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A comphrehensive review of herb induced liver injuries

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Abstract
Herb-induced liver injuries (HILI) are increasingly recognized as significant causes of hepatic dysfunction worldwide, driven in part by the growing consumption of herbal and dietary supplements. Traditionally valued plants such as *Tinospora cordifolia*, *Withania somnifera*, *Aloe vera*, and *Garcinia cambogia* are widely used for therapeutic purposes; however, emerging evidence associates them with varying degrees of hepatotoxicity. The underlying mechanisms may involve metabolic disturbances, immune-mediated reactions, or impairment of detoxification pathways within the liver. Histopathological examinations often reveal hepatocellular necrosis, cholestatic changes, and inflammatory infiltration. Poor quality control, contamination, and unregulated manufacturing practices further increase the potential for toxicity.

Keywords: Herb-induced liver injury, hepatotoxicity, herbal medicines, *Tinospora cordifolia*, *Withania somnifera* and *Aloe vera*

Introduction
In India, traditional and alternative medical systems are collectively known as AYUSH, comprising Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy. Among these, Ayurveda is one of the oldest documented medical traditions, originating over two millennia ago. It is founded on empirical observations and promotes holistic health through herbal, mineral, and metallic preparations used for disease prevention and treatment. According to Ayurvedic philosophy, the human body and universe are governed by five elements-Vayu (air), Jala (water), Aakash (space), Prithvi (earth), and Teja (fire)-that form three doshas: Vata, Pitta, and Kapha. These govern physiological balance and health. However, Ayurveda lacks robust scientific evidence to support its diagnostic and therapeutic principles, with few well-designed clinical trials evaluating efficacy or safety. Unlike Traditional Chinese Medicine (TCM), which has successfully yielded therapeutic compounds such as artemisinin, Ayurvedic research remains limited in evidence-based validation. Ayurvedic herbal medicines (AHMs) are categorized as classical or proprietary formulations. Classical preparations adhere to ancient texts like the Charaka Samhita and Susruta Samhita, while proprietary products are industry-developed with variable composition, such as Himalaya® Liv 52™ and Charak® Livomyn™. Several studies from India have demonstrated Ayurvedic herbal medicine-induced liver injury (AHM-DILI) [1-2]. The Siddha system, primarily practiced in Tamil Nadu, shares similar therapeutic philosophies, while Unani medicine, influenced by Greek, Persian, and Arabic doctrines, remains popular across South and Central Asia [3-4]. Homeopathy, though included under AYUSH, differs substantially as it originated in Germany and lacks scientific validation for its highly diluted remedies [5]. The widespread use of complementary and alternative medicine (CAM) has drawn concern due to its association with drug-induced liver injury (DILI) and acute-on-chronic liver failure (ACLF). Studies have reported increasing cases of CAM-related hepatotoxicity, sometimes requiring liver transplantation [6]. The prevalence of CAM use ranges from 24% in Switzerland to 71.3% in South Korea, and 63% among Indian patients with cirrhosis. Mortality from CAM-induced liver injury varies between 5-19% in those without prior liver disease and exceeds 50% among patients with hepatic dysfunction [7]. Ayurvedic formulations, particularly polyherbal and proprietary preparations, have been implicated in severe liver injury and poor outcomes. Recent reports from India also link "immune-boosting" Ayurvedic and homeopathic remedies to hepatotoxicity during public health crises [8]. Recognizing this growing problem, the Asia-Pacific Association for the Study of the Liver (APASL) introduced the term "Ayush-liver injury", noting that CAMs accounted for nearly 72% of ACLF cases in the Asia-Pacific region [9-10]. Das *et al*. [11] identified unidentified herbal products as a major cause of acute liver failure (ALF) in Northeast India, and Udayakumar *et al*. [12] reported similar findings among patients treated by Tamil healers.

