



HERBAL AND DIETARY SUPPLEMENT-INDUCED HEPATOTOXICITY: RETHINKING PHARMACOVIGILANCE STRATEGIES IN THE INDIAN CONTEXT

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Abstract

Herbal and dietary supplements (HDS) are consumed extensively worldwide, often under the perception of being safe. However, herb-induced liver injury (HILI) has emerged as an important subset of drug-induced liver injury (DILI), with wide regional variability. Reports suggest that HDS account for about 20% of DILI cases in the United States and nearly 30% in European registries, whereas Asian data show heterogeneity, ranging from 70% in Singapore to 14% in India. The Indian scenario is particularly complex, with most data derived from tertiary-care studies rather than national registries. Pharmacovigilance efforts are currently split between the Pharmacovigilance Programme of India (PvPI), with Adverse Drug Reaction Monitoring Centres (AMCs), and the Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) pharmacovigilance network. Despite these structures, under-reporting, fragmented reporting systems, and lack of laboratory integration remain major barriers. This review discusses global and Indian perspectives on HDS-related hepatotoxicity and outlines future opportunities, including digital health tools, blockchain-based supply-chain monitoring, and integration of public health surveillance, to strengthen herbal safety monitoring in India.

Introduction

Herbal and dietary supplements (HDS) constitute one of the fastest-growing sectors of global healthcare, driven by increasing consumer demand for “natural” therapies. According to the latest Statista report, the global market for HDS is projected to reach nearly USD 300 billion by 2028 [1]. India is both a leading producer and a significant consumer in this sector, exporting Ayurvedic medicines and nutraceutical products to over 150 countries [2]. Although these products enjoy widespread cultural acceptance, concerns are rising over their safety, with hepatotoxicity emerging as one of the most serious adverse effects.

Herb-induced liver injury (HILI) contributes to 15–20 % of all reported drug-induced liver injuries (DILI) worldwide [3]. In India, the situation is complicated by extensive polyherbal use, inadequate

labeling, and minimal post-marketing monitoring. The Pharmacovigilance Programme of India (PvPI) and the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) pharmacovigilance network operate independently, leading to fragmented data [4,5]. Bridging these systems is essential for effective detection and prevention of herbal-related liver injury.

Global Overview of HDS-Induced Hepatotoxicity

Recent multi-center registries indicate a steep increase in HDS-related hepatotoxicity. In the United States, the DILIN registry attributes approximately 20% of DILI cases to supplements, predominantly bodybuilding, immune-boosting, or weight-loss products. Data from Asia demonstrate substantial variation, with HDS implicated in up to 70% of DILI cases in Singapore, whereas Indian registry data indicate that traditional and alternative medicines, including HDS, account for approximately 14% of DILI cases [6,7]. However, hospital-based cohorts indicate that the burden may be underestimated in national pharmacovigilance records. For instance, in a large tertiary-care study from southern India, Ayurvedic medicines accounted for 13.3% of all DILI cases that presented as acute liver injury (ALI) [8]. This suggests that while national data indicate a smaller proportion, selected referral centers are observing a substantial share of severe acute presentations attributable to herbal and traditional formulations. These differences across countries emphasize the importance of pharmacovigilance systems and regional registries in understanding the true burden of HDS-induced liver injury [9-13] (Table 1, Figure 1).

Region	Main reporting system	Predominant product classes
USA	US Food and Drug Administration (FDA) MedWatch	Bodybuilding & weight-loss supplements, green tea extract, multi-ingredient formulations
Europe (EU)	EudraVigilance	Green tea extract, Herbalife, slimming/weight-loss products
China	National Adverse Drug Reaction Monitoring Centre (NADRMC)	Traditional Chinese Medicine (TCM) multi-herb mixtures (e.g., Polygonum multiflorum, Psoralea, Gynura segetum)
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Kampo formulas, green tea extract, turmeric, Garcinia cambogia
Korea	Korea Institute of Drug Safety and Risk Management (KIDS)	Ginseng, Glycyrrhiza uralensis (licorice root), herbal tonics
India	Pharmacovigilance Programme of India (PvPI)	Ayurvedic and Siddha herbal formulations, multi-ingredient herbal products

Table 1. Global overview of herbal and dietary supplement inducing hepatotoxicity.
Predominant herbal and dietary supplement (HDS)-related cases associated with drug-induced liver injury (DILI) across different regions.

