

Review

Hepatotoxicity of Herbal and Dietary Supplements a Review of Diagnosis, Histologic Features, and Common Culprits: Bodybuilding and Weight Loss Supplements

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Abstract

Herbal and dietary supplements (HDS) are used by over half of American adults and represent a multi-billion-dollar industry. More recently, they have gained popularity, in part due to promotion on multiple social media platforms. However, the Food and Drug Administration (FDA) does not regulate these products rigorously, and up to 20% of acute liver injuries are attributed to HDS. The true incidence of HDS hepatotoxicity is unknown but thought to be underreported. According to the World Health Organization (WHO), HDS-induced liver injuries are now the fifth most common cause of liver disease-associated death. The most common type of supplements associated with liver injury are bodybuilding and weight loss supplements. This study represents a comprehensive literature review of HDS-induced liver injury with a focus on the two most common culprits: bodybuilding supplements and weight loss supplements. Future strategies recommended to mitigate hepatotoxicity include strengthening regulatory oversight through mandatory product listing, enhancing post-market surveillance with standardized reporting and registries, improving product quality via ingredient verification and contaminant testing and, possibly, implementing standardized risk labeling.

Keywords: drug-induced liver injury; literature review; body building supplements; SARMs



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1. Introduction

Drug-induced liver injury (DILI) refers to liver damage resulting from exposure to prescription medications, over-the-counter (OTC) drugs, herbal and dietary supplements (HDS), or other hepatotoxic substances. HDS encompass a wide range of products, including vitamins, minerals, dietary elements, food components, natural herbs, and synthetic herbal formulations. These are commonly used as complementary or alternative therapies for disease prevention or treatment, dietary supplementation, performance enhancement, physical fitness, weight loss, or general wellness. Typically, HDS are obtained without a prescription through pharmacies, online vendors, or mail-order services and are often consumed without medical supervision or monitoring [1]. When vitamin preparations are taken into account, over half of American adults report using dietary supplements, contributing to a market valued at approximately \$50 billion annually. While most individuals use these products for general wellness, approximately 40% report using them to manage specific health conditions. Due to their “natural” labeling, HDS are perceived as safe and effective, despite the lack of regulatory oversight. Importantly, HDS are not classified as drugs and, by definition, are not intended to diagnose, treat, cure, or prevent disease [2].

In the US, the Dietary Supplement Health and Education Act (DSHEA) of 1994 governs the definition and regulation of dietary supplements [3]. DSHEA regulates HDS as food products, and they are exempt from the rigorous safety and efficacy requirements imposed on pharmaceuticals. Manufacturers are not mandated to demonstrate product safety or therapeutic benefit before marketing. Although the Good Manufacturing Practices (GMP) of 2007 mandate accurate labeling, quality control, and safety assurance, numerous products list “proprietary formulas” to obscure ingredient disclosure, and even when ingredients are listed, dosages are frequently omitted. A 2019 DILIN study using high-performance liquid chromatography found that 51% of the 272 HDS products analyzed were mislabeled [4]. The FDA estimates that approximately 50,000 adverse events related to HDS occur every year, with liver and kidney injuries being the most commonly reported [5].

Between 2004 and 2013, the FDA received over four hundred New Dietary Ingredient (NDI) applications for novel botanical products [6]. During this period, several weight loss supplements—including usnic acid, OxyELITE Pro, and Hydroxycut—were issued FDA warnings due to hepatotoxicity concerns [7]. More recently, flavocoxid-containing products (e.g., *Limbrel*), composed of plant-derived flavonoids, were withdrawn from the market following reports of severe liver injury [6].

Data from the Drug-Induced Liver Injury Network (DILIN), a multicenter U.S. research initiative, revealed a significant increase in HDS-related liver injury cases—from 7% in 2004–2005 to 20% in 2013–2014 [1]. Between 2004 and 2019, 369 cases of HDS-induced liver injury were enrolled in the DILIN study, accounting for 19% of all DILI cases [8]. Similar trends have been reported in other Western registries, while the prevalence of HDS-related hepatotoxicity is notably higher in parts of Asia, comprising 70% of DILI cases in Korea and Singapore, and 40% in China [9].

Any adverse events may be reported by manufacturers or submitted directly by health-care professionals and consumers through MedWatch, the FDA’s safety reporting system. Based on these reports, the FDA may issue warnings or recommend product withdrawal when necessary [9]. Notably, the number of publications on herbal hepatotoxicity doubled between 2006 and 2016. This increase parallels the rise in HDS sales and consumption in the United States [6].

According to the World Health Organization (WHO), DILI is now recognized as the fifth leading cause of liver disease-related mortality worldwide [9].

The real incidence of hepatotoxicity associated with HDS is most likely underreported. Current estimates suggest that fewer than 1% of adverse reactions to HDS are formally documented [5]. Furthermore, data from the 2002 National Health Interview Survey indicate that only 33% of HDS users disclose their supplement consumption to healthcare providers [10]. These low disclosure rates, coupled with the increasing prevalence of HDS use among the general population, have raised significant concerns among regulatory agencies regarding the potential toxicological risks of HDS, including herbal-induced liver injury (HILI) [11]. To address this issue, the National Institutes of Health (NIH) has developed *LiverTox*, a searchable database cataloging drugs, herbal products, and dietary supplements associated with hepatotoxicity [5].

In this review, we present an overview of the classification and diagnostic criteria for drug-induced and herb-induced liver injury (DILI/HILI). We also provide an in-depth discussion of the two most prevalent forms of HILI, which are associated with the consumption of bodybuilding and weight loss supplements.

2. DILI Classification

DILI can be classified into two broad categories: *intrinsic* (due to drugs that may cause predictable, dose-dependent liver injury, acetaminophen being the most common) and

idiosyncratic (unpredictable, not dose-dependent reaction to drugs in susceptible individuals) [12]. As with DILI from conventional pharmaceuticals, most cases of HDS-induced liver injury are idiosyncratic rather than intrinsic reactions (as seen with acetaminophen, probably the most common dose-dependent, predictable DILI). DILI is a great imitator of other liver diseases; therefore, hepatotoxicity due to drugs, HDS, and toxins remains largely a clinical diagnosis based on meticulous history taking and exclusion of other causes of liver injury [13].

3. Herbal and Dietary Supplements (HDS) Classification

HDS can be broadly categorized into three main groups: (1) bodybuilding supplements, including anabolic steroids and nonsteroidal performance enhancers; (2) multi-ingredient formulations aimed at weight loss, immune support, mood enhancement, and energy boosting; and (3) herbal products, such as traditional botanical preparations used in Chinese or Ayurvedic medicine [14].

According to data from the DILIN Prospective Study, the most frequently observed cases of HDS-induced liver injury (HILI) are associated with performance-enhancing and bodybuilding supplements in men, and weight loss supplements in women. Other implicated categories include products marketed for mood disorders (e.g., depression and anxiety), immune support, sexual performance, joint health, and traditional Chinese herbs, as well as various miscellaneous supplements [1]. (Figure 1).