Devarbhavi *et al*. [13] observed Ayurvedic-related DILI in 1.3% of cases, with nearly half resulting in death. Philips *et al*. [6] found that unlabelled polyherbal preparations containing arsenic and mercury were strongly associated with fatal outcomes, and 35.7% of cirrhotic patients developed ACLF with a 53% mortality rate [7]. The identification of hepatotoxic ingredients in Ayurvedic medicines remains challenging due to mislabelling, contamination, adulteration, and the complex multi-herbal nature of formulations. Therefore, clinicians must remain alert to potential Ayurvedic herb-induced DILI when evaluating liver injury of unknown origin. This review aims to summarize the current evidence on hepatotoxicity linked to commonly used Ayurvedic herbs.

Pathophysiological mechanisms of liver injury caused by drugs and herbal supplements [14-18]

Most cases of drug-induced liver injury (DILI) and herb-induced liver injury (HILI) occur unpredictably and are considered idiosyncratic, meaning they arise from individual differences in genetic makeup, immune response, or metabolic capacity, rather than from dose-related toxicity. The pathogenesis of hepatocyte damage in such cases is multifactorial, involving interconnected metabolic, immunological, and genetic mechanisms that together contribute to various patterns of acute and chronic liver injury

Formation of Reactive Metabolites: Many hepatotoxic agents undergo biotransformation through hepatic cytochrome P450 (CYP450) enzymes. During this process, some drugs are converted into electrophilic reactive intermediates that can bind covalently to essential cellular components such as proteins, nucleic acids, or lipids. These adducts disturb normal cellular functions, impair detoxification systems, and may trigger immune recognition through the creation of neoantigens, thereby initiating hepatocellular necrosis or immune-mediated injury.

Mitochondrial Dysfunction: Mitochondria play a key role in hepatocyte energy metabolism and redox homeostasis. Certain drugs impair mitochondrial integrity by inhibiting oxidative phosphorylation, blocking mitochondrial DNA replication, or disrupting the electron transport chain. Such interference can cause ATP depletion, oxidative imbalance, and mitochondrial permeability transition (MPT), ultimately leading to cellular apoptosis or necrosis. This mechanism has been described with several agents known to impair mitochondrial energy production.

Oxidative Stress: An imbalance between reactive oxygen species (ROS) production and the antioxidant defense system leads to oxidative stress, which damages proteins, lipids, and DNA. This mechanism is frequently implicated in both pharmaceutical and herbal supplement-induced hepatotoxicity. Herbal and dietary supplements (HDS) such as green tea extract, kava, usnic acid, chaparral, greater celandine, and black cohosh are well-documented to generate excessive ROS, amplifying hepatic inflammation and contributing to disease progression.

Immune-Mediated Injury: Some drugs or their metabolites act as haptens, binding to liver proteins and forming antigenic complexes that activate adaptive immune responses. This reaction results in immune-mediated hepatitis, which may resemble autoimmune liver disease. Clinical features can include fever, rash, eosinophilia, and autoantibody positivity. Such immune-driven mechanisms are typically delayed and may persist even after discontinuation of the offending agent.

Bile Acid Transport Disruption: Several drugs inhibit bile salt export pump (BSEP) or related hepatic transport proteins, resulting in cholestatic liver injury. The accumulation of toxic bile acids within hepatocytes can trigger membrane damage, mitochondrial dysfunction, and inflammatory signalling, culminating in bile acid-induced cytotoxicity. This mechanism commonly underlies the cholestatic pattern of drug-induced liver damage.

Endoplasmic Reticulum (ER) Stress: The endoplasmic reticulum (ER) plays a vital role in protein folding and processing. Drugs that interfere with these functions cause ER stress, leading to activation of the unfolded protein response (UPR). While initially protective, sustained UPR activation promotes apoptosis through upregulation of pro-apoptotic factors such as CHOP. Persistent ER stress can therefore contribute to hepatocyte death and fibrosis progression.