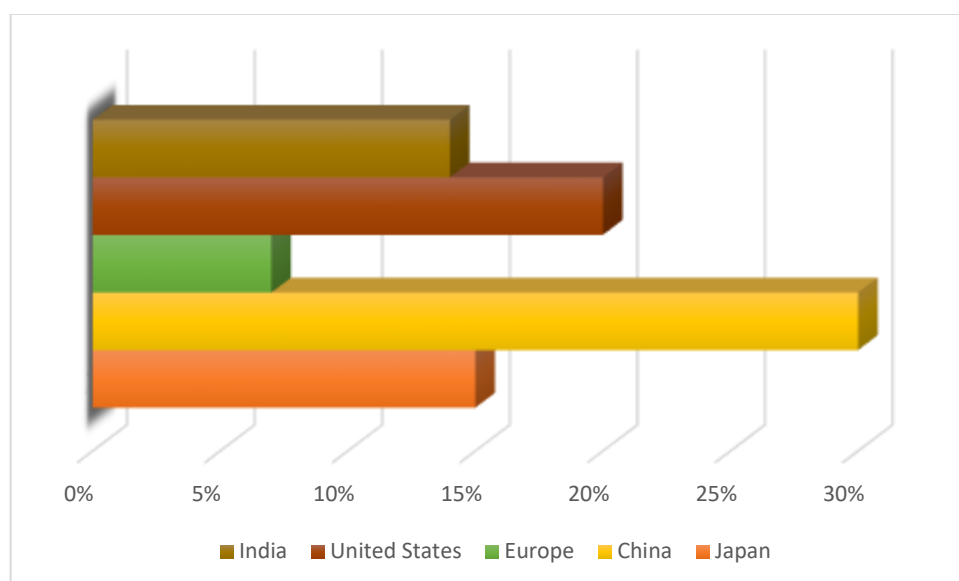


Figure 1. Global overview of herbal and dietary supplement-induced hepatotoxicity. Registry data show marked regional variation in the contribution of herbal and dietary supplements (HDS) to drug-induced liver injury (DILI), ranging from about 14% in India to nearly 20% in the United States, 7% in Europe, 26–30% in China, and 15% in Japan.

Mechanisms of Hepatotoxicity

HDS induced liver injury involves multiple mechanisms (Figure 2). Oxidative stress and mitochondrial dysfunction lead to hepatocellular necrosis, as with usnic acid in slimming supplements [14]. Reactive metabolite formation and immune activation, such as HLA-B*35:01–associated green tea extract hepatotoxicity, exemplify idiosyncratic injury [15]. Cholestatic injury results from inhibition of bile acid transporters (BSEP/MRP), seen with anabolic steroid supplements and ashwagandha [16]. Pyrrolizidine alkaloid–containing herbs (e.g., *Gynura segetum*) cause sinusoidal endothelial cell injury, leading to hepatic sinusoidal obstruction syndrome (HSOS) [17].