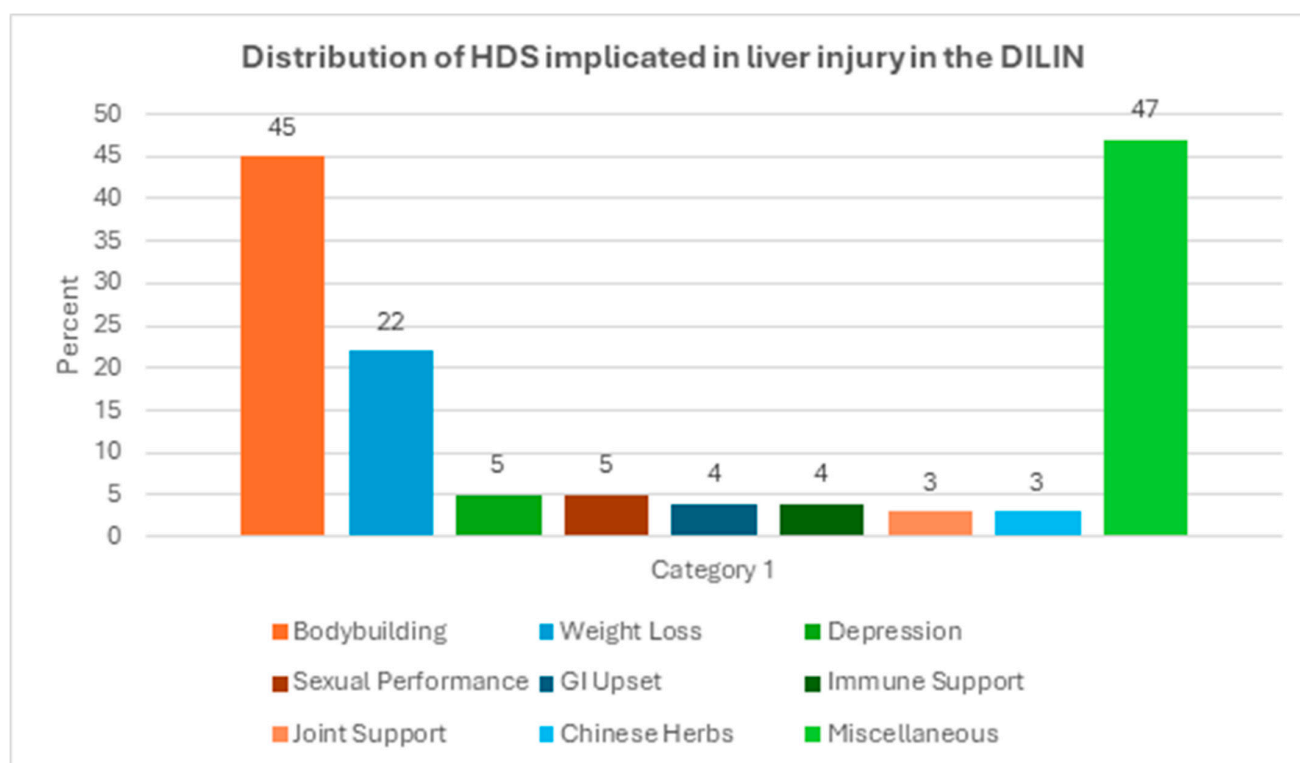


Figure 1. Distribution of HDS implicated in liver injury in the Drug Induced Liver Injury Network. Adapted from [15].

Currently, most HDS-associated liver injuries are linked to multi-ingredient nutritional supplements. In most instances, the specific component responsible for hepatotoxicity remains unidentified or can only be suspected. It is important to note that, because supplements are not required to demonstrate efficacy to support their label claims, the majority of these products lack robust clinical evidence. Instead, they rely heavily on

persuasive marketing language, which may mislead consumers regarding their safety and effectiveness. This underscores the need for heightened scrutiny and regulatory reform to ensure consumer protection and product transparency.

4. Mechanisms of Liver Injury Induced by Drugs and Herbal Supplements

Most cases of drug-induced liver injury (DILI) and herb-induced liver injury (HILI) are idiosyncratic, meaning they result from an individual's unique genetic, metabolic, and immunologic characteristics rather than from predictable, dose-dependent toxicity. The mechanisms of hepatocyte injury in drug-induced liver injury (DILI) are complex and often involve a combination of metabolic, immunologic, and genetic factors that contribute to both acute and chronic forms of liver damage through distinct yet overlapping pathways. Based on current clinical and experimental evidence [16], primary mechanisms include the following:

4.1. Formation of Reactive Metabolites

Many drugs are metabolized in the liver by cytochrome P450 enzymes. Some of these metabolic pathways produce reactive intermediates that can bind covalently to cellular proteins, lipids, or DNA, leading to direct hepatocyte damage or triggering immune responses.

4.2. Mitochondrial Dysfunction

Mitochondria are central to hepatocyte energy metabolism. Certain drugs impair mitochondrial function by inhibiting mitochondrial DNA replication or respiratory chain enzymes, inducing mitochondrial permeability transition (MPT), or causing ATP depletion. These effects can lead to oxidative stress, apoptosis, or necrosis.

4.3. Oxidative Stress

An imbalance between reactive oxygen species (ROS) production and antioxidant defenses can damage cellular components. This is a common mechanism in herbal and dietary supplements (HDS)-induced liver injury, as seen with agents like green tea extract and usnic acid.

4.4. Immune-Mediated Injury

Some drugs or their metabolites act as haptens, binding to liver proteins and forming neoantigens that trigger adaptive immune responses. This can result in autoimmune-like hepatitis, often with eosinophilia or other hypersensitivity features.

4.5. Disruption of Bile Salt Transport

Certain drugs inhibit bile salt export pumps (BSEP) or other transporters, leading to cholestasis and accumulation of toxic bile acids within hepatocytes.

4.6. Endoplasmic Reticulum (ER) Stress

Drugs that interfere with protein folding or trafficking can induce ER stress, activating the unfolded protein response (UPR) and potentially leading to apoptosis.

4.7. Genetic Susceptibility and Polymorphisms

Individual genetic differences, such as polymorphisms in drug-metabolizing enzymes (e.g., CYP450 isoforms, NAT2, UGTs), transporters (e.g., ABCB11, ABCC2), or immune response genes (HLA alleles), have been shown to influence susceptibility to DILI by

altering metabolism, promoting formation of toxic metabolites, or modulating immune reactivity, thereby contributing to variable clinical outcomes [17].

4.8. Disruption of Lipid Metabolism

Certain drugs can interfere with hepatic lipid homeostasis, leading to increased steatosis (fat accumulation in hepatocytes). This can progress to metabolic dysfunction-associated steatotic liver disease (MASLD), a condition marked by lipotoxicity, oxidative stress, and inflammation. MASLD may evolve into steatohepatitis, fibrosis, or even hepatocellular carcinoma. Mechanistically, this involves enhanced de novo lipogenesis, impaired fatty acid oxidation, and dysregulated lipid export, often exacerbated by mitochondrial dysfunction and transcriptional changes [18,19]. Drug-induced steatohepatitis (DISH) represents a more severe clinical entity, characterized by a poorer prognosis and outcomes. It closely mimics metabolic-associated steatohepatitis (MASH), as it is likewise marked by hepatic inflammation and, in some cases, fibrosis [19].

Oxidative stress is the most frequently reported mechanism of HDS-induced hepatotoxicity. This has been demonstrated in studies involving several commonly used supplements, including kava, green tea extracts, usnic acid, greater celandine, chaparral, and black cohosh.