Genetic Susceptibility: Individual genetic polymorphisms significantly influence susceptibility to DILI. Variations in drug-metabolizing enzymes (e.g., CYP450 isoforms, UGTs, NAT2), hepatic transporters (e.g., ABCB11, ABCC2), and immune-regulatory genes (notably HLA alleles) modify the metabolism and clearance of xenobiotics. These differences can enhance the formation of toxic intermediates or increase immune activation. For example, HLA-B*57:01 has been linked to flucloxacillin-induced liver injury, and NAT2 variants to isoniazid toxicity.

Dysregulation of Lipid Metabolism: Certain drugs disturb hepatic lipid regulation, leading to steatosis or fat accumulation in hepatocytes. Mechanistically, this involves increased lipid synthesis, reduced β-oxidation, and impaired lipid export, resulting in oxidative stress and inflammatory responses. Chronic disturbances in lipid metabolism may progress to metabolic dysfunction-associated steatotic liver disease (MASLD) or drug-induced steatohepatitis (DISH), both of which can evolve into fibrosis or cirrhosis with poor clinical outcomes.

Herb-Drug Interactions: Herbal and dietary supplements can significantly alter the pharmacokinetics of concurrently administered drugs. Many herbs induce or inhibit CYP450 enzymes and drug transporters, modifying the absorption, distribution, metabolism, and elimination (ADME) of conventional medications. These interactions can increase systemic exposure to hepatotoxic agents or produce harmful metabolites. For instance, St. John's Wort enhances CYP3A4 and P-glycoprotein activity, while green tea catechins inhibit CYP2C9, both affecting drug clearance and potentially heightening liver injury risk.

Various herbals that induced liver injury

***Curcuma longa* (Turmeric)**

Turmeric (*Curcuma longa* L.), a perennial herb native to India and a member of the Zingiberaceae (ginger) family, is widely recognized for its medicinal and culinary applications. The rhizome, the underground stem of the plant, is the principal source of its therapeutic properties and contains numerous bioactive constituents. These include curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, along with essential oils rich in mono- and sesquiterpenoids

[19]. Both turmeric and its primary active compound, curcumin, are extensively utilized in Ayurvedic formulations and as dietary supplements for their proposed anti-inflammatory, antioxidant, and hepatoprotective benefits [20]. Despite its long-standing traditional use, turmeric exhibits extremely poor oral bioavailability. Less than 1% of the ingested amount is absorbed, with most being excreted in feces. Moreover, curcumin, which accounts for only about 5% of turmeric's composition, has a short plasma half-life of approximately 5.45 hours, resulting in negligible systemic concentrations. Consequently, traditional consumption practices, such as adding small amounts of turmeric to milk, tea, or water, provide minimal therapeutic benefit [21]. In Ayurveda, turmeric has been prescribed for inflammatory conditions, digestive ailments, and liver disorders, including pharyngitis, inflammatory bowel disease, and fatty liver disease. It also contains polyphenols, phytosteroids, and other compounds that may exhibit immunomodulatory effects. However, while Ayurvedic practitioners emphasize its broad therapeutic potential, scientific validation through robust human studies remains limited, as most evidence derives from preclinical or small animal studies [22]. Emerging clinical evidence indicates that turmeric and curcumin supplements may cause idiosyncratic drug-induced liver injury (DILI) and autoimmune-like hepatitis (AIH). Lukefahr *et al*. [23] reported AIH in a 76-year-old woman after ten months of turmeric supplement use, with resolution following discontinuation. Similar AIH-like hepatitis cases were documented by Suhail *et al*. [24] and Lee *et al*. [25] Imam *et al*. [26] described hepatocellular DILI in a 78-year-old woman who consumed a curcumin supplement for dyslipidemia; her liver function normalized within six weeks after cessation. Luber *et al*. [27] reported two severe hepatocellular DILI cases from curcumin supplements, one confirmed by rechallenge. Chand *et al*. [28] also observed turmeric-related hepatotoxicity with symptoms such as rash, myalgia, and arthritis, which subsided after withdrawal.