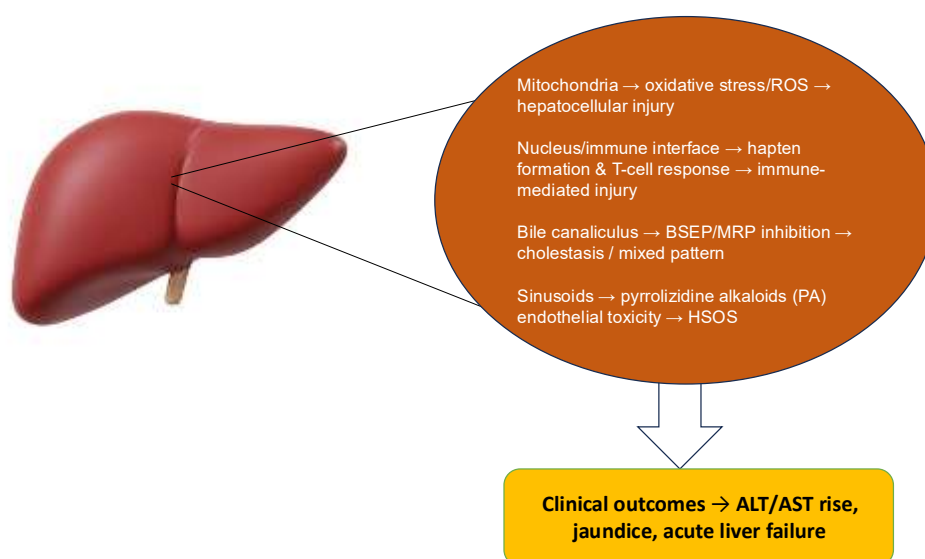


Figure 2. Pathogenesis of HDS-induced liver injury. Oxidative, immune, cholestatic, and vascular pathways yield hepatocellular, cholestatic, or mixed phenotypes.

These mechanisms manifest in distinct clinical phenotypes (Table 2). Hepatocellular injury (marked ALT elevation) is common with green tea extract; cholestatic or mixed patterns (elevated ALP/bilirubin) occur with ashwagandha and steroids; and vascular/HSOS presents with hepatomegaly, ascites, and jaundice after pyrrolizidine alkaloid (PA) exposure. Adulteration with steroids or heavy metals, and herb–drug interactions via CYP modulation, further complicate presentations [18]. Thus, HILI spans mild transaminitis to fulminant liver failure.

Herbal/Dietary Supplement	Scientific name	Common indication	Type of liver injury
Green tea extract (EGCG)	Camellia sinensis	Weight loss, antioxidant, energy	Hepatocellular; can progress to acute liver failure
Garcinia cambogia	Garcinia gummi-gutta (syn. G. cambogia)	Weight loss	Hepatocellular; severe cases incl. ALF/transplant
Turmeric / Curcumin	Curcuma longa	Anti-inflammatory, arthritis, wellness	Hepatocellular or mixed; autoimmune-like hepatitis reported
Ashwagandha	Withania somnifera	Stress relief, vitality, immunity	Cholestatic or mixed; prolonged jaundice
Kava	Piper methysticum	Anxiety, insomnia	Hepatocellular; fulminant failure reported
Black cohosh	Actaea racemosa (syn. Cimicifuga racemosa)	Menopausal symptoms	Hepatocellular or mixed; autoimmune features reported
Usnic acid (in slimming blends)	Derived from lichens (e.g., Usnea spp.)	Weight loss, “fat-burning”	Hepatocellular; mitochondrial toxicity
Bodybuilding anabolic products (often mislabeled as herbal)	Synthetic androgens/designer steroids	Muscle gain, physique	Cholestatic, prolonged jaundice
Multi-ingredient slimming/fitness formulas (e.g., Herbalife, Hydroxycut, OxyELITE Pro*)	Brand-dependent blends	Weight loss, fitness	Hepatocellular or mixed; severity varies by formulation/batch
PA-containing herbs (e.g., Tusanqi)	Gynura segetum, Senecio spp., Crotalaria spp.	Traditional remedies/tonics	Vascular; hepatic sinusoidal obstruction syndrome (HSOS)

Table 2. Major Herbal and Dietary Supplements (HDS), Their Indications, and Associated Liver Injury Phenotypes. Indications are claimed uses, not evidence of efficacy. Injury phenotypes reflect patterns most frequently reported in case series/registries: hepatocellular (ALT-predominant), cholestatic (ALP/bilirubin-predominant), mixed, and vascular (HSOS). *Multi-ingredient products and “pro-hormone”/steroid blends vary by lot; adulteration/mislabelling is common and drives phenotype variability.

Pharmacovigilance Frameworks for HDS

Pharmacovigilance (PV) of herbal and dietary supplements (HDS) is crucial given rising global use and safety concerns. At the international level, adverse event data are pooled in World Health Organization–Uppsala Monitoring Centre (WHO-UMC) Vigibase, which supports signal detection across countries [19]. Regulatory frameworks such as the EMA and US FDA have issued guidelines for herbal products, mandating labelling and adverse-event reporting [20,21].

