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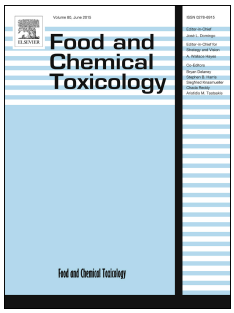

Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 3 of 6

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Liver Toxicity Related to Herbs and Dietary Supplements: Online Table of Case Reports. Part 3 of 6.

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Abstract: Background: No current list of potentially life-threatening, hepatotoxic herbs and dietary supplements based on PubMed case studies exists in a summarized tabular form. Methods: Documented case reports of herbs or dietary supplements appearing to contribute to liver injury were used to create a "Harmful Herb and Dietary Supplement List" of potentially hepatotoxic herbs and dietary supplements(PubMed 1966 to May, 2015, and cross-referencing). The spectrum of herbal induced liver injuries (HDSILI) researched included elevated liver enzymes, hepatitis, steatosis, cholestasis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, veno-occlusive disease, acute liver failure requiring a liver transplant, and death. Results: Over the past 50 years, approximately 19 herbs (minus germander and usnic acid that are no longer sold) and 13 dietary supplements (minus the six no longer sold and vitamin A & niacin due to excess) posed a possible risk for liver injures in certain individuals. The top three herbs with the most number of reported publications (but not cases studies) in descending order, were germander, black cohosh, kava extract, and green tea extract. Conclusion: These online tables will contribute to continued Phase IV post marketing surveillance to detect possible liver toxicity cases and serve to forewarn consumers, clinicians, and corporations.

Introduction

This is the third of six review articles investigating dietary supplements (DS; includes herbs): Article one covers DS definitions, usage, efficacy and safety; article two is an overview of DS regulation in the United States; and articles three through six cover case reports in tabular form related to liver toxicity, kidney toxicity, cardiotoxicity, and cancer published in the medical literature. Interest in complementary and alternative medicine (CAM), also known as functional, integrative, traditional, or holistic medicine, continues to grow, but “natural” is not always safe. Although the majority of botanical products appear inherently safe (Marcus, 2002), and some have demonstrated efficacy, this review focuses on the potentially life-threatening dietary supplements that increase cancer risk as detected through PubMed case reports. Case reports do not always demonstrate causation or association, but reoccurrences raise concerns (Haaz, 2006). In this review, the characteristics and prevalence of liver injuries are defined, the literature search methods employed are described, and a summary table of the results along with a brief discussion of selected DS are presented.

Defining Hepatotoxicity

DILI versus DSLI

The equivalent of drug-induced liver injury (DILI), which is caused by drugs, is herb- and dietary supplement-induced liver injury (DSILI; previously described as HILI, which only covers herbs and thus excludes many products in the broader dietary supplements category). The vast majority of pharmaceuticals have beneficial effects, but adverse event reports (AERs) or serious adverse events (SAEs) related to either drugs or DS do occur, though they are rare events. Because the liver is responsible for eliminating toxins from the body, it is at risk for drug- or DS-related liver injuries caused directly by

these substances or indirectly through their metabolites (Au, 2011). Subsequent injury can occur through cell stress, mitochondrial inhibition, and/or immune reactions. Table 1 lists the possible liver injuries associated with either drugs or DS in ascending order of severity (Stedman, 2002).

Hepatoxicity Symptoms

Consumers need to be aware of liver injury symptoms because when symptoms are recognized, the harmful substance can be immediately removed/discontinued to improve chances of recovery. Unfortunately, the typical symptoms—including fatigue, nausea, vomiting, loss of appetite, itching, abdominal pain or swelling, and dark urine color—are vague and mimic many other conditions. A physician should be immediately consulted if these symptoms appear, and especially if jaundice (yellowing of eye whites and inner palms) appears later on as the condition progresses (note, however, that jaundice does not always develop) (Zheng 2014).

Unpredictable versus Predictable Hepatotoxicity

Hepatotoxicity, like all toxicities, is either unpredictable (idiosyncratic, meaning peculiar to the individual) or predictable (classical or intrinsic) (Brent, 1999; Gunawan, 2004). Most reactions to drugs or DS are idiosyncratic because they cause toxicity in only a small percentage of the population, may not be dose dependent, may not be reproducible in animal models, and may result from an immune-mediated reaction (indicated by fever, rash, and eosinophilia) (Brent, 1999; Gunawan, 2004).

Time to Onset

Idiosyncratic reactions may occur within days or within up to one year, but usually by 6 months (Chalisani, 2014). Latency can be very short for certain drugs, averaging 2.5 days for the quinolones from ciprofloxacin, moxifloxacin, levofloxacin, and gatifloxacin. Serious outcomes from these short latencies can include liver transplant and/or death (Leise, 2014).

Classic liver injuries are predictable, are dose dependent, are reproducible in animal models, and may occur within hours to a few days post-exposure (Kaplowitz, 2004).

Risk Factors for Liver Injury

As discussed below, factors that increase the risk for DILIs or DSILIs include greater age, female gender, higher dose, malnutrition, alcoholism, genetics, race, concomitant drugs, and underlying disease (Andrade, 2008; Chalisani, 2010). To predict DILI risk for specific drugs in development, the DILIsym® software program (www.dilisym.com) and the Mechanism Based Integrated System of using *in vitro* assays (www.pip-dili.eu) can be used.

Age

Liver injury risk increases as people age (Andrade, 2008).

Gender

Females have a higher risk of developing DILIs, but this might be due to the types of drugs they more frequently consume, such as antidepressants. Autoimmune hepatitis triggered by drugs is almost exclusively diagnosed in women (Andrade, 2008).

Dose

A high daily dose (over 50-100 mg/day) of a medication may result in a higher DILI risk (Chen, 2013; Yu, 2014). Drugs withdrawn from the market in the United States are often administered in doses exceeding 50 mg (Chalisani, 2014). It is not surprising that some of the DS-related liver toxicities are also associated with excessive doses. For example, seeds of *Psoralea corylifolia* are routinely used in China for osteoporosis, but 10 times the usual dose resulted in a case of acute hepatitis (Nam, 2005).

Malnutrition

Protein-calorie malnutrition, restricted feeding, fasting, and starvation can increase the toxicity of some drugs. Fasting is actually recommended before scheduling certain chemotherapy drugs (Campbell, 1974).

Alcoholism

A liver compromised by alcohol abuse is more prone to DILI (Andrade, 2008).

Genetics

Patients respond differently to medications, and considerable evidence suggests that idiosyncratic DILI susceptibility is genetically determined (Urban, 2014). The International Serious Adverse Event Consortium (iSAEC), a nonprofit research organization, was founded in 2007 to identify DNA differences related to drug-related serious adverse events (www.saeconsortium.org).

Cytochrome P450 (CYP3A4) is the most abundant CYP enzyme in the liver, metabolizing approximately 50% of current drugs (Zhou, 2007). CYP gene defects are

responsible for some types of drug-induced hepatitis (Kawaguchi, 2004), and Zhou (2007) lists a number of drugs and chemicals from DS that are CYP3A4 inhibitors. Clinical consequences range from lack of therapeutic efficacy to severe toxicity, and in extreme cases, death (Zhou, 2007).

The mechanism may involve genetic influences on the P450 liver enzymes that metabolize drugs. Having particular alleles that either inhibit or promote certain liver enzymes, especially in the presence of competing drugs or DS, may predispose an individual to liver injury (Stedman, 2002). For example, a genetic basis for flucloxacillin DILI is well established, with an 80-fold increase in risk if the (HLA)-B*5701 allele is present.

In terms of DS, some individuals may have a genetic predisposition to kava toxicity, as Russmann found that two patients were poor-metabolizer phenotypes of cytochrome P4502D6 (Russmann, 2001). Kavalactones inhibit CYP enzymes (CYP1A2, CYP2D6) or cyclooxygenases (COX-1, COX-2), or deplete hepatic glutathione. Eight percent of Europid people have a CYP2D6 deficiency that may place them at a greater risk for kava toxicity than Pacific Islanders, of whom only 1% are CYP2D6 deficient (Chitturi, 2008).

Another DS example is green tea extract. Epigallocatechin gallate (EGCG), the suspected problematic agent in concentrated green tea extract, was found to be tolerated by most genetically heterogeneous mice (84%), but a small fraction (16%) experienced severe hepatotoxicity (10-87% liver necrosis), a situation similar to clinical cases in humans (Church, 2015). It has been suggested that this animal model can be used to detect rare liver injuries that may occur in consumer populations ingesting

concentrated herbal products. The species used to test for liver toxicity may be important, as rats are reportedly not very sensitive to hepatotoxicity, whereas both mice and hamsters are very sensitive (Davis, 1974).

Race

Asian race has been reported as an independent risk factor for DILI, especially for reducing the time period to liver transplant or death (Fontana, 2014). Aldehyde dehydrogenase enzyme levels in Asians are known to affect their ability to metabolize alcohol (Thomasson, 1993). Lee et al. (2013) found that related allele frequencies among Koreans were similar to those of Japanese and Chinese of Han descent, but differed from European-Americans and African-Americans. Up to 14% of Japanese carry the CYP2C19 poor-metabolizer phenotype

It has been suggested that the low incidence of liver injuries related to a particular weight-loss supplement (containing N-nitrosfenfluramine) may have contributed to DILIs in a few select individuals (Chitturi, 2008). Approximately 4% of the United States population is Asian, but 71% (5/7) of the people experiencing acute hepatitis with LipoKinetix use in one case series report were Japanese nationals (Favreau, 2002). Three Taiwanese sisters consuming a usnic-containing fat-burner experienced dark urine, jaundice, and hepatitis, respectively (Hsu, 2005).

Another example is the leading drug responsible for idiosyncratic DILI, the antibiotic amoxicillin-clavulanate (Lucena, 2011), which causes more liver injuries in people bearing certain alleles, especially among the Spanish population (Stephans, 2013).

Concomitant Drugs (or DS)

The competition for liver enzymes suggests that certain drug-drug, drug-DS, or DS-DS interactions can be predisposing factors for liver injuries. The possible competition between co-administered substances for liver enzymes would explain certain case reports where liver injury followed the addition of a drug or DS to a previously unproblematic drug or DS regimen (Chalisani, 2014 ACG). When the same enzymes in the liver must metabolize two substances, the rate of metabolism of one or both compounds may be altered (Zhou, 2007). Alcohol interferes with drug metabolism and is often contraindicated with certain drugs.

Underlying Disease

Co-morbidity may also increase the risk of liver injuries and mortality is significantly higher in individuals with pre-existing liver disease (Chalasani, 2015). This is concerning since approximately 18% of chronic liver disease patients surveyed were taking herbal supplements (Ferrucci, 2010). Perhaps the safest approach for people on medications with pre-existing medical conditions is to avoid any DS, except perhaps a standard multivitamin/mineral supplement. Likewise, anyone undergoing a transplant or skin grafts may best avoid DS entirely, especially St. John's wort, which has been reported to reduce cyclosporine levels, resulting in the rejection of transplanted organs or graft loss (Zhou, 2007). Milk thistle, often used to promote liver health, reduces the mean trough level of the HIV drug, indinavir, by 25% (Zhou, 2007).

Causality Scoring Systems

DILI or DSILI diagnosis is primarily a process of elimination based on mathematical probability (Garcia-Cortes, 2011). Expert opinion remains the gold standard, with a

physician reviewing the patient's history, blood test results, hepatobiliary imaging, and, possibly, liver biopsy results (Chalasani, 2014). After a liver injury is clearly diagnosed, the cause is pinpointed through any of several methods divided into three categories: (1) expert opinion, (2) probabilistic approaches, and/or (3) scoring scales (liver-specific or general) (Garcia-Cortez, 2011).

