Use of Herbal Dietary Supplements in the USA

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Herbal and dietary supplement (HDS) use has grown exponentially in the United States. Unfortunately, the incidence of HDS-related liver injury has proportionally increased. Despite the potential for certain HDSs to cause clinically significant liver injury, they are not regulated by the Food and Drug Administration. The efforts have been made to regulate HDSs but are far removed from the scrutiny of prescription medications. Scant literature exists on HDSs and their risks of causing liver injury.

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1. Regulation of Herbal and Dietary Supplement (HDS)

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the Food and Drug Administration (FDA) is not required to review or approve HDSs for safety or efficacy before they are marketed [1]. Individual HDS manufacturers are only required to notify the FDA before marketing their products if the HDS contains a new dietary ingredient, defined as any dietary ingredient marketed after 1994 [1]. Otherwise, individual HDS manufacturers are responsible for determining the safety, dietary ingredient composition, and appropriate serving size of HDSs without any oversights [1]. Individual HDS manufacturers are also allowed to market HDSs with non-specific claims and benefits, such as weight loss and liver support, without documented evidence [2].

Federal law requires individual HDS manufacturers to label HDSs as food supplements and provide a full list of dietary ingredients [1]. Despite this requirement, however, many HDSs have been recalled for containing contaminated ingredients or dietary ingredients that are different from those listed on the product label [3]. Quality analysis studies have demonstrated the contamination of HDSs with various heavy metals and pesticides [4]. A recent study investigated the accuracy of dietary ingredient labels on HDSs and found a mislabeling rate of 51% [5]. All of the mislabeled HDSs lacked one or more of the compounds listed on the dietary ingredient label, and some also contained one or more compounds not listed on the dietary ingredient label [5]. Mislabeling rates were highest among HDSs marketed as weight loss supplements and those with appearance- and performance-related claims [5].

The implications of HDS mislabeling and contamination include adverse events such as hepatotoxicity. Cases of HDS-induced liver injury after the consumption of yellow turmeric (Curcuma longa) supplement were identified in

Scandinavian countries [6]. Further investigations identified the compound Nimesulide, a non-steroidal anti-inflammatory, present in the HDSs as the precipitating cause of drug-induced liver injury (DILI) in these cases [6]. The incidence of HDS-induced liver injury is increasing and is associated with the rise in HDS use. Of the DILI cases in the US, 20% are related to HDS-induced liver injury, and many of these cases are related to HDSs containing more than one dietary ingredient [2]. The HDSs that are the most associated with DILI include those marketed with appearance- and performance-related claims [5].

Before HDS consumption, the FDA recommends that consumers reach out to their healthcare providers to discuss safe use [3]. HDSs often contain more than one dietary ingredient that can result in unintended interactions and adverse events. HDSs can also impact the pharmacokinetics of prescription drugs, resulting in unintended HDS–drug interactions [3]. Under the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006, individual HDS manufacturers are responsible for reporting serious adverse events that can be attributed to HDS consumption to the FDA [7]. Many of the serious adverse events reported to the FDA occurred in HDSs containing multiple dietary ingredients [8].

2. Hepatotoxic Effects

The liver is involved in many bodily processes, including endocrine and exocrine functions, immunologic functions, and a wide range of metabolic functions, such as the breakdown of carbohydrates, fats, and proteins. One of the liver's exocrine functions involves bile production, a mixture of bile acids, water, phospholipids, cholesterol, and electrolytes. Many drug metabolites rely on bile as a route of excretion. The liver also aids the production of albumin; clotting factors; amino acids; and urea, made from ammonia, which the liver transaminases and deaminates from amino acids [9].

Many molecules in the bloodstream are eliminated by the liver's two-phase biotransformation and elimination system. Phase I, known as hydroxylation, includes various Cytochrome P450 enzymes that add reactive oxygen sites to these target molecules. Phase II involves various conjugation enzymes that add water-soluble groups to aid in elimination. Foods and nutrients have been shown to be necessary for and able to modulate this system. Phase 1 cytochrome enzymes transform their starting molecules via oxidation, peroxidation, and reduction reactions by adding hydroxyl, carboxyl, and/or amino acid groups to their starting molecules. These reactions create electrophilic molecules that have the potential to injure their surrounding structures. Cytochrome phenotypes and numbers vary between different people, meaning that their ability to handle certain drugs and nutrients via this pathway may differ significantly. This variation can affect drug efficacy, side effect profiles, and toxicity [10].