In India, PV is coordinated through two parallel structures. The PvPI, launched in 2010 under the Indian Pharmacopoeia Commission (IPC), now oversees more than 1000 ADR Monitoring Centres (AMCs) across the country [22]. PvPI integrates data into Vigibase via VigiFlow and has begun to include phytopharmaceuticals under its scope. However, herbal product reports represent only a small fraction of the database, reflecting under-reporting.

The AYUSH Pharmacovigilance Programme, initiated in 2017, functions through one national coordination centre, five intermediary centres, and 42 peripheral centres (Figure 3) [23]. Reporting still relies heavily on paper-based Ayurveda, Siddha, Unani, and Homoeopathy (ASU&H) ADR forms, limiting integration with PvPI. This “dual system” creates gaps in signal detection but also provides an opportunity for eventual harmonization. Strengthening linkages between PvPI and AYUSH PV is key to capturing the true burden of HDS-induced hepatotoxicity in India.

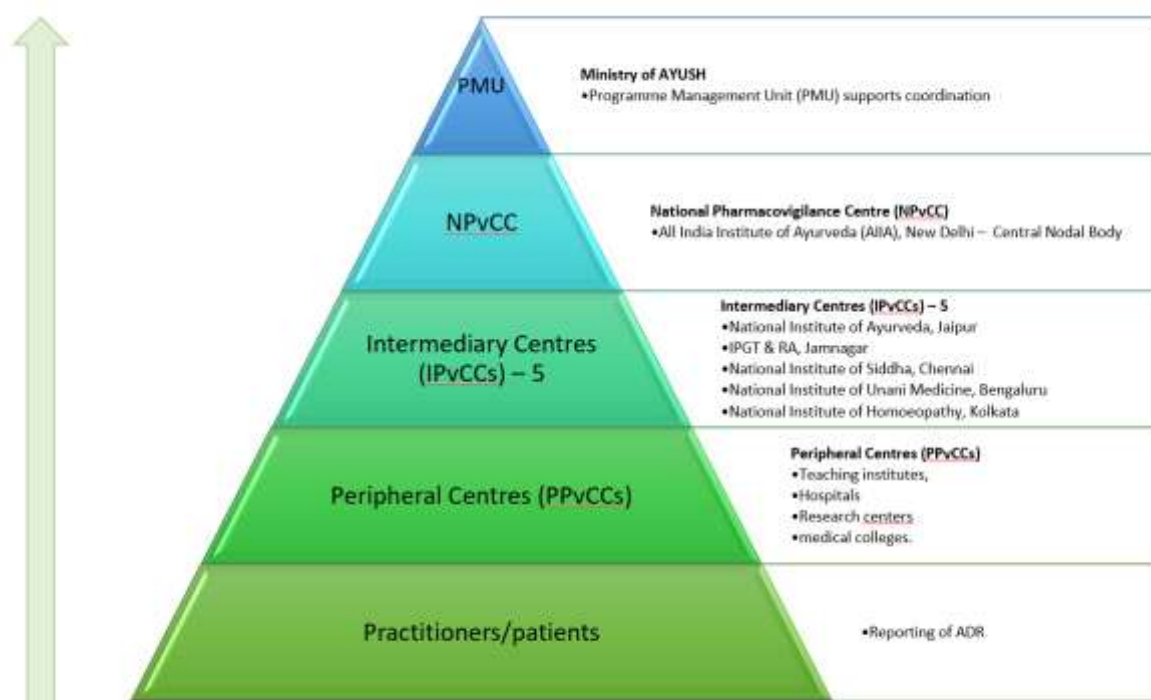


Figure 3. Organizational structure and information flow in the Pharmacovigilance Programme of ASU&H drugs in India. Adverse drug reactions (ADRs) reported by practitioners and patients are first documented at PPvCCs, located in teaching institutes, hospitals, research centres, and medical colleges. These reports are validated and forwarded to IPvCCs, which currently number five across India. The AIIA, NPvCC, New Delhi, serves as the central nodal body for collating data, performing causality assessment, and coordinating with the Ministry of AYUSH. The Programme Management Unit (PMU) supports overall implementation and oversight.