The most commonly used liver-specific scale is that developed by the Council for International Organizations of Medical Sciences (CIOMS), also known as the Rouseel Uclaf Causality Assessment Method (RUCAM) (Garcia-Cortez, 2011). A checklist is reviewed by a clinician, who assigns points to each variable. The total score is evaluated using a probability scale: ≤ 0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥ 9, highly probable/definite. The MV Scale or Clinical Diagnostic Scale (CDS) is a shortened version of the CIOMS scale (Maria, 1997) (Teschke, 2013a). On the other hand, the more recently developed Digestive Disease Week–Japan (DDW-J) scale (Takikawa, 2003) derived from the CIOMS scale was reported by Garcia-Cortez (2011) to be superior to that of the CIOMS. Non-liver-specific scales or those not validated for hepatotoxicity include the Naranjo Scale used in clinical trials (Naranjo, 1981), the WHO-UMC causality assessment (WHO), and the ad hoc approach (Kaplowitz, 2001). The strengths and weaknesses of these different causality assessment tools were reviewed by García-Cortés and associates (2011).

Some researchers have expressed the "urgent need for a universally accepted stepwise causality assessment" scoring scale that should then be further evaluated in the field (Teschke, 2008). They stressed the importance of replacing the currently approved, but different, approaches of hospitals, physicians, health care agencies, manufacturers, and

expert groups, which use their own method(s) that may or may not be free of conflicts of interest. Legitimate concern has been expressed regarding the US Pharmacopeia's (USP's) use of the Naranjo and not the CIOMS scale or its validated update to conduct DS liver-specific causality assessments (Teschke, 2012a).

These scoring systems are important because drug or DS-related liver failure rarely occurs, and if a cluster of failures occur, it is imperative to quickly track down the cause and prevent further cases. A cluster of cases often points to one common denominator that can be mathematically determined as either a random or statistically significant event. Another strong support for causation is similar symptoms with re-exposure to a substance—i.e., symptoms stabilize following withdrawal, reappear with reintroduction, and disappear again following a second withdrawal. These rechallenge tests unintentionally created by the patient are the gold standard in diagnosing hepatotoxicity (Teschke, 2008).

Causality Assessment Considerations

Approximately 47% of suspected DILI cases are in fact not caused by drugs, and researchers have stated the same is true for DSILI cases. "In 573 cases of initially assumed HILI (DSILI), 48.5% showed alternative causes. They called for thorough clinical evaluations and appropriate causality assessments in future cases of suspected DSILI" (Teschke, 2013c). These alternative causes included co-medication (DILI and other HILI) (43.9%), biliary and pancreatic diseases (11.5%), autoimmune diseases (10.4%), pre-existing liver diseases (including cirrhosis; 9.7%), viral hepatitis (9.7%), nonalcoholic and alcoholic liver diseases (5.4%), and infectious diseases involving the

liver (4.7%). Establishing liver injury causality is necessary for accurate prevalence determinations or comparisons.

Treatment of DILI

DILI treatment consists of immediately withdrawing the responsible medication; many patients start to improve within hours or days (Chalisani, 2014). In one study, most of the 70 patients with elevated liver enzymes and a normal liver biopsy recovered (Strasser, 2015). However, approximately 14% go on to develop chronic liver disease (Chalisani, 2014). DILI from antidepressants may be irreversible (Voican, 2014). A minority of patients experience acute liver failure and may die or require emergency transplantation (Fontana, 2010).

Sometimes the liver has an autoimmune reaction to certain drugs or metabolites that bind to a liver protein (such as cytochrome p450), generating an antigen, or result in dead cells; both can trigger the immune system (Yuan, 2013). Particular attention should be given to patients who present with positive autoantibodies or a history of weight gain or alcohol consumption. (Chalsani, 2014).

Prevalence of DILI and DSILI in North America & Europe

DILI cases, whether they are caused by drugs or DS, are not tracked through annual surveillance. DILI is rare for most drugs, occurring in approximately one per 10,000-1,000,000 persons exposed (Fontana, 2010). However, epidemiologic data suggest that the rate might be as high as 20 DILI cases per 100,000 people exposed in Western countries (Leise, 2014). The prevalence of DILI is largely unknown, as hospitals and

liver centers do not appear to have similar causality determinations or report to one agency.

Retrospective and Prospective Prevalence Studies

DILI epidemiology research results are influenced by study design, study definitions, inclusion or exclusion of acetaminophen, geography, culture, genetics, inclusion or exclusion of complementary medicine (definitions vary), and whether the researchers report conflicts of interest (Björnsson, 2013; Leise, 2014). Few prospective population-based studies have attempted to decipher the relatively low frequency of liver injuries (Fontana, 2010). Several relevant findings are briefly summarized here even though data from registries cannot be considered population based (Raschi, 2015).

Among 83,265 in-patient admissions at the Mayo Clinic in Scottsdale, Arizona over 7 years (1998-2006), only 0.048% (N=40) were due to DILI. That is equivalent to 5.7 cases per year. Seventy percent of these (27/40) were due to acetaminophen (APAP), and 33% (13/40) to non-APAP drugs, primarily antibiotics (Carey, 2008). No cases of liver injury caused by herb use were reported at this location during these 7 years.

Although DILI is a relatively rare occurrence (Chalasani, 2008), the FDA cites it as the number one reason for withdrawing drugs from the marketplace over the past 50 years (FDA-b, 2009). Only about 1% of all marketed drugs were withdrawn or restricted (Wysowski, 2005), so those causing hepatotoxicity would represent only a fraction of 1%. More than 800 drugs have been implicated in DILIs (Kaplowitz, 2004). Excluding APAP, the drugs most commonly involved are antibiotics and antiepileptics, which are responsible for over 60% of the DILIs (Chalasani, 2010). Drugs are the number one

cause among the approximately 2000 annual cases of acute liver failure (ALF) in the United States (FDA, 2009). However, about half of these DILIs were due to APAP (Lee, 2012), and almost half of the APAP-related cases were suicide attempts with excessive doses (FDA, 2007). Fontana (2008) estimated that 500 deaths due to APAP occur in the U.S. annually. In 2015, the other major causes of acute liver failure, in descending order, were undetermined (12%), non-APAP drugs (11%), autoimmune conditions (7%), hepatitis B (7%), and hepatitis A (2%).

Acute liver failure is the diagnosis in approximately 11% of the DILIs in the United States. One of the most serious consequences of liver injuries, liver transplant, is even less common (Leise, 2014).

DILI versus DSILI Prevalence

The true prevalence of DSILI is unknown (Stickel, 2015). However, DS contribute significantly less than pharmaceuticals to reported cases. When considering all liver injuries and not just acute liver failure, Bunchorntavakul et al. estimated that, “based on available data of DILI cohorts from the US and Europe, herbal products are implicated as a cause of hepatotoxicity in 2-11% of patients” with DILI (Bunchorntavakul 2013).

In 2003, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Drug-Induced Liver Injury Network (DILIN) consisting of 8 academic medical centers and a data coordinating center (www.dilin.org) (Fontana, 2014). A DILIN retrospective evaluation of United States liver injuries enrolled the first 300 patients diagnosed with drug-induced liver injuries between September 2004 and December 2007 (Chalasani, 2008). They suspected single prescription drugs in 73%

(217/300; 72 cases/year) of DILIs, multiple agents in 18% (55/300; 18 cases/year), and DS in 9% (28/300; 9 cases/year). The most common single causative drug was the antibiotic amoxicillin-clavulanate (combination drugs do not undergo FDA clinical studies because each drug has already been tested), followed by isoniazid and then non-steroidal anti-inflammatory drugs (Leise, 2014). Acetaminophen cases, responsible for almost half of acute liver failures, were excluded from the calculations, which inflates the DS percentage. Also, the 9% of DS cases reported by Chalasani (2008) involved a total of 28 supplements, but 7 (25%) of these contained anabolic steroid-like substances for muscle enhancement. Excluding these products results in a more accurate estimate of DSILI cases, at 7% (21/300; 7 cases/year). If liver injuries from all causes were included, and not just those caused by drugs and/or DS, then the percentage of liver injuries from DS would be even lower.

Even fewer DSILIs were observed in Spain, where only 2% (11/570) of DILI cases were associated with DS (1994 to 2004) and 81% (461/570) were related to drugs (Andrade, 2005). In Iceland, Björnsson et al. (2013) reported that the crude annual DILI rate was 19.1/100,000 inhabitants with amoxicillin-clavulanate most commonly implicated based on their prospective study of 96 patients. Italy's DILI rate was estimated to be 1.3% (136/10,270) in an 11-year retrospective study (2000-2011) (Licata, 2014).

Prevalence of Acute Liver Failure Leading to Liver Transplant or Death

The most serious DILIs, which result in liver transplant and/or death, are significantly more likely to be caused by drugs than DS. Among 446 cases of liver disease in a Spanish study (1984-2004), drugs resulted in 5 liver transplants and 15 deaths, whereas medicinal herbs were implicated in no liver transplants and 1 death (Andrade,

2005). In essence, over this 10-year period there were 1.5 deaths a year and a liver transplant every other year due to drugs, but only 1 death and 0 liver transplants due to herbs. In the United States, Chalasani et al. reported 13 liver transplants resulting from DILI (6%; 13/217), compared to 1 liver transplant due to DSILI (4%; 1/23), for the 3.25-year period between 9/2004 and 12/2007 (Chalasani, 2008). More importantly, while 11% (23/217) of DILIs resulted in death, none of the DSILIs did. A DILIN prospective study by Chalasani (2015) reported that 10% of the 899 patients underwent a liver transplant (4%) or died (6%) within 6 months. These cases appear to be drug related, as DS were not mentioned as contributing to serious events.

Russo et al. investigated the number of drug-induced acute liver failures resulting in transplantation by reviewing records for 1990 to 2002 from the United Network for Organ Sharing liver transplant database (Russo, 2004). Of the 2,291 transplant cases, 15% or 357 were due to acute hepatic necrosis from drugs (range 8-20%/year). Of these, 270 met criteria for inclusion in their study, and acetaminophen was responsible for approximately half of acute liver failures (46%; 124/270). Non-acetaminophen cases were primarily due to other drugs (51%; 137/270); only 7 cases (5.1%) in a 12-year period were attributed to herbs—three of these were kava-kava, chaparral tea, and vitamin A. That amounts to one DS-related liver transplant case every 4 years. When the entire 357 DILI cases are included (and not just the 270 not related to acetaminophen), 97% are attributable to drugs, but only 3% to DS.

The DILIN's goal was to quantify the number of DILIs in the United States. In 2014, Fontana and associates evaluated the records of the first 660 cases of DILI from the DILIN and reported that 62 of these cases resulted in liver transplant or death (Fontana,

2014). Of these, 52 DILI cases (8% of 660)comprised 22 liver transplants, 9 liver failure deaths, and 4 non-hepatic deaths. The 10 cases (1.5% of 660 DILI) associated with DS resulted in 8 liver transplants, 1 liver failure death, and 1 non-hepatic death. These cases occurred over a period of 7 years (9/2004-6/2011), so the average numbers of liver transplants and deaths per year for drugs were 3.1 and 1.3 respectively, while numbers per year for DS were 1.1 and 0.14.