In clinical practice, HDS–drug interactions are also of significant concern. Many healthcare providers and patients remain unaware of the hepatotoxic risks associated with these interactions. Certain HDS can induce or inhibit cytochrome P450 (CYP) enzymes, thereby altering the absorption, distribution, metabolism, and excretion (ADME) of co-administered drugs. These pharmacokinetic changes may predispose individuals to liver injury [6].

5. Clinical Diagnosis of Drug and Herbal-Induced Hepatic Injury

Diagnosing DILI and HILI is particularly challenging due to their ability to mimic virtually any liver disease, their variable histologic patterns, and their overall rarity. HILI, like DILI, is a diagnosis of exclusion. The keys to diagnosing drug and HDS liver injury include [20,21] the following:

- Temporal association: exposure to the suspected agent must precede the onset of liver injury, though latency periods can vary widely.
- Exclusion of alternative causes: common liver diseases (e.g., viral hepatitis, autoimmune hepatitis, biliary disorders, genetic conditions) must be ruled out.
- De-challenge: liver injury typically improves upon discontinuation of the possible offending supplement or drug.
- Rechallenge: a second exposure could lead to a more rapid and pronounced liver injury.

The Roussel Uclaf Causality Assessment Method (RUCAM), developed in 1993 by the Council for International Organizations of Medical Sciences (CIOMS), is the most widely used tool for objectively assessing the likelihood that a drug or supplement caused liver injury [22–24]. The RUCAM system assigns points based on clinical signs, lab results, serologic tests, and imaging findings related to liver injury. These points are combined into a total score that estimates how likely it is that a specific medication caused the liver damage [24].

RUCAM is now a widely accepted tool for evaluating the causality of drug-induced and herb-induced liver injury (DILI/HILI). It is frequently cited in scientific literature and used to support regulatory decisions involving medications suspected of causing liver damage. The scoring system includes eight distinct elements grouped into seven categories, each contributing to a comprehensive profile—or “signature”—of the liver injury (Table 1).

When applied correctly, the final scores should show minimal variation between different evaluators. These elements are as follows:

- (1) time to onset (+1 or +2).
- (2) course (−2, 0, +1, +2, or +3).
- (3) risk factors (2 scores: 0 or +1 each).
- (4) concomitant drugs (0, −1, −2, or −3).
- (5) nondrug causes of liver injury (−3, −2, 0, +1, or +2).
- (6) previous information on the hepatotoxicity of the drug (0, +1, or +2); and
- (7) response to rechallenge (−2, 0, +1, or +3).

Table 1. Causality by Roussel Uclaf Causality Assessment Method/Council for International Organizations of Medical Sciences score (RUCAM/CIOMS).

Drug: _____	Initial ALT: _____	Initial ALP: _____	R Ratio = [ALT/ULN] ÷ [Alk P/ULN]: _____		
Injury type	Hepatocellular (R > 5)		Cholestatic (R < 2) or mixed (R= 2–5)		Assessment
1. Time to onset	Initial treatment	Subsequent treatment	Initial treatment	Subsequent treatment	Score
From the beginning of the drug:					
-suggestive of DILI	5–90 days	1–15 days	5–90 days	1–90 days	+2
-compatible with DILI	<5 or >90 days	>15 days	<5 or >90 days	>90 days	+1
From cessation of the drug:					
-compatible	<15 days	<15 days	<30 days	<30 days	+1
Note: If reaction begins before starting the medication, or >15 days after stopping (hepatocellular), or >30 days (cholestatic), the injury should be considered unrelated to medication and RUCAM score cannot be calculated.					
2. Clinical course after stopping the drug	Change in ALT between peak value and ULN		Change in ALP between peak value and ULN		Score
-highly suggestive of DILI	Decrease > 50% within 8 days		Not applicable		+3
-suggestive of DILI	Decrease > 50% within 30 days		Decrease > 50% within 180 days		+2
-compatible with DILI	Not applicable		Decrease < 50% within 180 days		+1
-inconclusive of DILI	No information, or decrease >50% after 30 days		Persistence; or increase; or no information		0
-not DILI	Decrease <50% after 30 days OR recurrent increase		Not applicable		–2
Note: If drug is continued, RUCAM score cannot be calculated.					
3. Risk factors	Alcohol		Alcohol or pregnancy		Score
Alcohol or pregnancy	Yes		Yes		+1
	No		No		0
Age	>55		>55		+1
	<55		<55		0
The interpretation of the final score: 0 or less indicate that the drug is “excluded” as a cause; 1 to 2 that it is “unlikely”; 3–5 “possible”; 6–8 “probable”; and >8, “highly probable”. When comparing RUCAM to other causality assessment instruments, other terms are sometimes used for “highly probable”, including “highly likely” and “definite.”					

The total score ranges from −9 to +14, though in most clinical scenarios—where rechallenge is avoided and certain risk factors are absent (like alcohol abuse, pregnancy, or age above 55 years)—the practical scoring range is narrower (e.g., −7 to +9). Interpretation of the final score is as follows:

- ≤0: Excluded

- 1–2: Unlikely
- 3–5: Possible
- 6–8: Probable
- 8: Highly probable

In cases of cholestatic or mixed liver injury, the scoring range for the clinical course is narrower—limited to 0 to +2 instead of the broader −2 to +3 range seen in hepatocellular injury. Consequently, when factors like rechallenge, alcohol use, pregnancy, or age over 55 are absent, the total RUCAM score can only span from −5 to +8. This restricted range often results in cases being classified as “probable” rather than “highly probable.” [25].

Evaluation of liver injury typically begins with a review of serum liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), 5'-nucleotidase, total and direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, prothrombin time (PT), international normalized ratio (INR), lactate dehydrogenase (LDH), total protein, globulins, and albumin. These parameters help characterize the pattern and severity of hepatic injury.

A hepatocellular pattern is indicated by elevations in ALT and AST that are disproportionately higher than ALP and bilirubin levels. In contrast, a cholestatic pattern is characterized by elevations in ALP and bilirubin that exceed those of ALT and AST. A mixed pattern involves concurrent elevations in both transaminases and ALP. Isolated hyperbilirubinemia refers to elevated bilirubin levels with normal ALT, AST, and ALP.

To further classify the pattern of liver injury, the R ratio is commonly used [26]. It is calculated as

$R = (ALT/ALT_ULN) \div (ALP/ALP_ULN)$, where ULN denotes the upper limit of normal. An R ratio >5 suggests a hepatocellular pattern, <2 indicates cholestatic injury, and a ratio between 2 and 5 is consistent with a mixed pattern.

In general, cholestatic injury is more frequently observed in older adults and typically presents with jaundice, pruritus, elevated ALP, and only mild transaminase elevations. This form of injury is rarely life-threatening. In contrast, hepatocellular injury is more common in younger individuals and is associated with systemic symptoms such as malaise, abdominal pain, and jaundice. Approximately 10% of hepatocellular cases may progress to acute liver failure, necessitating hospitalization, intensive management and possibly liver transplant.

6. Histological Diagnosis and Morphological Patterns of Drug and Herbal-Induced Hepatic Injury

Drug-induced liver injury can present histologically with either cholestatic, hepatocellular or mixed patterns, and rarely as steatosis or drug-induced steatohepatitis (DISH).