Phase 1 enzymes: CYP1 enzymes are involved in processing hormones, various pharmaceuticals, procarcinogens, polycyclic aromatic hydrocarbons, and other environmental toxins. CYP2A-E enzymes are involved in processing ketones, glycerol, fatty acids, drugs, xenobiotics, and hormones and have been shown to have several phenotypes that affect drug metabolism. CYP3A enzymes are involved in processing caffeine, testosterone, progesterone, androstenedione, and polyaromatic hydrocarbons. CYP4 enzymes are primarily found outside of the liver and play a smaller role in drug processing.

Phase 2 enzymes: UDP-glucuronosyltransferases are essential in processing steroid hormones and bilirubin. These enzymes covalently link glucuronic acid to their target molecule. Sulfotransferases transfer a sulfuryl group to their target molecule, which often reduces their target molecule's reactivity and toxicity. Glutathione S-Transferases are enzyme complexes that transfer a glutathione group to their target molecules and are induced when reactive oxygen species are being created. Amino acid transferases transfer an amino acid to their target molecule to aid in elimination. N-acetyl transferases transfer acetyl groups to their target molecules. Methyltransferases methylate their target molecules and play a vital role in estrogen detoxification.

Other Pathways: Nrf2 is a transcription factor that helps to regulate detoxification and antioxidant systems. When activated, Nrf2 dissociates from the cytosolic protein and translocates into the nucleus to promote phase II detoxification enzymes. NrF2 is protective against stress-related conditions and toxicity from drugs or herbals. Metallothionein is also a key regulator with the ability to regulate heavy metal detoxification. The cysteine rich protein is regulated by certain stimuli such as heavy metals, oxidative stress, and zinc. In certain conditions, such as inflammatory bowel disease, metallothionein has shown to be decreased in intestinal mucosa [10].

Mechanisms for liver injury resulting from HDSs can come in several forms. Anabolic steroids, which are sometimes marketed as "bodybuilding supplements," can cause injury to the liver via a cholestatic mechanism, leading to increased bilirubin levels and, in some cases, jaundice and itching [2]. Green tea extract (GTE), along with many other HDSs, has an unknown liver injury mechanism but causes a pattern of transaminitis similar to that of the liver injury caused by acute hepatitis [2]. Liver biopsies in patients with acute liver injury related to GTE use may show eosinophils, inflammation, and necrosis in a pattern similar to the one induced by acute hepatitis [11]. Multi-ingredient nutritional supplements (MINS) often include several ingredients, and toxicity can be caused by a specific component of the regimen or an unknown adulterant, making it difficult to determine the mechanism of injury [2].

Recent data have suggested that liver injury is immune mediated by haptenization or via molecularly mimicry and that certain drugs' reactive metabolites may stress hepatocytes to stimulate the adaptive immune system by binding to proteins, which further stimulate T-Cells to express Fas ligand (FASL) and tumor necrosis factor (TNF) to induce cell death [12][13].

3. Genetic and Demographic Susceptibility

The number of patients who suffer from drug-induced liver injury (DILI) caused by HDSs is difficult to determine, as it is often unclear if patients are using these substances. However, there are data estimating that HDSs are responsible for 20–40% of acute liver failure (ALF) cases due to DILI. A Chinese study of 26,000 cases of DILI showed that only 1% of cases associated with HDSs led to ALF, but of the patients who died from ALF, HDSs were the leading cause [14]. The demographics of patients with DILI caused by HDSs in Europe, Asia, and the US were investigated. It was concluded that the typical clinical patient presentation was a young, otherwise healthy female presenting with elevated bilirubin and aminotransferases [14]. DILI in patients using HDSs for bodybuilding usually

presents with increased bilirubin and prolonged jaundice in young men. Hepatocellular DILI leads to higher rates of death and transplantation and predominantly presents in middle-aged women [15].

Differences in cytochrome P450 genetic polymorphisms affect drug metabolism and have been linked to the accumulation of toxic drug or metabolite levels, suggesting a genetic predisposition to developing hepatotoxicity [16].