Bacopa monnieri and Centella asiatica (commonly known as Brahmi and Gotu Kola)

Brahmi and Gotu Kola are widely recognized in Ayurvedic medicine for their purported neurocognitive and memory-enhancing effects, although they are botanically and pharmacologically distinct. Bacopa monnieri (Brahmi), a perennial, non-aromatic, creeping herb also known as water hyssop, belongs to the family Plantaginaceae. Its key bioactive components include steroidal saponins (bacosides), and alkaloids such as brahmine, herpestine, and nicotine, which are believed to contribute to its nootropic and adaptogenic properties. In contrast, Centella asiatica (Gotu Kola), or Indian pennywort, is a perennial flowering plant native to India and Southeast Asia. Its principal bioactive compounds are triterpenoid saponins such as asiaticoside, brahmoside, and thankuniside, known for their antioxidant and neuroprotective potential [29]. Despite their traditional reputation for safety, both herbs have been implicated in cases of herb-induced liver injury (HILI). Teschke and Bahre reported a case of severe hepatocellular liver injury in an elderly woman consuming multiple Ayurvedic formulations, with Brahmi tablets showing a "possible" association based on CIOMS causality assessment [30]. Clinical studies exploring the hepatic safety of Brahmi remain scarce. Gotu Kola, although widely used, has also been associated with adverse effects including contact dermatitis and potential reproductive toxicity due to specific triterpenoid glycosides [31-32]. A notable Argentinian study described several women who developed severe cholestatic hepatitis after taking Gotu Kola for weight loss. Liver biopsies revealed granulomatous and necro-inflammatory hepatitis with eosinophilic degeneration, and one case progressed to cirrhosis upon re-exposure. Most patients recovered after discontinuation and corticosteroid therapy, but recurrence upon rechallenge supported immune-mediated hepatotoxicity [33]. Another report documented acute liver failure in a 15-year-old following six weeks of Gotu Kola intake, with full recovery after cessation [34]. The hepatotoxicity of Gotu Kola may arise from triterpenoid saponins such as asiaticoside, which undergo hepatic metabolism to reactive intermediates capable of inducing apoptosis and necrosis in hepatocytes and cholangiocytes, paralleling mechanisms observed in other hepatotoxic herbs like germander and Chinese skullcap [30].

Cassia angustifolia

Cassia angustifolia, commonly known as Indian or Tinnevelly senna, belongs to the Fabaceae family, which also includes various ornamental plants. Traditionally, its leaves, flowers, and fruits have been utilized in Ayurvedic and Egyptian (Alexandrian) medicine for their laxative properties. The Alexandrian species, *Cassia acutifolia*, contains 6-hydroxymusizin glucoside, while *C. angustifolia* is rich in tinnevellin glucosides. The principal bioactive constituents of senna are anthraquinone glycosides, primarily sennosides A and B, which act as stimulant laxatives and are sometimes promoted as natural agents for weight reduction [35]. Beuers *et al*. [36] documented a case of severe cholestatic hepatitis in a 26-year-old nurse who consumed senna-based medications for one month, corresponding to approximately 100 mg sennosides daily along with senna herbal tea twice weekly. Liver biopsy revealed centrilobular necrosis and portal inflammation without autoantibodies. Her hepatic function normalized upon discontinuation but relapsed upon re-exposure, confirming senna-induced hepatotoxicity. The metabolic activation of sennosides into Rhein anthrone-a compound structurally similar to the hepatotoxic laxative danthron-is thought to be responsible for its liver toxicity. Similar mechanisms have been implicated in rhubarb-related hepatotoxicity. Sonmez *et al*. [37] described a 77-year-old man with bridging hepatocellular necrosis and canalicular cholestasis after senna use, who gradually recovered following cessation. In another report, Seybold *et al*. [38] linked acute hepatitis to senna tea consumption in a young woman carrying the CYP2D6*4 homozygous variant, suggesting that poor metabolizers are more susceptible to hepatotoxicity. Vanderperren *et al*. [39] further reported a case of acute liver failure (ALF) and acute kidney injury in a woman who consumed senna tea chronically, with elevated urinary cadmium levels, indicating heavy metal contamination. Fatal hepatotoxicity due to Senna occidentalis has also been documented, including outbreaks of hepato-myo-encephalopathy syndrome in Indian children [40]. Moreover, portal vein thrombosis following senna ingestion has been reported in otherwise healthy individuals [41].