It is not known how many of these liver transplants and deaths were due to illegal anabolic steroids because a full list of DS products implicated was not provided in the article (Chalasani, 2008 and 2015; Fontana, 2014). The prevalence of DSILIs would be even lower if products containing anabolic steroids were excluded—as they should be because these known liver toxins are controlled substances that cannot be sold without a prescription, and products that contain them not legal dietary supplements. Without distinguishing legal DS from adulterated products, one cannot calculate an accurate annual incidence or prevalence of DSILIs and/or DS-related transplants and deaths. In an earlier DILIN study reviewing 300 subjects, 26% (7/27) of the implicated DS appeared to be designer anabolic steroids (Chalisani, 2008). Extrapolating that to the 10 cases in Fontana's (2014) study, removing 26% (2.6 cases) would result in only 7.4 cases of liver transplant or death over 7 years to equal 1 case a year.

Considering the broader picture, the American Liver Foundation estimates there are 6,000+ liver transplants a year (www.liverfoundation.org), and Table 2 reveals that almost half are due to hepatitis C and alcoholic liver disease (Luu, 2014). The overall contribution of DS to liver transplants and deaths compared to pharmaceuticals is

minimal, but both become significantly smaller in comparison to all other causes of liver transplants.

DILI and DSILI Prevalence in Asia, Africa, South America, and Other Areas

A real concern is the apparently higher rate of DSILIs in certain countries, especially in areas where traditional medicine is an integral part of society that has been practiced for thousands of years.

After Ayruvedic (Indian) medicine, one of the oldest traditions of herbal medicine originates in China, where it was practiced as far back as thousands of years BC (Stickel, 2015). Attributing liver injuries to a particular Chinese herb is difficult because traditional Chinese medicine (TCM) administers mixtures of several different herbs. Over 13,000 mixed herbal preparations exist, making it difficult to identify either the active component or the causative agent contributing to liver injury (Stickel, 2015).

In China, a database search (1994-2011) found the top four causes of DILI to be tuberculostatics (31%), the broad category of complementary and alternative medicines (CAMs) (19%), antibiotics (9%), and NSAIDS (5%) (Zhou, 2013). A retrospective study of 138 DILI patients in China (2008-2010) found that Chinese herbal medicines (54%; 74/138), antibiotics (8%;11/138), and dietary supplements (6%; 9/138 or 4-5 yearly) were primarily responsible (Lai, 2012). Korea had even higher rates of DS-related liver injuries at 70% as reported by Suk et al. (2012), who evaluated 371 cases reported by 17 different hospitals between 2005 and 2007. However, they admitted that their broad classification of various “herbal medications or preparation,” “health foods or dietary supplements,” and “folk remedies” “was a difficult and often a vague process” (Suk,

2012). Even then, their rate of combined drug- and DS-related deaths and liver transplants was low at 2% (7.42 cases/3 years or 2.47 cases annually). A retrospective study analyzing the 16,696 adverse events (due to conventional medicines, CAM, and cosmetics) in the Singapore Pharmacovigilance database (1998-2009) found that approximately 3.8% were due to CAM products (Patel, 2012). The majority of DS cases were for sexual performance preparations (46.4%; 291/627), followed by pain remedies (5.9%; 36/627) and weight-loss aids (4.3%; 27/627). Overall, approximately 52 adverse event cases including 2 deaths per year were due to CAM (1 death a year due to hepatotoxicity). Hypoglycemia was the number one CAM-associated adverse event (46%; 288/627), suggesting that potent hypoglycemic agents from plant sources may compete with metformin, one of the most popular oral hypoglycemic drugs for diabetes, and a medication itself originating from a plant.

The prevalence of DILI is difficult to accurately assess, and the prevalence of DSILI is even more so. Studies reporting on their prevalence are very limited, vary widely in methodology, and may include or exclude acetaminophen cases—preventing consistent comparisons. Further complicating matters, plant names and uses vary among geographical regions and DS are defined differently or are pooled under the less defined and broader CAM category. As a result, rates of DILI, and especially DSILI, are not readily determined.

Creating Tables of Harmful DS

An “online table” providing a summary of potentially life-threatening, hepatotoxic herbs based on a thorough review of PubMed case reports has been previously unavailable in

the United States. The goal of this research review was to create a “Toxic Table” summarizing the DS case reports reported in PubMed associated with liver injuries.

LiverTox.nih.gov does list selected drugs and DS associated with liver injuries, but the list is not yet complete, herbs not associated with liver injuries are included, and it is not summarized in tabular form. One review found that 60 different herbs, herbal drugs, and herbal dietary supplements (non-herb dietary supplements were not included) were related to liver injuries (Teschke, 2012b). In contrast, the purpose of this publication was to create a series of online “Harmful Herb and Dietary Supplement Tables” based on case reports (reviews not included) related to liver, renal, cardiac, and neoplastic illnesses that could then receive ongoing, immediate updates, along with offering a standard DSILI reporting form for clinicians that could be written up in coauthorship with the present author to be quickly published in PubMed.

This virtual online table can now be updated by researchers with each newly reported case report in order to provide immediate awareness of potentially hepatotoxic DS (link) (**Tables 3 & 4)**. This will be the “*first online review article”* that can be updated with emerging research reports, and will serve as a template for other review articles facing the constant challenge of being outdated by the date of publication. These “Toxic Tables” can be used to forewarn consumers, clinicians, and manufacturers.

Methods: Literature Search

Documented PubMed case reports (1966 to June, 2016, and cross-referencing) of DS appearing to contribute to liver toxicity were listed in “Toxic Tables.” The broad search

included the keywords of “plant extracts” or “plant preparations” with “liver toxicity” and “toxicity” [“human” species always checked]. The narrowed search included the keywords of “herb” () or “dietary supplement” (combined with “liver” to generate an overview list, and possibly “toxicity” to narrow the selection. Specific herb “names” found through this process were combined with “liver toxicity.” “Hepatotoxic” “herbs” or “supplement” or “dietary supplement” were searched for more precise articles. The letter “s” was added or removed to herb or dietary supplement to generate the greater abstract number. Case reports were excluded if they involved herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, mushrooms, poisonous plants, self-harm, excessive doses (except vitamins/minerals), legal or illegal drugs, drug-herbal interactions, and confounders of drugs or diseases. Since commercial dietary supplements often include a combination of ingredients, they were treated separately. Lastly, a third table of case reports consists of publications including insufficient data to assess DSILIs. The spectrum of herb-induced liver injuries researched included elevated liver enzymes, hepatitis, steatosis, cholestasis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, veno-occlusive disease, acute liver failure requiring a liver transplant, and death. Only the most serious liver injuries were listed (e.g., elevated enzymes, fatigue, abdominal pain, dark urine, etc. were not listed). English articles were the primary focus, but some reports in other languages were considered.

Results: DS-Related Liver Injuries

Approximately 21 herbs were related to liver injury case reports that include, but are not limited to: aloe vera (*Aloe barbadensis*), arrowroot juice (*Maranta arundinacea* & others?), black cohosh (*Actaea racemosa*), cascara (*Cascara sagrada*), celandine

(*Chelidonium majus L*.), chaparral (*Larrea divaricate*), comfrey (*Symphytum officinale*), fo-ti (*Polygonum multiforum*), gota kolu (*Centella asiatica*), green tea extract (*Camellia sinensis*), groundsel (*Senecio vulgaris),* Hathisunda (*Heliotropium eichwaldii*), Impila (*Callilepsis laureola*), Jin bu huan (*Lycopodium serratum*), kava (*Piper methysticum*) extract, pennyroyal (*Mentha pulegium*), rattlebox (*Crotalaria sessiliflora*), senna (*Cassia angustifolia*), skullcap (*Scutellaria lateriflora*), thistle (*Atractylis gummifera*), and valerian (*Valeriana officinalis L*.). Two additional herbs, Germander (*Teucrium chamaedrys L*.) and usnic acid (*Usnea lichens),* are no longer allowed for sale in the United States. Approximately 16 DS were related to liver injury case reports that include, but are not limited to: Bakuchi tablets, conjugated linoleic acid (CLA), Euforia, Exilis, glucosamine/chondroitin, Herbalife®, Inneov masa capilar®*,* Kalms Tablets, Lipolyz® or Somalyz*, Ma huang*, Move Free Advanced, niacin (nicotinic acid), Pro-Lean, Sennomotokounou, UCP-1, and vitamin A (excess). Nine additional DS (or older formulations) are no longer sold in the United States including anabolic steroids, Flavocoxid, Hydroxycut, LipoKinetix®, OxyElite Pro®, Sennomotokounou, Venencapsan®, venoplant, and usnic acid. The names, ingredients, and corporations of dietary supplements can change so those listed here may not reflect current products on the market. The DS with the most number of reported publications, but not always cases studies, in descending order, were germander, black cohosh, kava extract, and green tea extract.

Discussion

Herb-Related Liver Injuries

Over the last 50+ years (1966-2015), approximately 21 herbs have been reported in PubMed to be associated with liver toxicity in case report publications. Although the number of publications does not always reflect the number of case reports, the herbs with the highest number of publications (not cases), in descending order, were (number in the last 10 years is in parentheses):

Germander (*Teucrium chamaedrys L.*)	– 23 (7)	no longer sold
Black cohosh (*Actaea racemosa*)	– 13 (12)	USP warning label
Kava (*Piper methysticum*) (extract)	– 10 (1)	Not admitted by USP
Green tea extract	– 9 (8)	
Chaparral (*Larrea divaricate*)	– 9 (0)	
Aloe vera (*Aloe barbadensis*)	– 7 (7)	
Greater celandine (*Chelidonium majus L.)*	– 7 (3)	
	Total =	78 (1.56 publications/year)

Germander, the herb with the largest number of publications, no longer appears for sale (as a single ingredient) in a Google search (English language) as of December 2015. The US Pharmacopeia (USP) has already declared that certain supplements are only safe when labeled with a suitable labeling statement, and stated that kava was the only herb to date judged as not safe irrespective of label statements. Kava is no longer available in certain countries, but is sold in the United States and via the Internet. USP also suggests warning labels for black cohosh and green tea extract with regard to possible liver damage. At least two published reports associate liver injury with drinking excessive quantities of green tea. Chaparral, aloe vera, and celandine are also sold on the Internet. It is recommended that the USP review these herbs for possible proper

labeling statement warnings. Based on reports from the last ten years, and the fact that germander appears to be unavailable, black cohosh (12 publications), green tea extract (8), and aloe vera (7) currently appear to be the main potentially problematic herbs. However, in terms of quantity, these three herbs resulted in 27 publications over the last decade, or approximately 3 reports annually.

The remaining herbs had 6 or fewer publications each in the last 10 years. However, five are still sold on the Internet: fo-ti (Shou Wu Pian) has been associated with 18 cases of hepatitis; pennyroyal was implicated in two deaths, indicating that infants should not be given this herb as a colic treatment; senna is a laxative related to a liver necrosis report; skullcap was associated with 2 liver transplants and a death; and valerian was related to a liver fibrosis report.

Other herbs with serious rare implications, but not widely available on the Internet, include impila, associated with liver and kidney failure and death, especially in children; rattlebox (appears to be harvested from local plants), which should not be used in infants, especially in Mexico or the Southern states, as a death has been reported; thistle (not milk thistle), reportedly related to liver failure and death; and usnic acid extracted from lichen, which appears to no longer be sold due to liver toxicity and death reports. However, moss, lichen, and a liquid extract of unknown concentration were being sold on the Internet.