Challenges in Pharmacovigilance of Herbal and Dietary Supplements in India

Despite the establishment of the PvPI and the dedicated ASU&H pharmacovigilance network under AYUSH, several systemic challenges continue to hinder effective monitoring of HDS-induced hepatotoxicity in India (Figure 4). Herbal ADRs account for less than 3% of total reports in PvPI, even though HDS consumption is widespread [22]. This under-reporting is partly driven by cultural

beliefs that “natural means safe,” as well as limited awareness among physicians and AYUSH practitioners. The existence of parallel reporting structures, with PvPI under IPC and AYUSH PV coordinated by the NPvCC at AIIA, due to limited interoperability for HDS-related liver injury and weakening India’s contribution to WHO-UMC Vigibase [25].

Another barrier lies in regulatory and quality-control issues: many marketed formulations are polyherbal mixtures, frequently adulterated with steroids, NSAIDs, or heavy metals such as lead, mercury, and arsenic [18]. Unlike pharmaceuticals, herbal products are not subject to Risk Management Plans (RMPs) or Periodic Safety Update Reports (PSURs). In addition, case reports from India often omit key data such as treatment timelines, dechallenge or rechallenge results, and precise product identity, which diminishes the applicability of structured causality tools like Roussel Uclaf Causality Assessment Method (RUCAM) or Revised electronic Causality Assessment Method (RECAM) [26].

Resource limitations also play a role. Although the Pharmacopoeia Commission for Indian Medicine & Homoeopathy (PCIM&H) serves as an appellate laboratory, it is not routinely integrated into ADR workflows, leaving most suspect herbal products untested [27]. Furthermore, the lack of harmonized coding systems poses difficulties for data aggregation and comparison. Indian reports still rely on descriptive entries rather than standardized Herbal ATC codes used globally [19]. These factors collectively underscore the urgent need for harmonization between PvPI and AYUSH PV, integration of laboratory testing, and enhanced training of healthcare providers to better capture the true burden of HDS-induced hepatotoxicity in India.

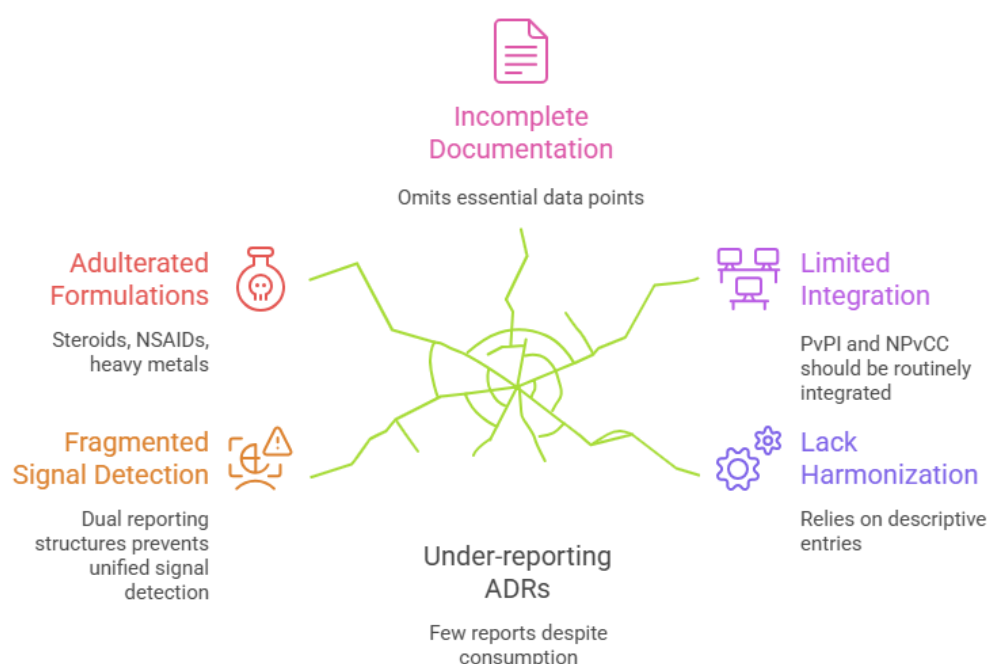


Figure 4. Key challenges in herbal and dietary supplement (HDS) safety reporting in India. Fragmented systems, poor documentation, adulteration, and under-reporting hinder reliable signal detection for HDS-induced hepatotoxicity.