***Morinda citrifolia* (Indian mulberry or Noni juice)**

Morinda citrifolia, commonly known as noni, is a tropical plant from the Rubiaceae (coffee) family, widely cultivated in various tropical and subtropical regions. Because of its strong, pungent odor, it is often referred to as "cheese fruit" or "vomit fruit." Traditionally, noni juice and extracts have been used in Ayurvedic, Polynesian, and Southeast Asian medicine to treat

ailments ranging from mouth ulcers and diabetes to infections such as HIV/AIDS. However, there is insufficient clinical evidence supporting these therapeutic claims, and most of the data cited are based on animal and laboratory studies, frequently exaggerated by commercial producers to promote product sales [42]. Phytochemical investigations have identified several bioactive compounds in noni, including alkaloids (xeronine), polysaccharides, anthraquinones such as damnacanthal and morindone, and glycosides like citrifolinoside. These constituents are thought to contribute to both the potential pharmacological effects and the reported hepatotoxic risks associated with noni consumption. Clinical evidence of liver injury linked to noni products has been documented in multiple countries [43]. In one reported case [43], a 45-year-old man developed acute hepatitis after consuming noni juice daily for three weeks as a health tonic. Liver biopsy revealed inflammation of the portal tracts, eosinophilic infiltration, and cholestasis, which resolved completely within ten days of discontinuing the product. Another study [44] described acute liver failure requiring transplantation in a 29-year-old man, and acute hepatitis in an elderly woman following prolonged noni juice intake. Biopsies in both cases demonstrated centrilobular necrosis, ballooning degeneration, and mixed inflammatory changes. Subsequent case reports from Europe and the United States have shown similar findings, with hepatocellular injury patterns, portal eosinophilia, and perivenular necrosis, typically improving after the product was stopped [45]. Despite these consistent observations, noni manufacturers continue to challenge the evidence of hepatotoxicity, often relying on non-systematic or anecdotal claims of safety. Nevertheless, the possibility of idiosyncratic liver injury associated with noni consumption remains an important clinical and pharmacovigilance concern [46].

***Aloe barbadensis* mille (*Aloe vera*)**

Aloe vera is a perennial, drought-resistant, and succulent herbaceous plant resembling a cactus, classified under the Liliaceae family. It has been used for centuries in traditional systems of medicine for treating dermatological conditions, enhancing wound healing, and as an oral antioxidant. The name “Aloe” originates from the Arabic term Alloeh, meaning “bitter and shiny substance,” while “vera” is Latin for “true.” Ancient Egyptians regarded it as the “plant of immortality.” The fleshy leaves of *Aloe vera* contain several pharmacologically active compounds such as glucomannans (notably acemannan), alprogen (an anti-inflammatory glycoprotein), anthraquinones (including aloin and emodin), and plant hormones such as auxins and gibberellins, which contribute to its diverse therapeutic actions [47]. The first case of aloe-induced hepatotoxicity was documented in Germany by Rabe *et al*. (2005) [48] in a middle-aged woman who developed acute cholestatic hepatitis after ingesting 500 mg aloe tablets daily for four weeks. Histopathological examination revealed portal and lobular inflammation, eosinophilic granulomas, bridging necrosis, and bile stasis. Her liver function normalized following discontinuation of the supplement. The hepatotoxic mechanism was attributed to aloe alkaloids interfering with cytochrome P450 enzymes, leading to accumulation of toxic metabolites that induce hepatocellular injury. Later reports [49] and case studies from Sweden, Korea, and other regions confirmed similar pathological findings-hepatocyte ballooning, apoptosis, cholestasis, and lobular inflammation dominated by eosinophils. Apart from hepatotoxic effects, *Aloe vera* has been linked to systemic toxicities including renal impairment, excessive intraoperative bleeding (due to prostaglandin interaction with anesthetics), Henoch-Schönlein purpura, and melanosis coli [50]. Data from pharmacovigilance systems such as the Spanish DILI Registry also report cases of severe herbal supplement-induced liver injury, particularly associated with Herbalife® products containing aloe extracts. Despite *in vitro* evidence suggesting hepatoprotective potential, controlled clinical studies in humans remain insufficient [51]. An instance of aloe-associated acute hepatic decompensation was documented by Vázquez-Fernández *et al*. [52] involving a patient with chronic hepatitis C-related cirrhosis who developed acute, severe cholestatic jaundice following *Aloe vera* ingestion. Overall, clinical evidence suggests that oral administration of *Aloe vera* for periods ranging from two to twenty-four weeks may precipitate severe cholestatic hepatitis in susceptible individuals and can trigger acute hepatic decompensation in patients with pre-existing chronic liver disease.

