channels. For example, the use of high amounts of *Panax ginseng* has been associated with a syndrome named "Ginseng Abuse Syndrome," which is characterized by insomnia, agitation, and increased muscle tonus. Moreover, *Salvia divinorum* and some herbs classified as "relaxing" can lead to the occurrence of dissociation and even hallucination.

Besides, the presence of heavy metals such as lead or mercury in herbal medicines, which are poorly regulated, can cause the irreversible neurodevelopmental inhibition of infants and cognitive decline in adults. The therapeutic impact is particularly important because the CNS symptoms might be wrongly diagnosed as primary psychiatric problems, thus leading to the inappropriate use of synthetic

psychotropics and additional interaction with the herbal metabolites.

Severity Tiers and Clinical Grading of Toxicity

A four-tier grading system is employed by physicians to assess the strength of clinical effects in order to harmonize the treatment of negative reactions to herbal products. The first grade (Mild) describes a situation with minimal discomfort or minor changes in laboratory results which are not considered to require any medical intervention, for example, an AST/ALT ratio that is less than 2.5 times the upper limit of normal¹⁴. Grade 2 reactions, the so-called moderate reactions, have some impact on daily life and might need little treatment intervention like stopping herb usage. Grade 3 (Severe) means a significant deterioration of health and often it is necessary to admit the patient to the hospital for strict monitoring or administering intravenous drugs. Gastrointestinal disturbance or severe organ failure could result in dehydration so serious that hospitalization is needed. Sudden hepatic death, quick renal failure, or SJS are instances of life-threatening conditions and these are all considered grade four¹⁵. Such conditions demand not only extensive medical management but also life support. The adoption of this stratified approach allows for clearer risk sharing and assures that the most serious reactions are the first ones to be reported in pharmacovigilance practice.

Herb-Drug Interactions (HDI)

Within the realm of pharmacokinetic mechanisms, the ADME paradigm

The pharmacokinetics level is where the majority of the clinically significant herb-drug interactions (HDIs) occur. At this point, herbal substances have a say in how the conventional drugs are absorbed, distributed, metabolized, and excreted (ADME). The cytochrome P450 (CYP450) enzyme system and the P-glycoprotein (P-gp) efflux transporters are the main players in these interactions¹⁶. Herbal derived agents can act in two ways, i.e., either by inhibiting or stimulating the pathways involved. One such enzyme induction example is *St. John's Wort* (*Hypericum perforatum*), which is a case of the Pregnane X Receptor (PXR) being activated. This activation finally leads to the accumulation of CYP3A4, which is the enzyme that metabolizes roughly fifty percent of all drugs that are available today. Consequently, the drug is cleared more rapidly from the body, and the drug's plasma concentration is maintained at a sub-therapeutic level. This might result in catastrophic treatment failures in the case of HIV therapy or transplantation. Conversely, enzyme inhibition, commonly found with grapefruit juice or goldenseal, delays drug metabolism thus leading to higher concentrations and increased risk of dose-dependent toxicity.

¹³ World Health Organization. (2025). *Safety monitoring of natural medicines: Guidelines for pharmacovigilance*. <https://www.who.int/publications/i/item/9789241515436>

¹⁴ Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177. <https://doi.org/10.3389/fphar.2013.00177>

¹⁵ National Institute of Diabetes and Digestive and Kidney Diseases. (2024). *LiverTox: Clinical and research information on drug-induced liver injury*. <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

¹⁶ Gurley, B. J. (2025). Clinically relevant herb-drug interactions: A 30-year historical assessment. *Journal of Dietary Supplements*, 22(1), 1–27. <https://doi.org/10.1080/19390211.2024.2327544>

Pharmacodynamic Mechanisms: Synergism and Antagonism

Pharmacodynamic interactions take place when the drug's pharmacological effect on its target site is directly changed, but the drug's amount present in the body does not necessarily change. These interactions can be classified as synergistic (additive) or antagonistic. The "G-herbs," which include Ginkgo, Garlic, Ginseng, and Ginger, are often involved in synergistic interactions because they possess antiplatelet properties. When these herbs are taken along with anticoagulants (like warfarin) or antiplatelet medications (like aspirin), there is a possibility of increasing the suppression of primary hemostasis¹⁷. This can lead to a significant increase in the risk of spontaneous hemorrhage or brain bleeding occurring. Antagonistic interactions are significant as well. For instance, it has been shown that Green Tea Extract (EGCG) can bind to and negate the effects of certain chemotherapeutic agents, such as Bortezomib, thereby making the cancer treatment ineffective. Such interactions are more difficult to predict and monitor than pharmacokinetic changes because they occur at the level of the receptor or the molecular target.