6.1. Cholestatic Injury

There are three morphologic types of cholestatic injury:

(a). Bland (simple) cholestasis. Histologically, the hepatic lobules show cholestasis within hepatocytes and dilated canaliculi, predominantly in zone 3 (perivenular), with occasional hepatocyte rosettes. The portal tracts and lobules show no, or only minimal inflammation, predominantly lymphocytes, and no obvious bile duct damage (Figure 2).

(b). Cholestasis with inflammation (cholestatic hepatitis). This pattern is the most common pattern of drug-induced liver injury. Cholestasis is accompanied by hepatocellular damage and necrosis. The portal tracts are expanded by a mixed inflammatory infiltrate composed of lymphocytes, numerous eosinophils, occasionally neutrophils. Proliferation of cholangioles is present, sometimes with a neutrophilic infiltrate (Figure 3A). Lobular inflammation can be present, predominantly lymphocytic admixed with foamy histiocytes (Figure 3B). In severe cases, perivenular necrosis and hepatocytic dropout and numerous

ceroid laden macrophages may be present. Confluent/bridging necrosis can be seen in severe cases. Cholestasis is usually around the central veins, but in severe cases it can extend into the mid-zones and even periportal (Figure 3C). Numerous bile plugs can be seen (Figure 3D).

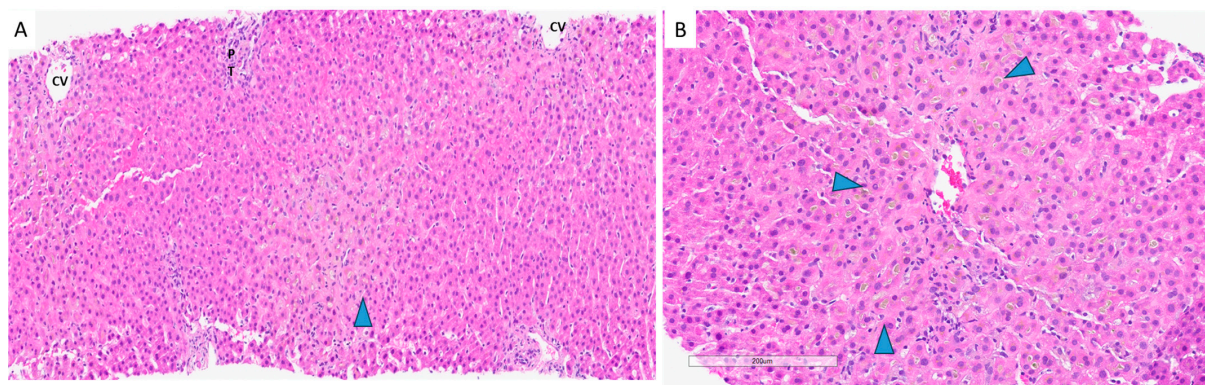


Figure 2. Simple cholestasis pattern. (A). Portal tracts are unremarkable, with no inflammation or bile duct injury. Centrivenuar and mid zonal canalicular cholestasis (arrow heads). Hematoxylin and eosin, 4×. (B). Marked canalicular cholestasis around central veins (arrow heads). Hematoxylin and eosin, 10×. CV, central veins; PT, portal tracts.

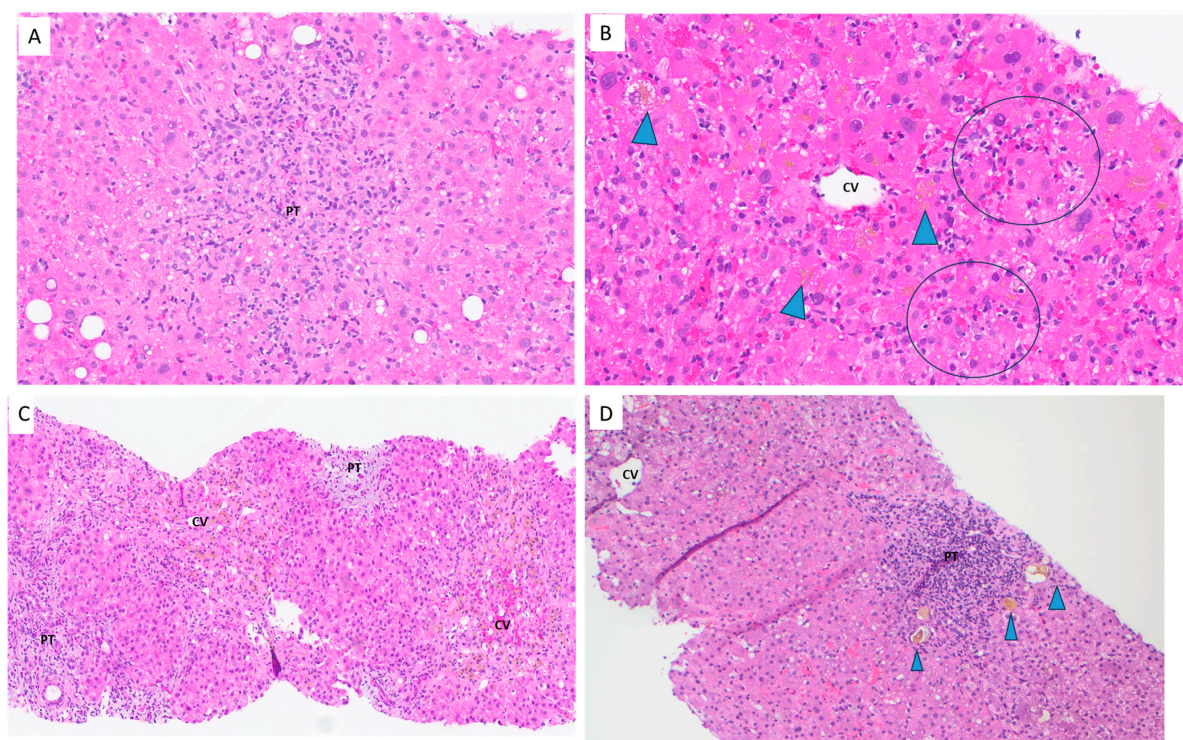


Figure 3. Cholestatic hepatitis. (A). Portal inflammation, composed of neutrophils and eosinophils, with rare plasma cells and lymphocytes. Proliferation of cholangioles is noted, associated with neutrophilic infiltrate (acute cholangiolitis). Hematoxylin and eosin, 10×. (B). Mild lobular inflammation can be present, composed of lymphocytes and histiocytes (circles). Around the central veins there is abundant intracellular cholestasis present, green-yellow in color (arrow heads). Hematoxylin and eosin, 10×. (C). The portal tracts show mixed inflammatory infiltrate, including abundant eosinophils, lymphocytes and rare plasma cells, with associated bile ductular proliferation. Around the central veins there is marked hepatocellular dropout, with abundant histiocytes and cholestasis. Hematoxylin and eosin, 10×. (D). Portal inflammation, predominantly lymphocytic, with rare eosinophils with numerous canalicular bile plugs in the periportal areas (arrowheads). The perivenular areas show mild hepatocytic dropout and histiocytes. Hematoxylin and eosin, 4×. CV, central veins; PT, portal tracts.