***Withania somnifera* (Ashwagandha)**

Withania somnifera (L.) Dunal, commonly known as Ashwagandha, Indian Winter Cherry, or Indian Ginseng, is one of the most significant medicinal herbs used in Ayurvedic medicine. Traditionally regarded as a rejuvenating tonic (rasayana), it is prescribed for a wide range of conditions, including fatigue, anxiety, cognitive decline, infertility, and immune dysfunction. Although widely promoted for enhancing vitality, longevity, and stress tolerance, clinical validation through robust, well-controlled human trials is still limited, leaving uncertainties regarding its efficacy and safety. The pharmacologically active constituents of Ashwagandha include flavonoids, alkaloids (cuscohygrine, anahygrine), coagulins, phytosteroids, and withanolides-a group of steroidal lactone triterpenoids known for their biological activity. Among these, withaferin A has been proposed to exhibit antioxidant, anti-inflammatory, and hepatoprotective effects, though evidence from human studies remains inconclusive [53]. The first documented case of Ashwagandha-induced liver injury (HILI) was reported [54] in Japan, involving a 20-year-old male with anxiety disorder who developed acute intrahepatic cholestasis after taking Ashwagandha supplements. Liver biopsy showed canalicular bile plugs and inflammatory changes, and the patient recovered completely after discontinuing the supplement and receiving ursodeoxycholic acid and phenobarbitone. Subsequently, Björnsson *et al*. reported five additional cases from Iceland and the U.S. Drug-Induced Liver Injury Network (DILIN). These patients, aged 28-55 years, developed cholestatic jaundice within 2-12 weeks of Ashwagandha intake. Biopsy findings revealed cholestatic hepatitis, and recovery occurred over 5-20 weeks after cessation. Chemical analysis of the products confirmed the presence of Ashwagandha without contamination by other hepatotoxic substances [55]. Recently, the LIVERECI consortium published the largest series of Ashwagandha-related hepatotoxicity cases. In 2020, Denmark, citing hepatotoxic, hormonal, and abortifacient risks, banned Ashwagandha supplements, a move later supported by Germany and Sweden, emphasizing growing international concerns regarding its safety profile and the need for stronger regulatory oversight [56].