In summary, the most egregious herb, germander, is no longer for sale; the next three most prominent offenders (black cohosh, kava, and green tea extracts) have or should have designated warning labels; and the last three, chaparral, aloe vera, and greater

celandine, had infrequent liver injury reports over the last 50 years and may require warning labels. Chaparral was actually removed from the GRAS list in 1970, but is still found for sale on the Internet. No liver toxicity cases attributed to chaparral have occurred in the last 10 years, which is positive news because liver failure was previously reported. Only 10 total publications involving aloe vera or greater celandine have appeared in the last 10 years, hepatitis was the worst symptom reported, and there were no reports of liver transplant or death; nevertheless, caution may be justified. The remaining herbs have far fewer publications, but that does not negate their possible implications in liver toxicity—especially fo-ti, pennyroyal, senna, skullcap, and valerian.

Although traditional herbs from Asian, African, or other countries were not included in this review, a review of Traditional Chinese Medicine (Teschke, 2014) suggests that they appear to have a higher rate of HILI. Therefore, the need to review TCM remedies for related liver injuries may be greater, and any new case reports can be inserted into the “Toxic Tables.” These tables document DSILI case reports, and although not all are yet included, additional past or future reports from all possible published sources may be submitted for addition to the table.

Dietary Supplement-Related Liver Injuries

Identifying a dietary supplement is not always an easy task. Dietary supplement formulations can and often do change with or without product name changes. There are many reasons this occurs. One motivation is receiving a Warning Letter from the FDA regarding a particular ingredient. In addition, a single product name may designate a range of different products identified by sub-category names (Supplement A, Supplement A-Max, Supplement A-Max Super). As such, this review simply reports on

the previously published reports of dietary supplements that may or may not represent current product names and/or ingredients. In some cases, PubMed authors did not include the dietary supplement's brand name and/or other ingredients.

This review identified approximately 16 dietary supplements (minus 9 no longer sold) related to liver toxicity in PubMed publications over the last 50 years. Only case reports were included, so a review listing dietary supplements related to liver injuries without case report information did not meet the criteria for this report. Even if such a list was provided, a dietary supplement was usually only listed once or twice, which can pale in comparison to sales. A great many factors can contribute to these single instances lacking sufficient information and thus being included in Table 5; the three most common confounding factors were underlying disease in subjects, use of mixed herbs, and inclusion of drugs. Also, approximately 24% of dietary supplements listed in previous prevalence studies were actually designer anabolic steroids—that is, illegal drugs rather than supplements.

As mentioned previously, many bodybuilding products may contain steroid substances, which are known liver toxins, and thus should be excluded from DS statistics as illegally marketed controlled substances. Under current regulations they should be removed from store shelves as well. To include dietary supplements or illegal drugs related to liver toxicity in a list of legitimate drugs related to liver toxicity is not equitable. The same applies to including drugs, especially illegal drugs, in a list of dietary supplements implicated in liver injuries. As such, steroid dietary supplements were not included in this review, nor should they be included in future reviews unless the goal is to increase the perceived harm caused by legitimate dietary supplements. Failing to mention whether anabolic steroids and other drugs are included and in what amounts when

reporting DSILIs makes the degree of risk legal DSDS present more difficult to discern. Currently, when research articles that omit this information are cited in the U.S. media through press releases, a possibly unfounded bias against DSDS is being propagated.

Weight-Loss Products. Navarro (2013-b) stated that DS sold for bodybuilding and weight loss are the most commonly associated with DSILI. It is not surprising that weight-loss products—specifically, certain product lines of Herbalife, Hydroxycut, and Oxy Elite Pro that may no longer be sold—feature in the highest number of published case reports related to liver injuries. These were highly successful products marketed to millions of people and so sheer volume may have contributed to the probability of adverse reactions. Some of these products were “fat burners,” defined as dietary supplements claimed to speed fat loss by increasing energy metabolism (burning calories), breaking down fat, and reducing cravings. The “burn” is claimed to be manifested by a higher body temperature and/or heart rate, both of which simulate the experience of exercise (Krishna, 2011). However, these effects may be due to stimulants and/or extracted and/or synthesized chemicals that may be harmful to the liver, heart, or other organs.

The list of possible fat burner ingredients includes caffeine, carnitine, green tea extract (EGCG), conjugated linoleic acid (CLA), garcinia cambogia (hydroxycitric acid extract claimed to inhibit ATP-citrate lyase, the enzyme response for fatty acid synthesis), forskolin (not for pregnant women; an extract from the Indian coleus plant that increases cAMP), chromium, kelp (which can negatively affect the thyroid gland), and fucoxanthin (brown seaweed pigment) (Jeukendrup, 2011). Sibutramine, an appetite suppressant,

or other drugs have been found in fat burners but not on their labels, which violates FDA adulteration and labeling laws.

The most serious problem associated with fat burners or other designer dietary supplements is the recent trend to isolate a single ingredient from a plant (either by extracting or synthesizing it) and place it in the dietary supplement without informing the FDA by submitting it as a New Dietary Ingredient (NDI) or submitting a New Drug Application (NDA). Article 2 of this series discusses this problem and the existing regulations under which this process is illegal. An example is aegeline, a single chemical from the sacred bael plant from India that was synthesized and inserted into one of the OxyElite Pro product lines (Long, 2013). The FDA sent out Warning Letters to the manufacturers of OxyElite Pro, along with other fat burners such as certain green tea extract-containing products, Hydroxycut, and LipoKinetix.

Illegal sale of medications as DS remains a concern. For instance, the FDA recalled Akttive High Performance Fat Burner Gold because it was adulterated with the drugs sibutramine, desmethylsibutramine, and phenolphthalein.

Withdrawal of Hepatotoxic Products. As a result of FDA actions and/or other factors, approximately 36% (9/25) of the DS related to liver toxicity in these tables are no longer sold. These include anabolic steroids, Flavocoxid, Hydroxycut® (earlier version), LipoKinetix®, Oxy Elite Pro®, Sennomotokounou, Venencapsan®, Venoplant, and usnic acid (highlighted in gray in Tables 3 & 4). It is possible that many of the listed dietary supplements now have different formulations and no longer contain the suspect

ingredient(s). Only one product listed in the Tables was still sold on the Internet, and that was usnic acid, but it consisted of a liquid extract of an undisclosed concentration.

A Balanced Perspective

This review reveals that over the past 50 years, only 19 herbs (minus germander and usnic acid) and 13 dietary supplements (minus the six no longer sold) posed a possible risk for liver injures in certain individuals. Vitamin A and niacin were on the list due to excessive intake (a disqualifying criteria), and it should not be forgotten that these are known liver toxins at high doses. The list would be slightly longer if Chinese herbs were included, but this was a difficult task given that these remedies traditionally do not consist of just one herb, and many of the relevant case reports may be published in other languages. Nevertheless, these case reports can be added to the online tables in the future.

In summary, making the following corrections to the calculations determining the DS contribution to liver injuries in previous articles yields a more balanced perspective:

1) Liver injury prevalence is unknown. There is no annual incident count collected by one government or non-profit agency from clinicians and hospital liver centers. As such, the prevalences of DILIs and DSILIs obtained from DILIN were not derived from a population-based study (Vuppalanchi, 2015), and most research is either retrospective or prospective and based at selected clinical settings over a selected time period and with an arbitrary subject number selection. As a result, no two prevalence studies are similar and therefore making comparisons between studies and for different time periods (years) is difficult.

2) Liver injuries are rare. What is known is that the prevalence for DILIs is so low that these injuries are classified as rare. In comparison, the prevalence for DSILIs is even lower—that is, they are even rarer. Drugs far outnumber DS as DILI causes and the most commonly responsible drugs are antibiotics, anti-eleptics, and non-steroidal anti-inflammatory drugs (NSAIDs). Over 1100 classical drugs (estimates vary widely) are potentially hepatotoxic (Larrey, 2005), but only approximately 16 DS products have documented hepatotoxicity cases based on this review. Nine additional DS are no longer sold in the United States.. More specifically, The Physicians' Desk Reference (PDR, 2016) listed 370 drugs possibly causing hepatic abnormalities, 124 drugs contraindicated in people with liver disease, and 90 drugs labeled as possible causes of acute liver failure (Kaplowitz, 2004). Many of these drugs remain on the market despite liver injury potential with the expectation that the physician will conduct liver enzyme tests. One example is methotrexate, used for over 50 years; it can improve psoriasis symptoms in 60% of patients, but 33% experience liver injuries that may simply include elevated enzymes (Barker, 2010). Tyrosine kinase inhibitors (TKIs) were found related to increased ALT, AST(Iacovelli, 2014).
3) Current DSILI estimates appear inaccurate. Improved scientific accuracy of DSILI statistics would be achieved by:
    a) Adding DS categories. A recent publication stated that "…among DILI cases DS are the second most common cause" (Chalisani,– 2014), but this ranking was determined by dividing the 609 drugs studied into nine categories while combining all 145 DS into a single category for comparison (Chalisani, 2015). The DILIN actually created 13 categories

for DS, but these categories were not used when reporting that DS were the “second most common cause” of liver injuries (Vuppalanchi, 2015).

b) Removing anabolic steroids or other ingredients masquerading as DS from valid DSILI statistical calculations. These products are illegal and their harmful ingredients already regulated by the FDA or other regulatory agencies (McGuffin, 2013).

c) Including acetaminophen. APAP, the number one cause of acute liver failure and responsible for about 1000 of the approximately 2000 annual cases of acute liver failure, is frequently excluded when evaluating the impact of drugs responsible for DILIs. This unfairly lowers the total number of drugs, while simultaneously inflating the proportion of liver injuries caused by DS. One solution is to exclude only APAP cases due to self-harm, as that is a misuse of the drug.

d) Including all causes of liver injuries. Comparing DSILIs to the total number of liver injuries *from ALL causes* provides an accurate perspective of the total number of liver injuries due to DS. The data become unfairly skewed when comparing liver injuries from drugs and DS to their combined totals. For instance, all the other causes of liver transplant listed in Table 2 should be included, along with etiologies for acute liver failure such as undetermined; hepatitis A, B, or C; autoimmunity; ischemia; Wilson’s; Budd-Chiari; pregnancy, and other (see Figure 1).

e) Naming the specific DS products related to liver injuries. Not disclosing the DS related to liver injuries calls into question any statistical conclusions because the reported proportion of DSILI cases cannot be challenged (e.g., how many were illegal steroid drugs?). Unfortunately, such

conclusions are often accepted and repeatedly cited in subsequent studies without scientific scrutiny.

4) The vast majority of serious liver injuries are unrelated to DILI/DSILI. Liver transplant and death are the most serious outcomes of liver injuries; fortunately, only a very small percentage of people experience them. Neither drugs nor DS are primarily responsible. Table 6 shows that the incidences of liver transplant and death resulting from drug use averaged from three major studies equal only 2.4 and 3.1 cases annually, respectively; barely 1 liver transplant and no deaths annually result from DS use. That totals to approximately 5.5 per year for drugs, 1 per year for DS. Omitting the cases due to illegal drugs (approximately 24%) reduces the number of annual cases due to DS by one fourth (0.85 minus 0.20), to equal 0.65 per year. More importantly, these extremely low values for both drugs and DS would become close to zero if all causes of liver injury, such as hepatitis C, were included in the calculations. The U.S. media's emphasis on these "rising" numbers of DSILI cases (less than 1 death a year) is disproportionate given that hepatitis C infection resulted in 1,800 liver transplants (Table 2) and 19,368 deaths in 2013 (CDC, 2015).