(c). Chronic cholestasis and vanishing bile duct syndrome. In early stages, the bile ducts show severe epithelial injury, with nuclear hyperchromasia, anisonucleosis and vacuolated cytoplasm. Numerous neutrophils and eosinophils are seen in the portal tracts. Later in the disease, the portal tracts develop ductopenia (vanishing bile duct syndrome), with ductular proliferation and persistent inflammation. Cholate stasis is usually present (feathery degeneration of periportal hepatocytes, copper deposition and xanthomatous transformation or Kupffer cells). This pattern is less present with HDS-induced injury and is more common with prescription medications.

6.2. Hepatocellular Injury

Hepatocellular injury is usually a consequence of an intrinsic type of hepatotoxicity and is characterized by damage to hepatocytes, either acute or chronic.

(a). Acute hepatocellular injury can be in the form of individual cell necrosis (apoptotic hepatocytes), zonal coagulative type necrosis, especially perivenular (acinar zone 3), *bridging* necrosis, occasionally showing necro-inflammatory bridges from central veins to portal tracts (Figure 4), and the most severe form, submassive/massive necrosis. Portal tracts usually remain normal and even with the most severe/submassive necrosis, there is usually a rim of surviving hepatocytes in zone 1 (periportal). Clusters of Kupffer cells filled with PAS-positive ceroid pigment are usually present in the necrotic areas. The differential diagnosis includes ischemia, viral hepatitis (hepatitis A, B, C and D) or acute hepatitis due to known hepatotropic viruses (herpes). Viral hepatitis can be ruled out by serology.

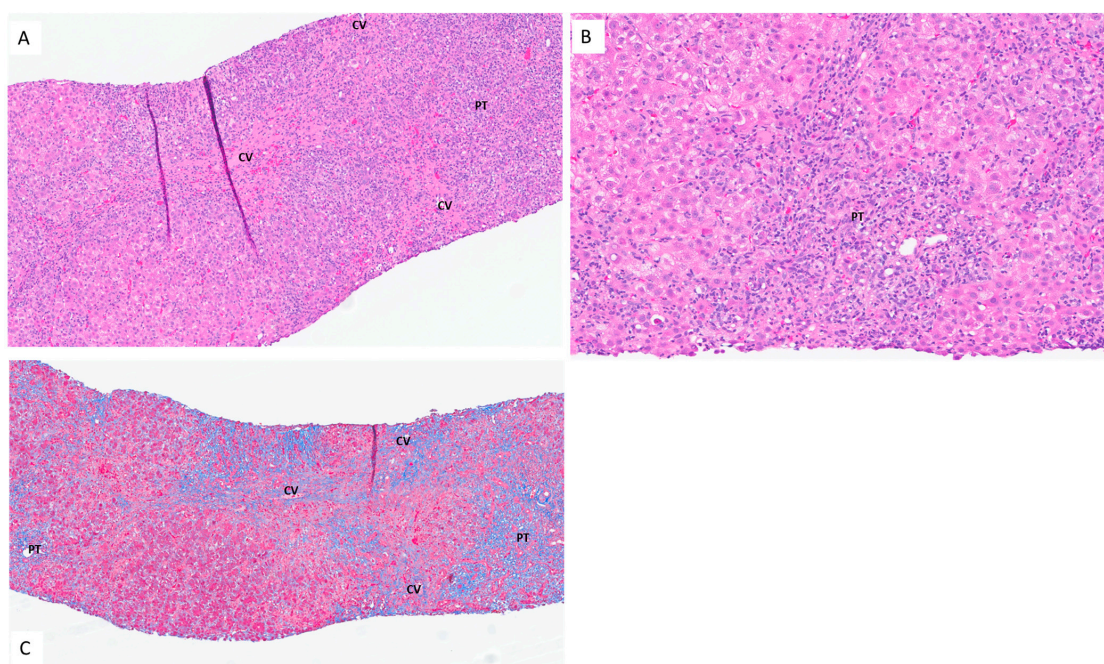


Figure 4. Acute hepatocellular injury with bridging necrosis. (A). Marked portal and lobular inflammation and bridging necroinflammatory activity, extending from central vein to central vein and central vein to portal tracts. Hematoxylin and eosin, 5 $\times$. (B). Portal tracts are expanded by a mixed inflammatory infiltrate, including lymphocytes, neutrophils, eosinophils, and occasional plasma cells. Marked bile ductular proliferation is present, occasionally with neutrophilic infiltrate. Hematoxylin and eosin, 10 $\times$. (C). Trichrome stain highlights early collagen deposition in the necroinflammatory bridges (light blue), with no established fibrosis. Masson trichrome stain, 6 $\times$.

(b) Chronic hepatocellular injury. Evolution of drug hepatotoxicity to chronic liver disease is relatively uncommon and usually requires prolonged or repeated exposure to the agent. Chronic hepatocellular injury is indistinguishable from chronic hepatitis from

other causes, such as viral hepatitis or autoimmune hepatitis. The presence or absence of eosinophils in the portal tracts has not proved reliable in indicating whether a chronic autoimmune hepatitis has an underlying drug etiology. Another type of chronic pattern of hepatocellular injury seen with drugs is granulomatous hepatitis. Unexplained epithelioid granulomata can also be seen with a cholestatic pattern of injury. Small collections of Kupffer cells (micro granulomata) are nonspecific and should not be interpreted as true granulomata. The classes of drugs most often implicated in granulomatous hepatitis include antihypertensive, antibiotics and anti-inflammatory / antirheumatic drugs. Another type of granulomata, fibrin ring granulomas have been described in allopurinol toxicity.

6.3. Steatosis and/or Steatohepatitis Due to Drug-Induced Liver Injury

Fatty change due to DILI can present with microvesicular or macrovesicular fat droplets in hepatocytes. The microvesicular steatosis is diffuse, involving all hepatocytes, which show multiple small lipid vacuoles and a central nucleus. Macrovesicular steatosis is characterized by a single large lipid vacuole which displaces the nucleus. Steatosis may be accompanied by mild lobular inflammation and occasionally by mild perivenular cholestasis and hepatocytic dropout. (Figure 5).