Multi-ingredient products are increasingly implicated as causes of acute liver injury; green tea is a common ingredient in these products [17]. The US Drug-Induced Liver Injury Network (DILIN) performed a formal causality assessment on over 1400 patients who suffered from liver injury. Patients with green tea liver injury were often jaundiced and symptomatic and had elevated levels of serum aminotransferase with a hepatocellular pattern of injury [15]. They also had mildly elevated alkaline phosphatase levels. In patients with green tea-associated liver injury, HLA typing showed HLA-B*35:01 in 72% of cases. This type was only found in 15% of liver injury cases due to other supplements and in 12% of cases where the injury was the result of other drugs. These differences were statistically significant [17].

4. Pharmacokinetic and Pharmacodynamics Changes in Chronic Liver Disease

Liver disease can affect pharmacokinetics in many ways. Liver blood flow and enzyme activity are both crucial to metabolize drugs. Some drugs with a high first-past metabolism are affected by changes in liver blood flow, while drugs with “low hepatic extraction” are more affected by hepatic failure [16]. Plasma proteins are also important to pharmacokinetics and can be affected by liver function [18]. Liver impairment also has the potential to affect drug availability, distribution, and biliary elimination [19].

Patients with chronic liver disease (CLD) may have a slower metabolism in the liver, as their ability to metabolize proteins depends on their current hepatic reserve. Patients with CLD are also more likely to have low serum albumin and elevated serum ammonia levels and suffer from zinc deficiency at a higher rate, which decreases the capacity for ornithine transcarbamylase to metabolize ammonia [20]. As liver disease progresses to cirrhosis, the liver loses more function. Loss of liver parenchyma decreases the number of enzymes that are active in drug metabolism. In patients with cirrhosis, cytochrome alterations can occur. These changes are variable with different comorbid conditions and the state of current disease progression. However, there is a general pattern in patients with cirrhosis that CYP1A and CYP31 concentrations decrease while levels of CYP2C, CYP2A, and CYP2B remain at their baseline concentrations. Alcohol and aldehyde dehydrogenase levels may also be affected. Sulphation rates may decrease as well, but glucuronidation reactions are mostly unaffected by cirrhosis [21].

Studies have shown that various nutrients and HDSs, including cruciferous vegetables, resveratrol, green tea, black tea, curcumin, turmeric, soybean, garlic, fish oil, rosemary, astaxanthin, and chicory root, are inducers of CYP1 enzymes [10]. CYP1 enzyme inhibition has been found in black soybean, black tea, turmeric, apiaceous vegetables, quercetin, daidzein, grapefruit, peppermint, dandelion, kale garlic, and chamomile [10]. Inducers of

CYP2 enzymes may include chicory root, quercetin, rosemary, garlic, and fish oil. Their inhibitors may include ellagic acid, green tea, turmeric, black tea, resveratrol, myricetin, watercress, chrysin, and medium-chain triglycerides [10]. Nutrients that induce CYP3 enzymes may include garlic, fish oil, rooibos tea, and turmeric. Inhibitors may include green tea, black tea, quercetin, grapefruit, myricetin, kale, and soybean. Inducers of CYP4 enzymes may include green tea and the caffeic acid found in coffee [10].

5. Interaction with Other Drugs

There are concerns regarding pharmacokinetic interactions between HDSs and conventional medication with the same absorption, distribution, metabolism, or excretion mechanisms. CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, OATP1A1, OATP1A2, OATP2B1, and P-gp are the most well categorized to date. The six CYP enzymes account for the metabolism of approximately 80% of all prescribed drugs (Zanger UM, Schwab M). In terms of drug metabolism, cytochrome P450 enzymes regulate gene expression and enzyme activities and impact genetic variation [22]. Two common HDSs that affect drug metabolism are goldenseal and St. John's wort. The drugs that are most affected and contraindicated due to concomitant use with St John's wort are metabolized via the CYP3A4 and P-glycoprotein pathways [23]. Specifically, St. John's wort may reduce the effectiveness of cyclosporine (Sandimmune), tacrolimus (Prograf), warfarin (Coumadin), protease inhibitors, irinotecan (Camptosar), theophylline, digoxin, venlafaxine, and oral contraceptives; one should avoid combining St. John's wort with over-the-counter and prescription medications [23].