When scientific accuracy is increased through these statistical corrections, DSILIs become significantly less frequent than previously reported or portrayed. The overall picture is that most people recover from DILI and DSILI, although a very small minority experience chronic liver disease, liver failure, liver transplant, and/or death. Table 6 reveals the reality that very few people either receive liver transplants or die due to DS-related hepatotoxicity. As such, it appears the "dangers" of dietary supplements have been inflated in the media, and need to be normalized for scientific accuracy. In this

balanced perspective, the existing DS that do pose a hepatotoxic risk to the public should be marked with warning labels (as drugs are) and/or removed from the shelf by existing regulatory authorities, especially if they are illegal and/or fraudulent products.

Current Regulations

The FDA, Federal Trade Commission, State Health Departments, Attorneys General, and Department of Justice work to protect the public from DS-related liver injuries (see Series article 2). As a result, almost one third (6/21) of the DS in this review table are no longer sold (indicated by shaded DS in Tables 3 & 4).

Clustered cases should, but sometimes do not, receive immediate attention. Before calling for stricter DS regulations, however, one should consider the likely effectiveness of this approach. If stringent FDA regulations cannot prevent the 1000 annual DILIs from occurring, then why apply the same regulations to DS when the vast majority are not liver toxic and any potential hazards affect only the 10% or less of the population consuming non-vitamin/mineral DS? If over 1000 drugs are potentially hepatotoxic (compared to approximately 20 DS), and these drugs have not been removed from the market for potential hepatotoxicity, then why is a stricter standard being applied to the dietary supplement industry? In fact, 22 DS represent only 0.02% of the average number of drugs that can be problematic to the liver.

Although rare, DSILIs do occur, and must be immediately intercepted by government agencies. The real solution is to fully and consistently enforce existing laws and regulations. Historically, inconsistent enforcement has allowed a few companies to cross the legal line without any consequences until as recently as 2015. Article one of

this series addresses this issue. Despite the often repeated theme that “regulation is not rigorous enough to assure complete safety of DS products,” the fact is that “enforcement” has not been sufficiently rigorous. The recent media emphasis placed on “regulation” appears to be another attempt to support legislative changes, but regulations are already in place and simply need to be “enforced.”

Limitations

The “Toxic Tables” in this review series are based on the PubMed indexing of peer-reviewed scientific journal articles and while comprehensive, are not entirely inclusive of all the literature, nor should it be viewed as such. Limiting the literature review to this resource ensures some degree of standardization. This review did not cover literature indexing resources of other countries or regions that may have more varied histories or usage of DS (including herbs) as part of their traditional treatments – for example, India (Ayruvedic), China (traditional Chinese medicine), Japan (Kanpo or Kampo), Polynesia, Africa, and South America, and elsewhere. Regional plant names and uses may be different and not identified with those commonly recognized in the United States or reported in PubMed. In addition, this review did not include non-peer reviewed, but possibly more plethoric reports integrated through international toxicity lists, MedWatch, NapAlert, Poison Control Centers, MedWatch, World Health Organization (WHO), commercial entities, and other agencies. The Institute of Medicine recommended that the FDA work with the nation's poison control centers as a source of adverse event reports, but the reliability of date is limited by factors such as inaccurate coding, co-medications, incomplete product information, lack of laboratory testing, and inadequate follow-up (Haller, 2008). Incompleteness is also a limiting factor for the tables presented

here as not all case reports may be included. Other case report limitations are discussed in Article 1 of this series (Brown, 2016).

Further limiting the results were the exclusion criteria of case reports involving herb combinations (some exceptions), Chinese herb mixtures, teas of mixed herb contents, mushrooms, poisonous plants, self-harm, excess dose (except vitamins/minerals), drugs or illegal drugs, drug-herb interactions, and confounders of drugs or diseases.

Drug-herb or herb-herb interactions can occur because some herbs act as substrates for cytochrome P450s (CYPs) and/or P-glycoprotein leading to altered drug clearance, response, and toxicity (Yang, 2006). The majority of drug-herb interactions were not severe (Posadzki, 2013), and extensively covered in other reviews (Hu, 2005; Posadzki, 2013; Yang, 2006). Drug-herb interactions are important to consider for the approximately one third (34.3%) of all US adults reporting concomitant DS and prescription medication use (Farina, 2014). It has been recommended that patients on immunosuppressant drugs, and especially transplant recipients, avoid herbs such as St. John's wort and others (chamomile, Earl grey teas, etc.) that can reduce cyclosporine levels (Rahimi, 2012; Nowack, 2005). In addition, the American Society of Anesthesiologists recommends discontinuation of herbal medicines two or more weeks prior to surgery (Dasgupta, 2006).

The most common adulterant in DS is drugs that are either added minutely through accidental contamination of uncleaned manufacturing equipment, or by a deliberate criminal act. Article 2 of this series addresses adulterated products defined by the FDA as "tainted products marketed as DS" (Brown, 2016). Regardless of their source,

toxicities are often under-reported, so published case reports may signal an emerging problem. Underreporting to regulatory authorities and publication in peer-reviewed journals is a repeating theme for case reports, especially in developing countries (Neergheen-Bhujun, 2013). Other reviews on DSILI have been published (Bunchorntavakul, 2012; Chitturi, 2008; Larrey, 1997; Licatta, 2013; Navarro, 2014-a, 2014-b, 2013-b; Pittler, 2003; Posadzki, 2013; Rohilla, 2014; Schiano, 2003; Seeff, 2015; Stickel, 2015, 2011, 2005; Teschke, 2014, 2012-b; Zheng, 2015; Zhou, 2015), but the current table attempts to cite all case reports in a tabular form, does not include reviews, restricts confounding variables, and can be continuously updated online.

Additional Case Reports

The case reports presented here do not reflect all the case reports in the literature, so additional case report submissions, pre-existing or new, are welcomed online. The author is available to assist in writing up case reports for publication, after which the data will be added to the online table.

Toxic Tables for Proactive Protection

These continuously updated online Toxic Tables can now be accessed by consumers, clinicians, and corporations to find DS and/or their ingredients that have been reported to be related to toxicity. If a DS is related to toxicity cases, regardless of how small due to idiosyncratic DS reactions, then why impart the risk to the consumer or corporation? The DS ingredients listed in these tables may need further consideration by government agencies, DS companies, manufacturers, distributors, and formulators.

The safest route for consumers is to avoid these potentially toxic DS. As always, until more information is available, it appears that DS consumption may not be prudent for people with liver, kidney, heart, and/or cancer conditions, organ transplant recipients, two weeks prior to surgery, pregnancy (except prenatal vitamins and minerals), lactation, concomitant medication, underlying disease with the exception of standard dietary therapies, and/or medical treatment without a physician's approval.

These online toxic tables and accompanying case reporting form will help provide continued Phase IV post marketing surveillance to detect possible DS toxicity cases (FDA-d). Perhaps this will help alert the government agencies responsible for upholding existing laws regulating DS, so that future outbreaks can be curtailed or even prevented.

Bullet Summary

Herbs

- Approximately 21 herbs have been related to liver injury case reports (1966 - June, 2016). Germander and usnic acid are no longer sold in the United States.
- The next three most prominent offenders (black cohosh, kava, and green tea extracts) may need warning labels.
    - USP accepts black cohosh into USP Compendia Category A, but with labeled warnings. Discontinue use with symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (see Article 1 in series).
    - USP did not admit kava into USP-NF monograph development process.
    - USP did not admit *Phyllanthus amarus* extract (whole herb in Class A).

- The last three, chaparral, aloe vera, and greater celandine, had infrequent liver injury reports over the last 50 years, but may still need warning labels.
- The remaining herbs have far fewer publications, but that does not negate their possible implications in liver toxicity — especially fo-ti, pennyroyal, senna, skullcap, and valerian.
- Traditional Chinese Medicine herbal medicinals appear to have a higher HILI rate, suggesting a greater need to review them for related liver injuries.
- Patients taking immunosuppressant drugs, and especially transplant recipients, should avoid herbs such as St. John's wort and others (chamomile, Earl grey teas, etc.) that can reduce cyclosporine levels.
- The American Society of Anesthesiologists recommends discontinuation of herbal medicines two or more weeks prior to surgery.

Dietary Supplements

- Approximately 16 DS in the literature have been related to liver injury case reports (1966 - June, 2016). Approximately 36% (9/25) of the DS related to liver toxicity in these tables are no longer sold. Vitamin A and niacin were on the list, but due to excess intake.
- DS sold for bodybuilding and weight loss, especially "fat burners," are most commonly associated with DSILI. Anabolic steroids are illegal and not DS.
- The most serious problem associated with fat burners or other designer dietary supplements is the recent trend to isolate a single ingredient from a plant (either by extracting or synthesizing it) and place it in the dietary supplement without

informing the FDA by submitting it as a New Dietary Ingredient (NDI) or submitting a New Drug Application (NDA) (see Article 2 in series).

- The names, ingredients, and corporations of DS can change so those listed here may not reflect current products on the market.

Balanced Perspective

- Liver injuries are rare, and DSILIs are even more rare.
- Current DSILI estimates in the literature should be corrected by:
    1. Removing anabolic steroids and other drugs/NDI from DSILI calculations.
    2. Including acetaminophen, the number one cause of acute liver failure, and all other causes of liver injuries for valid DSILI estimations.
    3. Listing the DS related to liver injuries (as done for drugs).
    4. Balancing perspective by reporting the annual liver transplant and death resulting from drug use that averages 2.4 and 3.1 cases respectively, compared to about only 1 liver transplant and zero deaths annually from DS (2014).
    5. Realizing that the U.S. media's emphasis on "rising" numbers of DSILI cases is disproportionate to the facts.
- DS that do pose a hepatotoxic risk should be marked with warning labels (as drugs are) and/or removed from the shelf by existing regulatory authorities, especially if they are illegal and/or fraudulent products ("tainted products marketed as DS").

References

Abu el Wafa Y, Benavente Fernández A, Talavera Fabuel A, Pérez Ramos MA, Ramos-Clemente JI. [Acute hepatitis induced by *Camellia sinensis* (green tea)]. [Article in Spanish] An Med Interna. 2005;22(6):298.

Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, Yoshioka M, Ishii H. Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. Ann Intern Med. 2003;139(6):488-92.

Alderman S, Kailas S, Goldfarb S, Singaram C, et al. Cholestatic hepatitis after ingestion of chaparral leaf: confirmation by endoscopic retrograde cholangiopancreatography and liver biopsy. Am J Gastroenterol 1994;19(3):242-7.

Anderson IB, Mullen WH, Meeker JE, Khojasteh-BakhtSC, Oishi S, Nelson SD, Blanc PD. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. Ann Intern Med. 1996;124(8):726-34.

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borras A, Soler A, Salmerón J, Martin-Vivaldi R; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129(2):512-21.

Andrade RJ, López-Ortega S, López-Vega MC, Robles M, Cueto I, Lucena MI. Idiosyncratic drug hepatotoxicity: a 2008 update. Expert Rev Clin Pharmacol. 2008;1(2):261-76.

Apestegui CA, Julliard O, Ciccarelli O, etal. Energy drinks: another red flag for the liver allograft. Liver Transpl 2011; 17:1117–1118.

Appelhans K, Smith C, Bejar E, Henig YS. Revisiting acute liver injury associated with herbalife products. World J Hepatol. 2011;3(10):275-7.