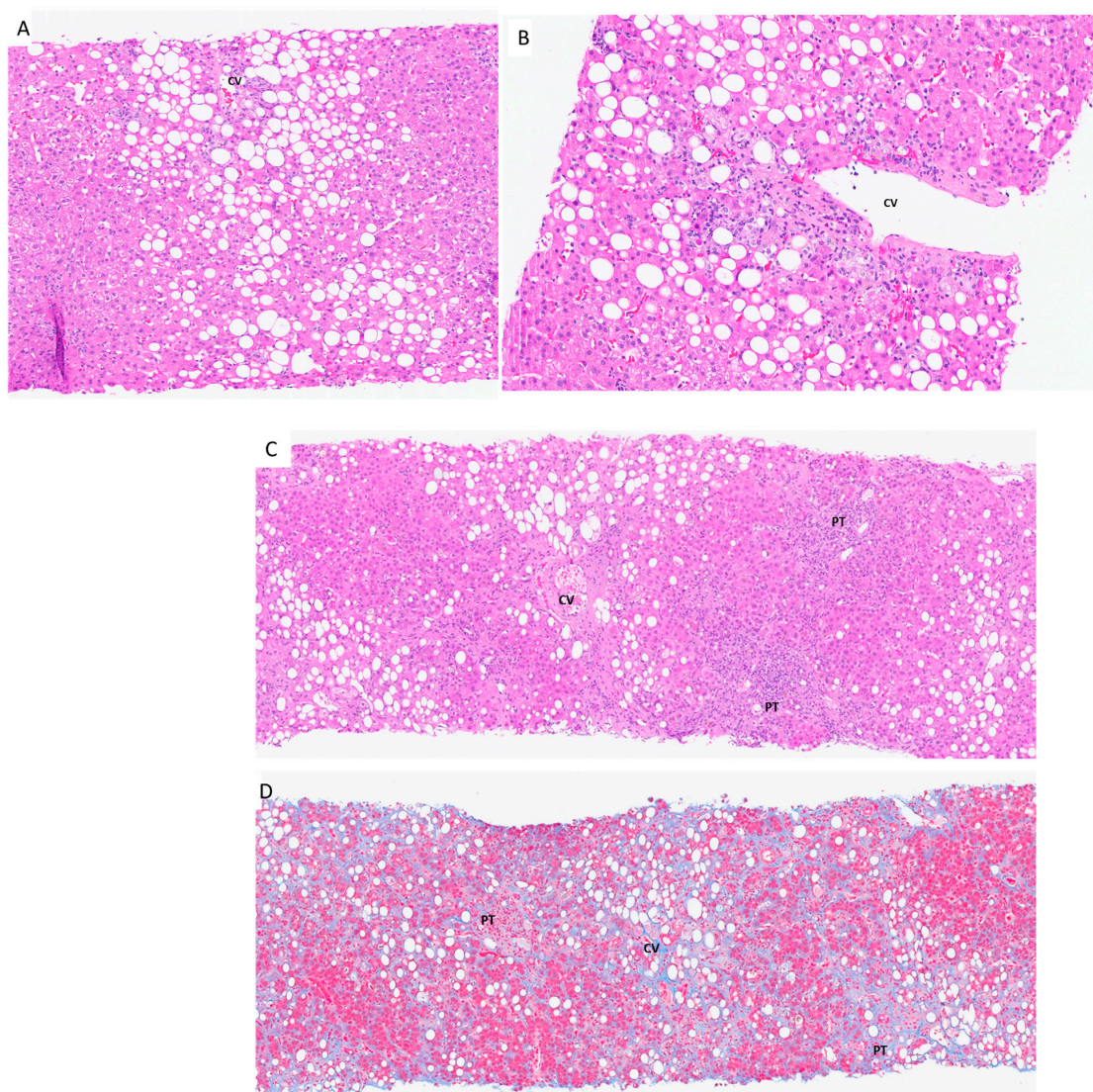


Figure 5. Steatotic pattern Macrovesicular steatosis is present around zone 3 and extending into the mid zones. Around the central veins there is hepatocytic dropout, with numerous histiocytes and

rare eosinophils. Minimal intracellular cholestasis is also present. (A). Hematoxylin and eosin, 4×. (B). Hematoxylin and eosin, 10×. Steatotic pattern associated with cholestasis. Patient was taking GOLO, a weight loss supplement. (C). Lobular and canalicular cholestasis with associated and hepatocyte apoptosis. Lobular inflammation with neutrophilic aggregates and histiocytes. Portal inflammation with lymphocytes, histiocytes and plasma cells and rare eosinophils. Moderate macrovesicular steatosis with patchy hepatocyte ballooning with rare Mallory–Denk bodies are also seen. Hematoxylin and eosin, 6.3× (D). Mild periportal and pericellular fibrosis in a “chicken wire” pattern. Masson trichrome stain, 6.3×. CV, central veins; PT, portal tracts.

7. Hepatotoxicity Due to Bodybuilding Supplements: Selective Androgen Receptor Modulators (SARMs)

Selective androgen receptor modulators (SARMs) are synthetic agents that have gained popularity in bodybuilding for their ability to promote muscle growth and increase bone density, while reportedly producing fewer androgenic side effects than traditional anabolic steroids.

Among the most used SARMs are RAD-140 (Testolone or Radarine) and MK-2866 (Ostarine), both of which exhibit high affinity for androgen receptors in skeletal muscle and bone, with reduced activity in reproductive tissues [27]. These agents were at first developed for potential therapeutic use in certain conditions such as sarcopenia, osteoporosis, and cancer-related cachexia [28]. However, their use remains investigational, and they are not approved by the U.S. Food and Drug Administration (FDA) for clinical application. Despite this, SARMs are widely accessible online and over the counter, often marketed as dietary supplements. Due to their performance-enhancing potential and potential misuse by athletes in professional or college-level sports, they were placed on the World Anti-Doping Agency (WADA) prohibited list [29].

RAD-140 (Testolone, Hangzhou Keying Chem Co., Ltd., Hangzhou, China; Radarine, Magnus Pharmaceuticals, Mumbai, India). Several case reports have documented hepatotoxicity associated with RAD-140, typically presenting as a cholestatic pattern of liver injury in otherwise healthy young men [30–32].

MK-2866 (Ostarine, Suzhou Myland Pharm & Nutrition Inc., Suzhou, China), another commonly used SARM, similar to RAD-140, is not approved for human use in the United States or internationally. It is not legally included in any pharmaceutical products or dietary supplements, as noted by the U.S. Anti-Doping Agency’s Supplement 411 High Risk List [33].

MK-677 (Ibutamoren, Suzhou Myland Pharm & Nutrition Inc., Suzhou, China) is a growth hormone secretagogue that stimulates endogenous growth hormone release. Although not classified as a SARM, MK-677 is often marketed alongside them. MK-677 is not approved for human consumption and is prohibited in dietary supplements and commercial products. Despite this, it remains accessible through compounding pharmacies both in the U.S. and internationally. The FDA has issued warning letters to companies illegally marketing products containing MK-677, which are frequently mislabeled as dietary supplements, research chemicals, or marked “For Research Use Only.” [34].

MK-677 has been associated with a range of adverse effects, including congestive heart failure, reduced bone mineral density, elevated fasting glucose, impaired insulin sensitivity, and increased risk of hyperglycemia [35]. Other reported side effects include anxiety, gastrointestinal symptoms, fluid retention, musculoskeletal pain, and increased appetite.

A study analyzing 44 dietary supplements marketed as SARMs found that 39% contained unapproved substances such as MK-677, GW501516 (a PPAR- δ agonist), and SR9009 (a Rev-Erb α agonist) [36]. Mass spectrometric analysis revealed that only 52% of the products contained SARMs, while the remainder were misbranded or adulterated.

The precise mechanism of SARM-induced hepatotoxicity remains unclear but is believed to resemble that of anabolic steroid-related liver injury. It is likely idiosyncratic and may involve immune-mediated pathways.

8. Hepatotoxicity Due to Weight Loss Supplements

Several ingredients commonly found in weight loss supplements have been implicated in liver injury, including green tea extract (GTE), garcinia cambogia, usnic acid, black cohosh, ma huang (*Ephedra sinica*), and multi-ingredient products such as Herbalife, Hydroxycut, and OxyELITE Pro.