High-Risk Drug Classes and Patient Vulnerabilities

Therapeutic classes of drugs with a narrow therapeutic index (NTI) are the ones most likely to be affected by major drug interactions (HDIs). Very slight differences in the plasma concentration of the drug may lead to either adverse effects or the drug being ineffective. The drugs that pose the largest risk are anticoagulants and antiplatelets because the clinical effect of an interaction (severe bleeding, for example, or thromboembolism) is immediate and life-threatening. Immunosuppressants used in organ transplantation, such as cyclosporine and tacrolimus, also face adverse effects because of the stimulation of CYP3A4 by herbal supplements that may lead to acute graft rejection. In oncology, cytotoxic chemotherapy and oral targeted therapies are both associated with double the risk. On one hand, herbal inhibitors may raise the level of toxicity (for example, acute neutropenia), and on the other hand, inducers may lower the level of the drug to such an extent that it causes tumor resistance. Patients with chronic comorbidities, especially the elderly who usually are on polypharmacy regimens, are the ones that suffer the most from these "silent" interactions. This is due to the fact that their declining renal and hepatic function further lowers the safety margin making them more prone to the adverse effects of the interactions.

High-Risk Drug Class	Representative Drug	Herbal Perpetrator	Interaction Mechanism	Clinical Outcome
Anticoagulants	Warfarin	St. John's Wort	CYP2C9 Induction	Reduced INR; Risk of

				Clotting
Anticoagulants	Warfarin	Danshen / Ginkgo	Pharmacodynamic Synergy	Increased INR; Risk of Bleeding
Immunosuppressants	Cyclosporine	St. John's Wort	CYP3A4/P-gp Induction	Organ Transplant Rejection
Cardiovascular	Digoxin	St. John's Wort	P-gp Induction	Reduced Heart Rate Control
Antiretrovirals	Indinavir / Nevirapine	St. John's Wort	CYP3A4 Induction	HIV Treatment Failure
Calcium Channel Blockers	Felodipine / Verapamil	Grapefruit / Goldenseal	CYP3A4 Inhibition	Hypotension / Tachycardia
Chemotherapy	Bortezomib	Green Tea (EGCG)	Direct Receptor Binding	Loss of Cytotoxic Efficacy

Table 3: Clinically Significant Herb-Drug Interactions by Drug Class, Source: Author Generated

Discussion and Policy

Regulatory Fragility and the Supplement-Medicine Dichotomy

The clinical difficulties pointed out in this review bring to light a significant regulatory paradox which governs the global herbal medicine market. In the majority of the jurisdictions, including the US where the DSHEA framework is applied and several ASEAN countries, herbal products are placed into the category of "food supplements" or "traditional medicines." This effectively diminishes the manufacturer's responsibility of providing proof while enhancing that of the regulatory authority. Such a categorization indicates a certain degree of safety which is frequently not in accordance with the highly concentrated and potent bioactive compounds the modern extracts

¹⁷ M, S., et al. (2025). Drug-herb interactions: A challenge and clinical concern in primary healthcare. *Frontiers in IJDDT*, Volume 16 Issue 8s, 2026

contain¹⁸. From the viewpoint of policy, this creates a situation where the safety measures are reactive rather than proactive; the actions to control are mostly taken after significant public damage has been proven. By the year 2026, there is an immediate requirement for the introduction of a standardized "third category" regulation that imposes pre-market chemical fingerprinting and omics-enabled authentication in order to ascertain the presence of no contaminants and the standard of active metabolites. Moreover, it is very critical to harmonize the global pharmacovigilance standards through WHO's VigiBase system to enable the fast identification of rare, idiosyncratic reactions that would otherwise remain unnoticed within the national silos.

The Role of "Herbovigilance" and Practitioner Accountability

The "silent epidemic" of herbal adverse reactions can only be resolved through a complete rethinking of clinical education and practitioner roles. Healthcare professionals are to revamp their approach completely from passive questioning to nonjudgmental active "herbovigilance" strategies which are very much imbued with empathy. One of these strategies is the systematic integration of herbal use questions in Electronic Health Records (EHRs), while AI-driven clinical decision support tools would be used to identify real-time potential herb-drug interactions (HDIs) through flagging¹⁹. The specialists in healthcare, especially those dealing with primary care, cancer, and heart diseases will be significant in their capacity as the first line of defense in the detection of organ toxicity signals. By making herbal medicine knowledge a part of their education, the medical school and informal training of doctors may slowly but surely blind the whole medical community to the "biochemical signatures" of ordinary herbal toxins. Also, requiring the same reporting of side effects of herbal substances as that of synthetic drugs will improve the data's quality very much and thus making it possible to calculate and ensure the safe use of traditional medicines in modern medical practice.

Conclusion

It is acknowledged that herbal medicines possess therapeutic potential, but the reviews presented here indicate that they have to comply with clinical toxicology regulations. Adverse reactions do occur and their repercussions may be serious, e.g., hepatic toxicity, renal toxicity, and drug interaction, which in some cases may even result in death. Henceforth, the belief that "natural is safe" must come down and be replaced by a system based on evidence and prioritizing uniform quality control, thorough post-market surveillance, and open communication between patients and providers. More rigorous regulatory control and the routine screening of herbal use in high-risk patients have been among the

clinical recommendations made to ensure that botanical products are of the same safety standards as the regular medicines

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