Araujo JL, Worman HJ. Acute liver injury associated with a newer formulation of the herbal weight loss supplement Hydroxycut. BMJ Case Rep. 2015;2015.

Au JS, Navarro VJ, Rossi S. Review article: Drug-induced liver injury--its pathophysiology and evolving diagnostic tools. Aliment Pharmacol Ther. 2011;34(1):11-20.

Bach N, Thung SN, Schaffner F. Comfrey herb tea-induced hepatic veno-occlusive disease. Am J Med. 1989;87(1):97-9.

Bajaj J, Knox JF, Komorowski R, Saeian K. The irony of herbal hepatitis. Ma-huang-induced haptotoxicity associated with compound heterozygosity for hereditary hemochromatosis. Dig Dis Sci 2003;48(10):1925-1928.

Barakat SE, Adam SE, Maglad MA, Wasfi IA. Effects of Cissus quadrangularis on goats and sheep in Sudan. Rev Elev Med Vet Pays Trop. 1985;38(2):185-94.

Barker J, Horn EJ, Lebwohl M, Warren RB, Nast A, Rosenberg W, Smith C; International Psoriasis Council. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol. 2011;25(7):758-64.

Bakerink JA, Gospe SM Jr, Dimand RJ, Eldridge MW. Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. Pediatrics 1996;98(5):944-7.

Banarova A, Koller T, Payer J. [Toxic hepatitis induced by Polygonum multiflorum]. [Article in Slovak] Vnitr Lek. 2012;58(12):958-62.

Bassan M. A case for immediate-release niacin. Heart Lung. 2012;41(1):95-8.

Batchelor WB, Heathcote J, Wanless IR. Chaparral-induced hepatic injury. Am J Gastroenterol 1995;90(5):831-3.

Belfrage B, Malmström R. [Several cases of liver affected by aloe vera]. [Article in Swedish] Lakartidningen. 2008;105(1-2):45.

Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). Ann Intern Med. 2006;144(1):68-71.

Benninger J, Schneider HT, Schuppan D, Kirchner T, et al. Acute hepatitis induced by greater celandine (Cheliodonium majus). Gastroenterology 1999;117(5):1234-7.

Ben Yahia M, Mavier P, Métreau JM, Zafrani ES, Fabre M, Gatineau-Saillant G, Dhumeaux D, Mallat A. [Chronic active hepatitis and cirrhosis induced by wild germander. 3 cases]. [Article in French] Gastroenterol Clin Biol. 1993;17(12):959-62.

Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. Lancet 1991;337:372-373.

Bilal M, Patel Y, Burkitt M, Babich M. Linoleic Acid Induced Acute Hepatitis: A Case Report and Review of the Literature. Case Reports Hepatol. 2015;2015:807354.

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144(7):1419-25, 1425.e1-3; quiz e19-20.

Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). Ann Intern Med. 2006;144(1):68-71.

Borum ML. Fulminant exacerbation of autoimmune hepatitis after the use of ma huang. Am J Gastroenterol. 2001;96(5):1654-5.

Bottenberg MM, Wall GC, Harvey RL, Habib S. Oral aloe vera-induced hepatitis. Ann Pharmacother. 2007;41(10):1740-3.

Brauer RB, Stangl M, Stewart JR, Pfab R, Becker K. Acute liver failure after administration of herbal tranquilizer kava-kava (*Piper methysticum*). J Clin Psychiatry 2003;64:216-8

Brent J. Three new herbal hepatotoxic syndromes. J Toxicol Clin Toxicol 1999;37(6):715-9.

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther. 2013;37(1):3-17.

Bujanda L, Palacios A, Sil varino R, Sanchez A, Munoz C. [Kava-induced acute icteric hepatitis], Gastroenterol Hepatol 2002;25:434-5.

Campbell TC, Hayes JR. Role of nutrition in the drug-metabolizing enzyme system. Pharmacol Rev. 1974;26(3):171-97.

Caravaca-Magarios F, Cubero-Gomez JJ, Arrobsvaca M. Renal and hepatic injuries in human intoxication with *Atractylis gummifera*. Nefrologia 1985;5:205-201.

Carey EJ, Vargas HE, Douglas DD, Balan V, Byrne TJ, Harrison ME, Rakela J. Inpatient admissions for drug-induced liver injury: results from a single center. Dig Dis Sci. 2008;53(7):1977-82.

Castaño G, Etchart C, Sookoian S. Vitamin A toxicity in a physical culturist patient: a case report and review of the literature. Ann Hepatol. 2006;5(4):293-395.

Castot A, Larrey D. [Hepatitis observed during a treatment with a drug or tea containing Wild Germander. Evaluation of 26 cases reported to the Regional Centers of Pharmacovigilance]. [French] Gastroenterol Clin Biol. 1992;16(12):916-22.

Catanzano G, Delons S, Benyahia TD. [2 cases of poisoning due to "gum thistle" (*Atractylis gummifera L*.). Clinical development and anatomo-pathologic lesions]. [Article in French] Maroc Med. 1969;49(529):651-5.

CDC (Centers of Disease Control & Prevention). Hepatic toxicity possibly associated with kava-containing products--United States, Germany, and Switzerland, 1999-2002. MMWR Morb Mortal Wkly Rep. 2002;51(47):1065-7.

CDC. Hepatitis temporally associated with an herbal supplement containing artemisinin - Washington, 2008. MMWR Morb Mortal Wkly Rep. 2009;58(31):854-856.

CDC. Chaparral-induced toxic hepatitis--California and Texas, 1992. MMWR Morb Mortal Wkly Rep. 1992;41(43):812-4.

Cerda C, Burguera M, Pares A. Hepatotoxicity associated with glucosamine and chondroitin sulfate in patients with chronic liver disease. World J Gastroenterol. 2013;19(32):5381-5384.

Chalasani N, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology. 2010;138(7):2246-59.

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J, Serrano J; United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenterology. 2015;148(7):1340-52.e7.

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135(6):1924-34, 1934.

Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950-66; quiz 967.

Chalasani N, Vuppalanchi R, Navarro V, Fontana R, Bonkovsky H, Barnhart H, Kleiner DE, Hoofnagle JH. Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: a case series. Ann Intern Med. 2012;156(12):857-60, W297-300.

Chao S, Anders M, Turbay M, Olaiz E, Mc Cormack L, Mastai R. [Toxic hepatitis by consumption Herbalife products a case report]. [Article in Spanish] Acta Gastroenterol Latinoam. 2008;38(4):274-7.

Chen GC, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, Eysselein V, Chung D, Reicher S, Pham BV. Acute liver injury induced by weight-loss herbal supplements. World J Hepatol. 2010;2(11):410-5.

Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology. 2013;58(1):388-96.

Cheng FK, Dunaway P. A case of supplement-induced hepatotoxicity. Case Rep Med. 2010;2010. pii: 262706.

Cheruvattath R, Orrego M, Gautam M, Byrne T, Alam S, Voltchenok M, Edwin M, Wilkens J, Williams JW, Vargas HE. Vitamin A toxicity: when one a day doesn't keep the doctor away. Liver Transpl. 2006;12(12):1888-91.

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol. 2008;23(3):366-73.

Chiu YK, Lai MS, Ho JC, Chen JB. Acute fish liver intoxication: report of three cases. Changgeng Yi Xue Za Zhi. 1999;22(3):468-73.

Chojkier M. Hepatic sinusoidal-obstruction syndrome: toxicity of pyrrolizidine alkaloids. J Hepatol. 2003;39(3):437-46.

Chow EC, Teo M, Ring JA, Chen JW. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust. 2008;188(7):420-2.

Christl SU, Seifert A, Seeler D. Toxic hepatitis after consumption of traditional kava preparation. J Travel Med. 2009;16(1):55-6.

Church RJ, Gatti DM, Urban TJ, Long N, Yang X, Shi Q, Eaddy JS, Mosedale M, Ballard S, Churchill GA, Navarro V, Watkins PB, Threadgill DW, Harrill AH. Sensitivity to hepatotoxicity due to epigallocatechin gallate is affected by genetic background in diversity outbred mice. Food Chem Toxicol. 2015;76:19-26.

Cohen DL, Del Toro Y. A case of valerian-associated hepatotoxicity. J Clin Gastroenterol. 2008;42(8):961-2.

Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. Menopause. 2004;11(5):575-7.

Cooke C, Carr I, Abrams K, Mayberry J. Arrowroot as a treatment for diarrhoea in irritable bowel syndrome patients: a pilot study. Arq Gastroenterol. 2000;37(1):20-4.

Crijns AP, de Smet PA, van den Heuvel M, Schot BW, Haagsma EB. [Acute hepatitis after use of a herbal preparation with greater celandine (*Chelidonium majus*)]. [Article in Dutch] Ned Tijdschr Geneeskd. 2002;146(3):124-8.

Curciarello J, De Ortúzar S, Borzi S, Bosia D. [Severe acute hepatitis associated with intake of Aloe vera tea]. [Article in Spanish] Gastroenterol Hepatol 2008; 31:436–438.

Dantuluri S, North-Lewis P, Karthik SV. Gotu Kola induced hepatotoxicity in a child - need for caution with alternative remedies. Dig Liver Dis. 2011;43(6):500.

Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. World J Gastroenterol. 2008;14(45):6999-7004.

Dasgupta A, Bernard DW. Herbal remedies: effects on clinical laboratory tests. Arch Pathol Lab Med. 2006;130(4):521-8.

Davis DC, Potter WZ, Jollow DJ, Mitchell JR. Species differences in hepatic glutathione depletion, covalent binding and hepatic necrosis after acetaminophen. Life Sci. 1974;14(11):2099-109.

Dao T, Peytier A, Galateau F, Valla A. [Chronic cirrhogenic hepatitis induced by germander]. [Article in French] Gastroenterol Clin Biol. 1993;17(8-9):609-10.

De Smet PA, Van den Eertwegh AJ, Lesterhuis W, Stricker BH. Hepatotoxicity associated with herbal tablets. BMJ. 1996;313(7049):92.

Diaz D, Ferroudji S, Heran B, Barneon G, Larrey D, Michel H. [Fulminant hepatitis caused by wild germander]. [Article in French] Gastroenterol Clin Biol. 1992;16(12):1006-7.

Dong H, Slain D, Cheng J, Ma W, Liang W. Eighteen cases of liver injury following ingestion of *Polygonum multiflorum*. Complement Ther Med. 2014;22(1):70-4.

Dourakis SP, Papanikolaou IS, Tzemanakis EN, Hadziyannis SJ. Acute hepatitis associated with herb (*Teucrium capitatum L.)* administration. Eur J Gastroenterol Hepatol. 2002;14(6):693-5.

Duque JM, Ferreiro J, Salgueiro E, Manso G. [Hepatotoxicity associated with the consumption of herbal slimming products]. [Article in Spanish] Med Clin (Barc). 2007;128(6):238-9.

Durazo FA, Lassman C, Han SH, Saab S, Lee NP, Kawano M, Saggi B, Gordon S, Farmer DG, Yersiz H, Goldstein RL, Ghobrial M, Busuttil RW. Fulminant liver failure due to usnic acid for weight loss. Am J Gastroenterol. 2004;99(5):950-2.

Ebrahim V, Albeldawi M, Chiang DJ. Acute liver injury associated with glucosamine dietary supplement. BMJ Case Rep. 2012;2012.

Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, Broide E, Ackerman Z, Kaluski DN, Lev B, Shouval D. Association between

consumption of Herbalife nutritional supplements and acute hepatotoxicity. J Hepatol. 2007;47(4):514-20.

Ellsworth MA, Anderson KR, Hall DJ, Freese DK, Lloyd RM. Acute liver failure secondary to niacin toxicity. Case Rep Pediatr. 2014;2014:692530.

Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. Mechanism of hepatotoxicity due to black cohosh (*Cimicifuga racemosa*): histological, immunohistochemical and electron microscopy analysis of two liver biopsies with clinical correlation. Exp Mol Pathol. 2014;96(3):279-83.

Escher M, Desmeules J, Giostra E, Mentha G. Hepatitis associated with Kava, a herbal remedy for anxiety. BMJ. 2001;322(7279):139.

Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg. 2003;138(8):852-8.

European Commission, Commission Decisions of 5 June 2003 authorizing the placing on the market of “noni juice” (juice of the fruit of *Morinda citrifolia* L.) as a novel food ingredient under Regulation (EC) Nr. 258/97 of the European Parliament and of the Council. *Official Journal of the European Union* 2003; L 144/12:12.6.2003.

European Commission on Health and Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food on Tahitian Noni Juice, 2002. Available at: http://ec.europa.eu/food/fs/sc/scf/out151_en.pdf.

Farina EK, Austin KG, Lieberman HR. Concomitant dietary supplement and prescription medication use is prevalent among US adults with doctor-informed medical conditions. J Acad Nutr Diet. 2014;114(11):1784-90.e2.

Favreau JT, Ryu ML, Braunstein G, Orshansky G, Park SS, Coody GL, Love LA, Fong TL. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann Intern Med. 2002;136(8):590-5.

FDA-a. Drug-induced liver toxicity. 08/05/2015. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm. Accessed 12/15/2015.

FDA-b. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. US Department of Health and Human Services, FDA, CDER, CBER, 2009.

FDA-c. Lipkinetix. 08/16/2013. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172824.htm. Accessed 12/1/15.

FDA-d. Postmarketing surveillance programs. FDA, 2014. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm. Accessed 6/26/16.

Federico A, Tiso A, Loguercio C. A case of hepatotoxicity caused by green tea. Free Radic Biol Med. 2007;43(3):474.

Fernández J, Navascués C, Albines G, Franco L, Pipa M, Rodríguez M. Three cases of liver toxicity with a dietary supplement intended to stop hair loss. Rev Esp Enferm Dig. 2014;106(8):552-5.

Ferrucci LM, Bell BP, Dhotre KB, Manos MM, Terrault NA, Zaman A, Murphy RC, Vanness GR, Thomas AR, Bialek SR, Desai MM, Sofair AN. Complementary and alternative medicine use in chronic liver disease patients. J Clin Gastroenterol. 2010;44(2):e40-5.

Fischer DJ, Knight LL, Vestal RE. Fulminant hepatic failure following low-dose sustained-release niacin therapy in hospital. Western Journal of Medicine. 1991;155(4):410–412.

Foley S, Butlin E, Shields W, Lacey B. Experience with OxyELITE pro and acute liver injury in active duty service members. Dig Dis Sci. 2014;59(12):3117-21.

Fong TL, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ 2nd, Hayashi P, Lee WM, Seeff LB. Hepatotoxicity due to hydroxycut: a case series. Am J Gastroenterol. 2010;105(7):1561-6.

Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, Serrano J, Lee WM, Chalasani N, Stolz A, Davern T, Talwakar JA; DILIN Network. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology. 2014;147(1):96-108.

Fontana RJ, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology. 2010;52(2):730-42.

Forouhar F, Nadel MS, Gondos B. Hepatic pathology in vitamin A toxicity. Ann Clin Lab Sci. 1984;14(4):304-10.

Fox DW, Hart MC, Bergeson PS, Jarrett PB, Stillman AE, Huxtable RJ. Pyrrolizidine (Senecio) intoxication mimicking Reye syndrome. J Pediatr. 1978;93(6):980-2.

Fu PP, Xia Q, Lin G, Chou MW. Pyrrolizidine alkaloids--genotoxicity, metabolism enzymes, metabolic activation, and mechanisms. Drug Metab Rev. 2004;36(1):1-55.

Fujii H, Takagaki N, Yoh T, Morita A, Ohkawara T, Yamaguchi K, Minami M, Sawa Y, Okanoue T, Ohkawara Y, Itoh Y. Non-prescription supplement-induced hepatitis with hyperferritinemia and mutation (H63D) in the HFE gene. Hepatol Res. 2008;38(3):319-23.

García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ; Spanish Group for the Study of Drug-Induced Liver Disease (Grupo de Estudio para las Hepatopatías Asociadas a Medicamentos GEHAM). Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol. 2011;55(3):683-91.

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, Navarro JM, Planas R, Soria MJ, Bruguera M, Andrade RJ. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. [Article in Spanish] Rev Esp Enferm Dig. 2008;100(11):688-95.

Garrido-Gallego F, Muñoz-Gómez R, Muñoz-Codoceo C, Delgado-Álvarez P, Fernández-Vázquez I, Castellano G. Acute liver failure in a patient consuming Herbalife products and Noni juice. Rev Esp Enferm Dig. 2015;107(4):247-8.

Georgiou M, Sianidou L, Hatzis T, Papadatos J, Koutselinis A Hepatotoxicity due to *Atractylis gummifera-L*. J Toxicol Clin Toxicol. 1988;26(7):487-93.

Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. Gastroenterology. 1991;100(6):1701-9.

Gloro R, Hourmand-Ollivier I, Mosquet B, Mosquet L, Rousselot P, Salamé E, Piquet MA, Dao T. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. Eur J Gastroenterol Hepatol. 2005;17(10):1135-7.

Goksu E, Kilic T, Yilmaz D. Hepatitis: a herbal remedy Germander. Clin Toxicol (Phila). 2012;50(2):158.

Gordon DW, et al. Chaparral ingestion. The broadening spectrum of liver injury caused by herbal medications. JAMA 1995;273(6):489-90.

Gori L, Galluzzi P, Mascherini V, Gallo E, Lapi F, Menniti-Ippolito F, Raschetti R, Mugelli A, Vannacci A, Firenzuoli F. Two contemporary cases of hepatitis associated with *Teucrium chamaedrys L*. decoction use: case reports and review of literature. Basic Clin Pharmacol Toxicol. 2011;109(6):521-6.

Gow PJ, Connelly NJ, Hill RL, Crowley P, Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust 2003; 178: 442-3.

Guan YS. A case report of hepatic veno-occlusive disease after ingesting dainties. World J Gastroenterol. 2006;12(41):6734-5.

Gunawan B, Kaplowitz N. Clinical perspectives on xenobiotic-induced hepatotoxicity. Drug Metab Rev. 2004;36(2):301-12.

Guévart E, Aguémon A. [Two cases of fulminant hepatitis during a curative treatment with an artesunate-amodiaquine combination]. [Article in French] Med Mal Infect. 2009;39(1):57-60.

Guo L, Shi Q, Fang JL, Mei N, Ali AA, Lewis SM, Leakey JE, Frankos VH. Review of usnic acid and Usnea barbata toxicity. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2008;26(4):317-38.

Guzman G, Kallwitz ER, Wojewoda C, Chennuri R, Berkes J, Layden TJ, Cotler SJ. Liver Injury with Features Mimicking Autoimmune Hepatitis following the Use of Black Cohosh. Case Rep Med. 2009;2009:918156.

Haaz S, Fontaine KR, Cutter G, Limdi N, Perumean-Chaney S, Allison DB. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. Obes Rev. 2006;7(1):79-88.

Haimowitz S, Hsieh J, Shcherba M, Averbukh Y. Liver failure after Hydroxycut™ use in a patient with undiagnosed hereditary coproporphyria. J Gen Intern Med. 2015;30(6):856-9.

Hamid S, Rojter S, Vierling J. Protracted cholestatic hepatitis after the use of prostata. Ann Intern Med. 1997;127(2):169-70.

Hamouda C, Amamou M, Thabet H, Yacoub M, Hedhili A, Bescharnia F, Ben Salah N, Zhioua M, Abdelmoumen S, El Mekki Ben Brahim N. Plant poisonings from herbal medication admitted to a Tunisian toxicologic intensive care unit, 1983-1998. Vet Hum Toxicol. 2000;42(3):137-41.

Hamouda C, Hédhili A, Ben Salah N, Zhioua M, Amamou M. A review of acute poisoning from *Atractylis gummifera L*. Vet Hum Toxicol. 2004;46(3):144-6.

Hardeman E, Van Overbeke L, Ilegems S, Ferrante M. Acute hepatitis induced by greater celandine (*Chelidonium majus*). Acta Gastroenterol Belg. 2008;71(2):281-2.

Harvey J, Colin-Jones DG. Mistletoe hepatitis. Br Med J (Clin Res Ed). 1981;282(6259):186-7.

Hayman RM, Dalziel SR. Acute vitamin A toxicity: a report of three paediatric cases. J Paediatr Child Health. 2012;48(3):E98-100.

Horowitz RS, Feldhaus K, Dart RC, Stermitz FR, Beck JJ. The clinical spectrum of Jin Bu Huan toxicity. Arch Intern Med 1996;156:899-903.

Hsu LM, Huang YS, Chang FY, Lee SD. 'Fat burner' herb, usnic acid, induced acute hepatitis in a family. J Gastroenterol Hepatol. 2005;20(7):1138-9.

Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, Duan W, Koh HL, Zhou S. Herb-drug interactions: a literature review. Drugs. 2005;65(9):1239-82.

Hullar TE, Sapers BL, Ridker PM, Jenkins RL, Huth TS, Farraye FA. Herbal toxicity and fatal hepatic failure. Am J Med. 1999;106(2):267-8.

Humberston CL, Akhtar J, Krenzelok EP. Acute hepatitis induced by kava kava. J Toxicol Clin Toxicol. 2003;41(2):109-13.

Iacovelli R, Palazzo A, Procopio G, Santoni M, Trenta P, De Benedetto A, Mezi S, Cortesi E. Incidence and relative risk of hepatic toxicity in patients treated with anti-

angiogenic tyrosine kinase inhibitors for malignancy. Br J Clin Pharmacol. 2014;77(6):929-38.

Jacobsen C, Semb S, Kromann-Andersen H. [Toxic hepatitis following consumption of the herbal medicinal product *Cascara Sagrada*]. Danish. Ugeskr Laeger 2009; 171:3367-9.

Jeukendrup AE, Randell R. Fat burners: nutrition supplements that increase fat metabolism. Obes Rev. 2011;12(10):841-51.

Jibrin I, Erinle A, Saidi A, Aliyu ZY. Saw palmetto-induced pancreatitis. South Med J. 2006;99(6):611-2.

Jiménez-Encarnación E, Ríos G, Muñoz-Mirabal A, Vilá LM. Euforia-induced acute hepatitis in a patient with scleroderma. BMJ Case Rep. 2012;pii: bcr2012006907.

Jimenez-Saenz M, Martinez-Sanchez Mdel C. Acute hepatitis associated with the use of green tea infusions. J Hepatol. 2006;44(3):616-7.

Jóhannsson M, Ormarsdóttir S, Olafsson S. [Hepatotoxicity associated with the use of Herbalife].
[Article in Icelandic] Laeknabladid. 2010;96(3):167-72.