Green tea extract (GTE) Green tea extract is derived from the leaves of *Camellia sinensis* and contains high concentrations of catechins, particularly epigallocatechin gallate (EGCG), which is believed to be the primary bioactive compound. While green tea as a beverage is widely consumed and generally considered safe, green tea extract (GTE) supplements—commonly promoted for weight loss and antioxidant benefits—contain significantly higher concentrations of catechins. These concentrated supplements have been linked to hepatocellular injury, particularly at doses exceeding 800 mg or with prolonged use [37,38]. The pattern of injury is predominantly hepatocellular, but mixed and cholestatic injuries have been reported [39]. While liver-related adverse events are rare, cases of acute liver failure requiring transplantation have been reported [40]. A systematic review of randomized controlled trials found that liver-related adverse events from GTE are uncommon; however, isolated cases of acute liver failure requiring transplantation have been reported. The risk appears linked to high-dose GTE supplements rather than traditional green tea consumption or low-dose extracts [19,21,41].

Garcinia cambogia supplement is manufactured by USA NutraLabs and contains hydroxycitric acid (HCA); it is marketed for weight loss by inhibiting fatty acid synthesis and suppressing appetite [42]. A comprehensive analysis that included five systematic reviews and meta-analyses, along with 25 additional clinical trials evaluating dietary supplements such as *Garcinia cambogia* for weight loss, concluded that the overall evidence supporting these products is weak, and none of the reviewed supplements can be recommended for clinical use [43].

Usnic acid (UA), a lichen-derived compound with antimicrobial, antitumor, antioxidant, analgesic, anti-inflammatory bioactivities, was marketed in weight loss products like LipoKinetix. Reports of severe liver injury led to its withdrawal by the FDA in 2001 [44,45].

Black cohosh (*Cimicifuga racemosa*) is a perennial plant native to eastern North America. Its rhizomes and roots are widely used for managing peri- and postmenopausal symptoms. The American College of Obstetricians and Gynecologists notes that it may provide short-term relief (up to 6 months) for vasomotor symptoms of menopause. However, multiple reports have linked its use to hepatotoxicity, and cases of adulteration—particularly with Asian *Cimicifuga* species—have been documented, with autoimmune like hepatitis [46,47], and even case reports of liver failure necessitating transplantation [41,48]. The causal relationship between black cohosh and hepatotoxicity remains uncertain. Subsequent meta-analyses have indicated that the product is both effective and safe [49]. A systematic

review identified 35 clinical studies and one meta-analysis encompassing 43,759 women, including 13,096 who received black cohosh supplements. Compared with placebo, black cohosh demonstrated significant benefits in alleviating neurovegetative and psychological menopausal symptoms, with no evidence of hepatotoxicity [50].

Ma Huang (*Ephedra sinica*), a traditional Chinese herbal remedy, has been used for centuries to treat respiratory conditions, joint pain, edema, and fever, and more recently as a weight-loss aid and central nervous system stimulant. Its active compound, ephedrine, is a potent sympathomimetic agent that can significantly impact the cardiovascular and nervous systems. Adverse effects such as myocardial infarction, stroke, and sudden death have been reported—even within recommended dosing limits and in individuals without preexisting cardiovascular disease. During the 2002–2003 SARS epidemic and the COVID-19 pandemic, *Ephedra sinica* was included in some traditional Chinese medicine protocols [51–53]. However, its use in modern dietary supplements has raised safety concerns, particularly regarding hepatotoxicity. Reports have linked Ma Huang to hepatitis, acute liver failure, and exacerbation of autoimmune hepatitis, with several cases requiring liver transplantation [54,55].

One high-profile product, Metabolife 356 (Metabolife International, Inc., San Diego, CA, USA), which contained *Ephedra sinica*, was investigated by the FDA and the U.S. Government Accountability Office following thousands of adverse event reports. Although early manufacturer-sponsored trials conducted on only 35 people reported only mild side effects (e.g., dry mouth, headache) [56], post-marketing surveillance revealed nearly 15,000 adverse events, including heart attacks, strokes, seizures, and five deaths, prompting its market withdrawal in 2004 [57].

The dangers of ephedra gained national attention after the 2003 death of a professional baseball player using an ephedra-containing supplement (Xenadrine RFA-1, Cytodyne Technologies (Lakewood, NJ, USA)/True North Nutrition Inc. (Richmond Hill, ON, Canada)). A similar incident involving a football player led the NFL to ban ephedra and implement random testing. A 2000 New England Journal of Medicine study documented at least 54 deaths and over 1000 complications linked to ephedra and ephedrine since the mid-1990s, with the FDA later attributing 80 deaths to its use [58].

Herbalife products are marketed globally in various forms, including drinks, capsules, and energy bars, each containing multiple botanicals and nutritional supplements. Some formulations include green tea or aloe vera, though concentrations are often unspecified and appear to have declined in recent years. Due to the complexity of these multi-ingredient products, identifying the specific hepatotoxic agent is challenging. Reported liver injuries are typically mild to moderate, hepatocellular in pattern, and resolve within 1–2 months of discontinuation. However, mixed and cholestatic patterns have also been observed, and the mechanism of toxicity remains unclear [12,59–61].

Hydroxycut, a widely marketed weight-loss supplement called Muscletech Hydroxycut® (Iovate Health Sciences Research, Oakville, ON, Canada), marketed by the manufacturer as a “fat burner”, gained popularity in the early 2000s, with over 9 million units sold in the USA in 2008. Shortly after Hydroxycut® was introduced to the market, the first case of liver injury was reported [62], followed by several additional publications documenting a total of 11 individuals who developed severe hepatotoxicity—all of whom recovered [63–65]. Originally formulated with *Ephedra sinica*, Hydroxycut® was withdrawn in 2004 due to safety concerns. Subsequently, despite reformulation and rebranding as “ephedra-free,” the FDA received 23 reports of liver injury through the MedWatch system, including one case of acute liver failure resulting in death of the patient [65,66].

Although the specific hepatotoxic component remains unidentified, several ingredients—such as *garcinia cambogia*, *Cissus quadrangularis*, caffeine, and green tea extract—have been implicated [65]. The pattern of liver injury is predominantly hepatocellular, though mixed and cholestatic presentations have also been observed. In severe cases, injury has progressed to fulminant liver failure requiring transplantation.

OxyELITE Pro (USPlabs LLC, Dallas, TX, USA) is a proprietary line of multi-ingredient dietary supplements commonly marketed for weight loss, bodybuilding, fat burning, and performance enhancement. Its use has been associated with clinically significant liver injury [67–70]. The original formulation contained DMAA (1,3-dimethylamylamine), an amphetamine derivative, also known as methylhexanamine or geranium extract, which led to weight loss in animal studies, but had been noted to have caused acute liver injury [67,68]. The initial formulation containing DMAA was removed from the market in 2013. The manufacturer changed the formulation and removed DMAA and aegeline, a naturally occurring alkaloid that was believed to cause weight loss, was added. Aegeline is extracted from the fruit *Aegle marmelos* (bael), native to India and Southeast Asia, and is commonly used in Ayurvedic medicine [5]. The manufacturer failed to notify the FDA about the inclusion of aegeline in OxyELITE Pro products [69]. Shortly thereafter, cases of severe hepatitis were reported among individuals consuming “OxyELITE Pro Super Thermogenic,” some of which required emergency liver transplantation, and a few resulted in death [69]. Between 2012 and 2014, the FDA received 114 adverse event reports associated with OxyELITE Pro use; among these, 33 patients (60%) required hospitalization, and three underwent liver transplantation [69]. In response to these reports and an FDA warning letter citing aegeline as an unapproved ingredient lacking safety data, USPlabs initiated a nationwide recall of OxyELITE Pro products in November 2013. The recall followed a public health alert and epidemiological investigations linking the supplement to an outbreak of severe liver injury, particularly in Hawaii, where multiple cases of acute hepatitis and fulminant liver failure were documented [70].