***Tinospora cordifolia* (Willd.) Hook.f. & Thomson (Giloy, Guduchi):** *Tinospora cordifolia* (Willd.) Hook.f. &

Thomson, widely recognized as Giloy in Hindi and Guduchi in Sanskrit, also known as the heart-leaved moonseed, is a climbing shrub extensively utilized in Ayurvedic and Siddha medicine. For centuries, different parts of the plant-including the stems, roots, and leaves-have been incorporated into numerous herbal formulations to manage diverse health disorders. However, despite its long history of use, conclusive clinical evidence supporting its therapeutic effectiveness in humans is insufficient. Phytochemical investigations reveal that *T. cordifolia* contains several biologically active compounds, including alkaloids (berberine, palmatine, tinosporin), diterpenoid lactones (clerodane and furanolactone derivatives), glycosides (tinocordiside and furanoid diterpene glucosides), steroids (giloinsterol and sitosterol), and aliphatic constituents like octacosanol. Experimental studies in animals and cell cultures have demonstrated anti-inflammatory, antioxidant, hypoglycemic, antineoplastic, and immunomodulatory effects. Nonetheless, such outcomes have not been consistently replicated in controlled human studies, and its current use in complementary medicine remains largely faith-based rather than evidence-based [57]. Recent research has identified Giloy as a major contributor to herb-induced liver injury (HILI) in India. Clinicians at the Jaslok Hospital and Research Centre, Mumbai, first reported a cluster of patients developing acute hepatitis after ingesting Giloy-based supplements [58-59]. The liver injury resembled autoimmune hepatitis, likely triggered by the plant's immune-enhancing properties, which may provoke or unmask latent autoimmune liver disease. Although initial concerns attributed these cases to adulteration with *Tinospora crispa*, advanced DNA barcoding and chromatographic analyses confirmed *T. cordifolia* as the true source. Subsequent nationwide data from the LIVERECI network reinforced its hepatotoxic potential. Histopathological features commonly include interface hepatitis, hepatocyte rosettes, and lymphoplasmacytic infiltration. While most patients improve after drug withdrawal and corticosteroid therapy, rare cases of acute liver failure or fatal outcomes emphasize the need for strict regulatory monitoring and clinical caution in the use of Giloy-based herbal preparations [60-61].

Garcinia cambogia (Malabar Tamarind)

Garcinia cambogia Desr., commonly referred to as Malabar tamarind, is a tropical fruit-bearing plant indigenous to South and Southeast Asia. Traditionally, it has been incorporated in Ayurvedic medicine for the management of constipation, rheumatic ailments, and intestinal parasitic infections, and more recently, as a weight-reduction supplement due to its proposed appetite-suppressing properties. The fruit is also widely used as a culinary flavoring agent and natural preservative. The major bioactive compound identified in G. cambogia is hydroxycitric acid (HCA), which has demonstrated in preclinical studies the ability to inhibit fatty acid synthesis, suppress appetite, reduce lipogenesis, and promote fat oxidation. These effects have fueled its marketing as a "natural" slimming aid. However, despite its popularity, robust clinical evidence confirming its efficacy and safety in humans remains limited [62]. Recent pharmacovigilance data and clinical case reports have increasingly linked G. cambogia consumption to drug-induced liver injury (DILI), either when taken as a single-ingredient extract or as part of multi-herbal weight-loss formulations. The hepatotoxic reaction appears idiosyncratic, with symptom onset reported between 2 and 150 days, typically within 1 to 4 weeks of ingestion [63]. Documented cases reveal that hepatotoxicity may occur across varying doses, although acute liver failure has been most often observed with daily doses around 2000 mg taken over shorter durations. Histopathological findings in affected patients have shown acute hepatocellular and cholestatic hepatitis, frequently accompanied by confluent or submassive necrosis, and in severe cases, giant cell transformation. Clinical outcomes have ranged from complete recovery upon discontinuation to fulminant hepatic failure, necessitating liver transplantation or resulting in death [64].