Opportunities and the Way Forward

India’s rising burden of HILI highlights the urgent need to strengthen pharmacovigilance infrastructure. A first priority is the harmonization of the dual reporting systems and establishing a shared reporting pathway and database would avoid duplication, facilitate unified signal detection, and ensure that HILI cases are captured comprehensively (Figure 5).

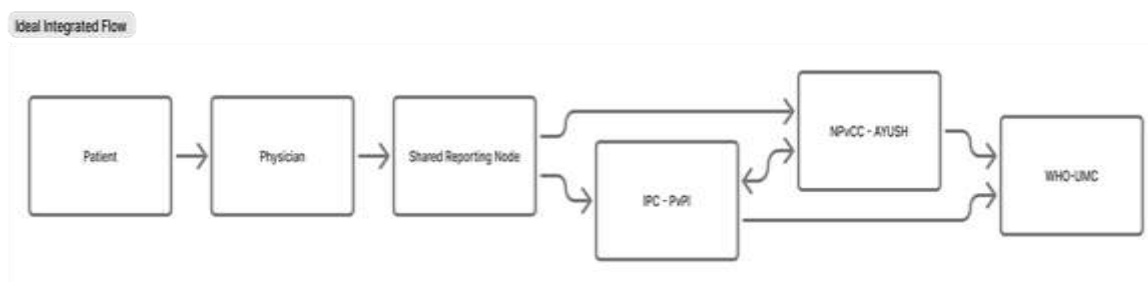


Figure 5. Proposed ideal integrated pharmacovigilance data flow between PvPI and AYUSH networks. A shared reporting node to both the Indian Pharmacopoeia Commission–Pharmacovigilance Programme of India (IPC–PvPI) and the National Pharmacovigilance Centre–Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (NPvCC–AYUSH). Both systems exchange validated data, which are subsequently transmitted to the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) for inclusion in the global VigiBase database.

Routine integration of laboratory testing into ADR workflows is also essential. Involving PCIM&H and accredited laboratories for chemical fingerprinting, adulterant detection, and heavy-metal screening would improve causality assessments, reduce “unassessable” cases, and support structured tools such as RUCAM or RECAM. Expanding digital reporting platforms, such as Ayush Suraksha and PvPI’s mobile applications, could further encourage point-of-care ADR submissions by physicians, AYUSH practitioners, and patients, with direct integration into VigiFlow.

Emerging AI-driven approaches offer additional promise. Machine-learning models have been successfully used to mine electronic health records and social-media streams for adverse event signals [28]. Integrating such algorithms into PvPI and AYUSH databases could enable early detection of hepatotoxicity clusters. Similarly, in-silico toxicology platforms like ADMET-AI predict hepatotoxicity risk of phytochemicals from chemical structures, allowing pre-market screening by regulators [29]. Blockchain initiatives in herbal supply chains, piloted in India, demonstrate how ingredient authenticity can be verified to curb counterfeiting and contamination. [30] Beyond technology, greater public health integration is needed where physicians should routinely inquire about herbal medicine use. This depicts the importance of incorporating pharmacovigilance training into both allopathic and AYUSH curricula.

Conclusion

Herbal and dietary supplements represent a growing cause of hepatotoxicity, yet their risks remain underestimated in India due to under-reporting, fragmented pharmacovigilance structures, and quality-control gaps. While PvPI and the AYUSH pharmacovigilance network provide a foundation, greater integration, standardized causality assessment, and improved training for healthcare professionals are urgently needed. Leveraging modern approaches such as AI-driven signal detection, and blockchain-enabled supply-chain transparency can transform India’s pharmacovigilance landscape. By strengthening both national systems and their linkage to WHO-UMC, India can not only safeguard public health but also set benchmarks for global HDS pharmacovigilance.

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