The liver injury pattern associated with OxyELITE Pro use is predominantly hepatocellular. Histologic examination typically reveals an acute hepatitis-like picture, and, in severe cases, confluent, submassive, or massive necrosis may occur, which, if unresolved, necessitates liver transplantation.

A summary of these supplements is included in Table 2.

Table 2. Summary of common body building and weight loss supplements (not a comprehensive list).

Supplement Category	Active Agent	Commercial Name
Body building supplements	RAD-140	Testolone Radarine
	MK-2866	Ostarine
	MK-677	Ibutamoren
Weight loss supplements	Epigallocatechin gallate, from leaves of <i>Camellia sinensis</i>	Metabolife 356, Xenadrine RFA-1, Muscletech Hydroxycut [®] , OxyELITE Pro, NOW Foods GTE 400 mg, Nature's Bounty GTE 315 mg
	hydroxycitric acid (HCA) from a tropical fruit	Garcinia cambogia included in multiple capsules: Pure Garcinia Cambogia Capsules—6in1 with Green Tea, Arjuna, Garlic Bulb, Turmeric & Black Pepper NatureWise Garcinia Cambogia Garcinia Plus
	Usnic acid (UA) from lichen species, including <i>Usnea</i> , <i>Cladonia</i> , and <i>Evernia</i>	LipoKinetix (withdrawn), some deodorants, creams, shampoos, and toothpaste
	<i>Cimicifuga racemosa</i> , perennial plant native to eastern North America	Remifemin[®] (Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany), Nature's Way Black Cohosh, NOW Foods Black Cohosh, Solaray Black Cohosh, Estroven[®] (Amerifit Brands, Inc., Amerifit Brands, Inc., Cromwell, CT, USA), Amberen[®] (Biogix, Inc., El Segundo, CA, USA), Herb Pharm Black Cohosh Liquid Extract, Traditional Medicinals Black Cohosh Tea
	<i>Ephedra sinica</i> /Ma Huang active ingredients Alkaloids (ephedrine and pseudoephedrine)	Metabolife 356 Xenadrine RFA-1 Bayer Herbal Ephedra Ma Huang Tea
	Multi-ingredient: botanicals and nutritional supplements	Herbalife Protein Shakes, Meal Replacements
	Initially <i>Ephedra sinica</i> Others: Garcinia cambogia, <i>Cissus quadrangularis</i> , caffeine, and green tea extract	Muscletech Hydroxycut [®] Hydroxycut [®] Original, Hydroxycut [®] Hardcore, Hydroxycut [®] Max
	Multi-ingredient	OxyELITE Pro OxyELITE Pro Original, OxyELITE Pro Super Thermogenic

9. Discussion

Herbal and dietary supplements (HDS) are increasingly recognized as significant contributors to drug-induced liver injury (DILI), accounting for approximately 20% of reported cases, some of which are severe. Despite their widespread use and perception as “natural” and safe, HDS are regulated as food products rather than pharmaceuticals, and therefore are not subject to the rigorous premarket safety and efficacy standards applied to prescription drugs. This regulatory gap, combined with variability in product composition, contamination, and adulteration, complicates the identification of hepatotoxic agents.

The idiosyncratic nature of HDS-related liver injury further challenges diagnosis. Data from the Drug-Induced Liver Injury Network (DILIN) indicate that performance-enhancing supplements in men and weight-loss products in women are the most frequently implicated categories, both of which often contain multiple, poorly characterized ingredients. Clinicians should maintain a high index of suspicion for HDS use in patients presenting with unexplained liver injury, particularly in younger individuals, as continued use may progress to fulminant hepatic failure or cirrhosis.

A comprehensive diagnostic workup is essential before diagnosing DILI. Other causes—such as viral hepatitis, autoimmune liver disease, genetic disorders, and acetaminophen toxicity—must be excluded before a diagnosis of DILI or HILI is made. Management typically involves discontinuation of the suspected agent and supportive care. In cases of worsening liver function or acute liver failure, early referral for liver transplantation is critical.

Ultimately, improving awareness among both clinicians and patients is key. Many patients do not disclose HDS use unless specifically asked. Healthcare providers must routinely inquire about supplement use and educate patients on the potential risks. Greater understanding of the epidemiology and mechanisms of HDS-related liver injury is needed to guide safer use and inform public health strategies.

A key future approach to minimizing liver toxicity from HDS is strengthening regulatory transparency and oversight at the premarket stage. One proposal is the implementation of a mandatory product listing (MPL) system, which would require manufacturers to register all supplements in a public FDA database, thereby improving traceability and enabling quicker safety interventions. In the US, this has been proposed to Congress in its 2025 legislative and budget proposals [59]. In its FY2025 budget request, the FDA explicitly called on Congress to amend the Dietary Supplement Health and Education Act (DSHEA) to require all dietary supplements to be listed with the agency—including submission of product labels and other essential information—via a centralized, publicly accessible database. This requirement is intended to bolster traceability and enable the FDA to “know when new products are introduced and quickly identify dangerous or illegal products on the market” to better protect consumers. This initiative builds on prior advocacy from the agency, highlighting how the expanding supplement market (from roughly 4000 products in 1994 to over 100,000 today) outpaces the current regulatory framework, which lacks visibility into marketplace activity.

In parallel, clarifying and tightening the new dietary ingredient (NDI) notification process would help ensure that novel or high-risk ingredients undergo adequate safety evaluation before reaching consumers. Recent updates to NDI guidance have emphasized the need for timely submissions and clearer criteria for what constitutes a new ingredient [59].

Additionally, maintaining and expanding public ingredient directories—such as FDA’s Dietary Supplement Ingredient Directory—would provide clinicians, regulators, and researchers with accessible information to support early signal detection and enhance market surveillance. Together, these measures would help create a more transparent and accountable supplement marketplace, ultimately reducing the risk of hepatotoxicity.

International alignment and the establishment of robust evidence standards will be crucial for reducing liver toxicity linked to herbal and dietary supplements. In Europe, the European Medicines Agency (EMA) has developed authoritative benchmarks through its Herbal Medicinal Products Committee (HMPC) monographs and the Traditional Herbal Medicinal Products Directive (2004/24/EC), which set clear expectations for quality, safety, and post-marketing monitoring of botanical products [60]. Closer U.S.–EU harmonization in these regulatory approaches could improve global consistency and strengthen consumer protection. At a broader level, the World Health Organization’s Traditional Medicine Strategy 2025–2034 emphasizes evidence-based use, safety, and integration of traditional remedies into healthcare systems, providing an overarching framework for national agencies to require rigorous safety assessments—including hepatotoxicity evaluations—for herbal and dietary supplements [61].

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