Pyrrolizidine alkaloid (PA)-containing herbs

Herbal plants containing pyrrolizidine alkaloids (PAs) include species such as Heliotropium, Trichodesma, Crotalaria (commonly utilized in Ayurveda), Chelidonium majus, Holarrhena, and Castilleja. These compounds are nitrogenous secondary metabolites derived from the amino acid ornithine and typically exist as esters formed between a necine base (amino alcohol) and one or more necic acids (mono- or aliphatic dicarboxylic acids). After ingestion, PAs are metabolized into dehydropyrrolizidine alkaloids (DHPAs), which are highly reactive intermediates. These metabolites can bind with sulfur, nitrogen, and oxygen atoms in cellular macromolecules, creating adducts that enter the nucleus and interact with DNA. This leads to genotoxicity, disruption of cellular function, and hepatocellular injury. The damage often extends into the space of Disse and sinusoidal regions, resulting in endothelial injury that can manifest as hepatic sinusoidal obstruction syndrome (HSOS). HSOS may further develop into acute or chronic liver failure, occasionally requiring transplantation or progressing to cirrhosis and portal hypertension. Additionally, DHPAs may circulate to the lungs, causing pulmonary vascular injury that contributes to secondary pulmonary hypertension and heart failure over time [65]. A metabolite known as tricodesmine exhibits neurotoxic effects, producing symptoms such as encephalitis, vertigo, stupor, and coma. Numerous reports from Africa and the Indian subcontinent have associated PA-containing herbal teas and traditional medicinal preparations with outbreaks of HSOS [66-67]. Accidental contamination of herbal products with PA-rich plants is also a documented cause of liver injury. Cases from India have linked honey contaminated with Crotalaria juncea pollen to PA-induced hepatotoxicity. Similarly, Holarrhena antidysenterica ("kutaja"), traditionally used in Ayurveda to manage diabetes, indigestion, hemorrhoids, and parasitic infections, has been implicated in HSOS. Experimental studies in animal models have shown hepatic damage, including sinusoidal congestion, hemorrhage, and centrilobular necrosis, consistent with PA-mediated hepatotoxicity [68].

Valeriana officinalis

Valeriana officinalis, commonly known as Valerian, is a perennial flowering herb indigenous to Europe and Asia. Its name originates from the Latin term valere, meaning "to be strong or healthy." The plant's root extract is composed of several active phytochemicals, including actinidine alkaloid, valerianine, valerene, and gamma-aminobutyric acid (GABA). Traditionally, Valerian has been employed in Ayurvedic and herbal medicine as a sedative and anxiolytic agent. Although its calming properties are widely recognized, the exact pharmacological mechanism remains uncertain. Experimental findings suggest that valerenic acid may act through the 5-HT5A serotonin receptor to influence the sleep-wake cycle, but valeric acid and other root-derived compounds alone have not demonstrated significant sedative

effects in laboratory models [69]. Cases of Valerian toxicity are rare. Reported overdoses have resulted only in mild and transient symptoms, typically resolving within 24 hours. Nonetheless, a few instances of Valerian-related liver injury have been described. The first such cases were reported in 1989, involving individuals who consumed herbal sleep aids containing Valerian along with other botanicals such as Chinese skullcap-another herb suspected of hepatotoxicity [70]. Later reports described patients who developed acute hepatitis or cholestatic jaundice after prolonged Valerian consumption [71]. Liver biopsies often revealed mild portal fibrosis, lymphocytic and eosinophilic infiltration, and perivenular necrosis, all of which subsided with conservative therapy [72]. The Berlin Case-Control Surveillance Program also identified several patients with probable Valerian-induced liver injury, primarily of hepatocellular or cholestatic type. Histological findings included extensive necrosis and mixed portal-lobular inflammation. Fortunately, all affected individuals showed gradual recovery following cessation of Valerian use. Although hepatotoxicity remains a rare adverse event, these cases highlight the importance of cautious use and monitoring of Valerian-based herbal supplements [73].

Conclusion

Herb induced liver injury represents a growing clinical and public health challenge worldwide. Although modern medicines are recognized causes of hepatotoxicity, the widespread use of herbal remedies has significantly contributed to the rising incidence of liver injury. Many herbal products, despite being labeled as natural, contain bioactive compounds capable of inducing immune-mediated or idiosyncratic hepatic damage. The absence of regulatory standardization, inadequate clinical validation, and potential adulteration further heighten the risk. Timely identification, comprehensive patient evaluation, and exclusion of other etiologies remain essential for diagnosis and management. Enhancing pharmacovigilance, encouraging evidence-based practice, and promoting awareness among clinicians and consumers are crucial steps toward minimizing hepatotoxic risk and ensuring the safe use of both herbal and conventional therapies.

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