6. Clinical Diagnosis and Management

6.1. Clinical Diagnosis

Due to HDS-induced hepatotoxicity, a wide range of clinical presentations and a lack of objective diagnostic tests make it difficult for providers to establish an early diagnosis and begin early management. Patients will present with scleral icterus, abdominal pain/discomfort, nausea/vomiting, pruritus, or choluria [2]. DILI is a diagnosis of exclusion. To make a final diagnosis of DILI, a provider must obtain a detailed history and exhaust alternative diagnoses with a comprehensive work-up to distinguish competing etiologies [2].

6.1.1. Classifications

The Roussel Uclaf Causality Assessment Method (RUCAM), introduced in 1993, was developed to quantify the strength of association between liver injury and the medication implicated as causing the injury [24]. When it was validated, the scale demonstrated 86% sensitivity; 89% specificity; and positive and negative predictive values of 93% and 78%, respectively [24]. The scale results were reproduced by four experts after a positive rechallenge by applying RUCAM to 50 suspected DILI cases. During the experts' reproduced assessment, they found an accuracy of 99%, 74%, and 37%, respectively, which indicated a major discrepancy between expert raters [24][25][26]. Flaws in the scale are due to the need to assess verifiable case information, long follow-up data, and the inability to discriminate between contaminant drugs [27].

RUCAM was later modified by Maria and Victorino. This modification, the M&V scale, incorporates extrahepatic disease manifestations [28]. The overall score corresponds to five probability degrees: definite, probable, possible, unlikely, and excluded. The M&V scale was validated using real and fictitious cases and was compared with the classifications provided by three external experts. The comparison showed 84% agreement between the scale and expert opinions [28]. However, the scale is limited by the number of identified cases and unknown latency periods [28][29][30].

The Revised Electronic Causality Assessment Method (RECAM) is a superior update to RUCAM. It underwent 12 versions based on iterative testing, and the final scoring between RECAM and RUCAM was conducted on 98 DILIN and 96 Spanish DILI cases. RECAM had better overall agreement with expert opinion and better discriminate diagnostic categories [28].

6.1.2. Hy's Law

Hy's law is based on the observational work of Hy Zimmerman [29]. Zimmerman's observations showed that pure hepatocellular injury is an indicator of potential DILI. According to this observation, drug-induced jaundice caused by a drug or chemical that induces hepatocellular injury leads to death or liver transplantation in >10% of cases [29].

The FDA includes three major components of DILI in their guidance to pharmaceutical companies for the pre-marketing phase of drug safety evaluations [30]:

- The drug causes hepatocellular injury, demonstrated by a higher incidence of the upper limit of normal ALT or AST that is three-fold greater than the (non-hepatotoxic) control drug or placebo.
- Among trial subjects with AT elevations, one or more also show TBL serum elevations >2 × ULN without initial findings of cholestasis (elevated serum ALP).
- No other explanation can be found for the increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the injury.

In a large population, two positive components are highly predictive that the drug has the potential to cause severe DILI [30].

The FDA also follows a standard process to evaluate liver safety in large clinical trials database using eDISH plot "evaluation of drug induced serious hepatotoxicity" [12]. eDISH provides a graphical representation broken down into four quadrants. The Temple Corollary quadrant is defined as a rise in serum ALT >3 ULN but not a concurrent rise in serum TBIL >2 × ULN [12]. This region suggests an increased risk of severe DILI.

6.2. Management

No data recommend a specific liver biochemistry monitoring plan when a potential hepatotoxic agent is prescribed in individuals with known CLD. The gold-standard treatment for DILI is to withdraw the offending medication. However, in severe cases, liver transplant will be indicated. Currently, there is no approved antidote for ALF resulting from idiosyncratic DILI. For these reasons, liver tests should be monitored in patients who are taking HDSs [23].

7. Drug-Induced Hepatotoxicity and Obesity

The increased incidence of drug induced hepatotoxicity in patients with obesity has emerged in recent clinical trials. Obesity is often associated with heart disease, T2D, hyperlipemia, non-alcohol fatty liver disease (NAFLD), and osteoarthritis. One of the hallmark features of NAFLD is hepatic steatosis [31]. Some drugs may worsen obesity-related NAFLD because of the increase in lipid deposition and necroinflammation [12]. Simultaneously, drug-induced liver toxicity may worsen due to a more hostile metabolic environment because of the increased lipid deposition and necroinflammation. This harsh metabolic environment is theorized to increase CYP2E1 expression/activity and reduce MRC activity, thus leading to an increased inflammatory state resulting in DILI [32].

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