Johnston DI, Chang A, Viray M, Chatham-Stephens K, He H, Taylor E, Wong LL, Schier J, Martin C[2], Fabricant D, Salter M, Lewis L, Park SY. Hepatotoxicity

associated with the dietary supplement OxyELITE Pro™ - Hawaii, 2013. Drug Test Anal. 2016;(3-4):319-327.

Jones FJ, Andrews AH. Acute liver injury associated with the herbal supplement hydroxycut in a soldier deployed to Iraq. Am J Gastroenterol. 2007;102(10):2357-8.

Joshi D, Cross TJ, Wong VS. Acute drug induced hepatitis secondary to a weight loss product purchased over the internet. Nutr J. 2007;6:13.

Joy D, Joy J, Duane P. Black cohosh: a cause of abnormal postmenopausal liver function tests. Climacteric. 2008;11(1):84-8.

Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. Rev Esp Enferm Dig. 2005;97(2):115-24.

Kafrouni MI, Anders RA, Verma S. Hepatotoxicity associated with dietary supplements containing anabolic steroids. Clin Gastroenterol Hepatol. 2007;5(7):809-12.

Kanat O, Ozet A, Ataergin S. Aloe vera-induced acute toxic hepatitis in a healthy young man. Eur J Intern Med 2006; 17:589

Kaplowitz N. Causality assessment versus guilt-by-association in drug hepatotoxicity. Hepatology. 2001;33(1):308-10.

Kaswala D, Shah S, Patel N, Raisoni S, Swaminathan S. Hydroxycut-induced Liver Toxicity.

Ann Med Health Sci Res. 2014;4(1):143-5.

Katz M, Saibil F. Herbal hepatitis: subacute hepatic necrosis secondary to chaparral leaf. J Clin Gastroenterol 1990;12(2):203-6.

Kawaguchi T, Harada M, Arimatsu H, Nagata S, Koga Y, Kuwahara R, Hisamochi A, Hino T, Taniguchi E, Kumemura H, Hanada S, Maeyama M, Koga H, Tomiyasu N, Toyomasu H, Kawaguchi M, Kage M, Kumashiro R, Tanikawa K, Sata M. Severe hepatotoxicity associated with a N-nitrosofenfluramine-containing weight-loss supplement: report of three cases. J Gastroenterol Hepatol. 2004;19(3):349-50.

Kawata K, Takehira Y, Kobayashi Y, Kitagawa M, Yamada M, Hanajima K, Murohisa G, Kawamura M, Iwaoka Y, Wada T, Morita S, Iwaizumi M, Makino S. Three cases of liver injury caused by Sennomotokounou, a Chinese dietary supplement for weight loss. Intern Med. 2003;42(12):1188-92.

Kauma H, Koskela R, Mäkisalo H, Autio-Harmainen H, Lehtola J, Höckerstedt K. Toxic acute hepatitis and hepatic fibrosis after consumption of chaparral tablets. Scand J Gastroenterol. 2004;39(11):1168-71.

Kim SY, Yim HJ, Ahn JH, Kim JH, Kim JN, Yoon I, Kim DI, Lee HS, Lee SW, Choi JH. [Two cases of toxic hepatitis caused by arrowroot juice]. [Article in Korean] Korean J Hepatol. 2009;15(4):504-9.

Kockler DR, McCarthy MW, Lawson CL. Seizure activity and unresponsiveness after hydroxycut ingestion. Pharmacotherapy. 2001;21(5):647-51.

Kowalski TE, Falestiny M, Furth E, Malet PF. Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. Am J Med. 1994;97(6):523-8.

Kraft M, Spahn TW, Menzel J, Senninger N, Dietl KH, Herbst H, Domschke W, Lerch MM. Fulminant liver failure after administration of the herbal antidepressant Kava-Kava]. [Article in German] Dtsch Med Wochenschr. 2001;126(36):970-2.

Krishna KP. The efficacy of Ayurvedic treatment for rheumatoid arthritis: Cross-sectional experiential profile of a longitudinal study. Int J Ayurveda Res. 2011;2(1):8-13.

Krishnan PV, Feng ZZ, Gordon SC. Prolonged intrahepatic cholestasis and renal failure secondary to anabolic androgenic steroid-enriched dietary supplements. J Clin Gastroenterol. 2009;43(7):672-5.

Laczek, J.; Duncan, M. Three cases of acute hepatitis in patients taking hydroxycut bodybuilding supplement. Am. J. Gastroenterol. 2008;103:S143–S144.

Lai RT, Wang H, Gui HL, Ye MZ, Dai WJ, Xiang XG, Zhao GD, Wang WJ, Xie Q. [Clinical and pathological features in 138 cases of drug-induced liver injury]. [Article in Chinese] Zhonghua Gan Zang Bing Za Zhi. 2012;20(3):185-9.

Laliberte L, Villeneuve JP. Hepatitis after the use of germander, a herbal remedy. CMAJ 1996;154(11):1689-92.

Lapi F, Gallo E, Giocaliere E, Vietri M, Baronti R, Pieraccini G, Tafi A, Menniti-Ippolito F, Mugelli A, Firenzuoli F, Vannacci A. Acute liver damage due to Serenoa repens: a case report. Br J Clin Pharmacol. 2010;69(5):558-60.

Larrey D. Hepatotoxicity of herbal remedies. J Hepatol. 1997;26 Suppl 1:47-51.

Larrey D, Pageaux GP. Drug-induced acute liver failure. Eur J Gastroenterol Hepatol. 2005;17(2):141-3.

Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, Michel H. Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. Ann Intern Med. 1992;117(2):129-32.

Lee J, Lee MS, Nam KW. Acute toxic hepatitis caused by an aloe vera preparation in a young patient: a case report with a literature review. Korean J Gastroenterol. 2014;64(1):54-8.

Lee JS, Cheong HS, Kim LH, Kim JO, Seo DW, Kim YH, Chung MW, Han SY, Shin HD. Screening of Genetic Polymorphisms of CYP3A4 and CYP3A5 Genes. Korean J Physiol Pharmacol. 2013;17(6):479-84.

Lee WM. Acute liver failure. Semin Respir Crit Care Med. 2012;33(1):36-45.

Legoux JL, Maitre F, Labarrière D, Gargot D, Festin D, Causse X. [Cytolytic hepatitis and wild Germander: a new case with reintroduction]. [Article in French] Gastroenterol Clin Biol. 1992;16(10):813-5.

Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc. 2014;89(1):95-106.

Lemaigre G, Tebbi Z, Galinsky R, Michowitcz S, Abelanet R. [Fulminating hepatitis caused by glue thistle (*Atractylis glummifera-L.),* poisoning. Anatomo-pathological study of 4 cases]. [Article in French] Nouv Presse Med. 1975 Nov 22;4(40):2565-8.

Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. Dig Dis Sci. 2005;50(3):538-9.

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. Intern Emerg Med. 2013;8(1):13-22.

Licata A, Maida M, Cabibi D, Butera G, Macaluso FS, Alessi N, Caruso C, Craxì A, Almasio PL. Clinical features and outcomes of patients with drug-induced autoimmune hepatitis: a retrospective cohort study. Dig Liver Dis. 2014;46(12):1116-20.

Linnebur SA, Rapacchietta OC, Vejar M. Hepatotoxicity associated with Chinese skullcap contained in Move Free Advanced dietary supplement: two case reports and review of the literature. Pharmacotherapy. 2010;30(7):750, 258e-262e.

Lobb A. Hepatoxicity associated with weight-loss supplements: a case for better post-marketing surveillance. World J Gastroenterol. 2009;15(14):1786-7.

Lonie TC. Excess vitamin A as a cause of food poisoning. N Z Med J. 1950;49(274):680-5.

Long J. USPlabs to eliminate aegeline from supplements amid hepatitis probe. 11/7/2013. http://www.naturalproductsinsider.com/news/2013/11/usplabs-to-eliminate-aegeline-from-supplements-am.aspx. Accessed 12/15/15.

Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust. 2003;179(7):390-1.

Lucena MI, Molokhia M, Shen Y, Urban TJ, Aithal GP, Andrade RJ, Day CP, Ruiz-Cabello F, Donaldson PT, Stephens C, Pirmohamed M, Romero-Gomez M, Navarro JM, Fontana RJ, Miller M, Groome M, Bondon-Guitton E, Conforti A, Stricker BH, Carvajal A, Ibanez L, Yue QY, Eichelbaum M, Floratos A, Pe'er I, Daly MJ, Goldstein DB, Dillon JF, Nelson MR, Watkins PB, Daly AK; Spanish DILI Registry; EUDRAGENE; DILIN; DILIGEN; International SAEC. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. Gastroenterology. 2011;141(1):338-47.

Luu, L. Liver transplants. Practice essentials. http://emedicine.medscape.com/article/776313-overview. Accessed 11/23/15.

Lyford CL, Vergara GG, Moeller DD. Hepatic veno-occlusive disease originating in Ecuador. Gastroenterology. 1976;70(1):105-8.

Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. Liver Transpl 2006; 126: 989-92.

MacGregor FB, Abernethy VE, Dahabra S, Cobden I, Hayes PC. Hepatotoxicity of herbal remedies. BMJ. 1989;299(6708):1156-7.

Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, Marles RJ, Pellicore LS, Giancaspro GI, Sarma DN. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause. 2008;15(4 Pt 1):628-38.

Mahady G, Low Dog T, Sarma DN, Giancaspro GI. Suspected black cohosh hepatotoxicity--causality assessment versus safety signal. Maturitas. 2009 Oct 20;64(2):139-40; author reply 141-2.

Manso G, López-Rivas L, Salgueiro ME, Duque JM, Jimeno FJ, Andrade RJ, Lucena MI. Continuous reporting of new cases in Spain supports the relationship between Herbalife® products and liver injury. Pharmacoepidemiol Drug Saf. 2011;20(10):1080-7.

Marcus DM, Grollman AP. Botanical medicines--the need for new regulations. N Engl J Med. 2002;347(25):2073-6.

Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology. 1997;26:664–669.

Mattéi A, Rucay P, Samuel D, Feray C, Reynes M, Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration. J Hepatol. 1995;22(5):597.

Mattei A, Bizollon T, Charles JD, Debat P, Fontanges T, Chevallier M, Trepo C. [Liver damage induced by the ingestion of a product of phytotherapy containing wild germander. Four cases]. [Article in French] Gastroenterol Clin Biol. 1992;16(10):798-800.

Mazokopakis E, Lazaridou S, Tzardi M, Mixaki J, Diamantis I, Ganotakis E. Acute cholestatic hepatitis caused by *Teucrium polium L*. Phytomedicine. 2004;11(1):83-4.

Mazzanti G, Di Sotto A, Vitalone A. Hepatotoxicity of green tea: an update. Arch Toxicol. 2015;89(8):1175-91.

McDonnell WM, Bhattacharya R, Halldorson JB. Fulminant hepatic failure after use of the herbal weight-loss supplement exilis. Ann Intern Med. 2009;151(9):673-4.

McGuffin M. Illegally marketed drug ingredients are not dietary supplements. JAMA Intern Med. 2013;173(22):2090-1.

Mengs U, Schwars T, Bulitta M, Weber K. Antitumoral effects of an intravesically applied aqueous mistletoe extract on urinary bladder carcinoma MB49 in mice. Anti cancer Res 2000;20(5B):3565-8.

Mengual-Moreno E, Lizarzábal-García M, Ruiz-Soler M, Silva-Suarez N, Andrade-Bellido R, Lucena-González M, Bessone F, Hernández N, Sánchez A, Medina-Cáliz I. [Case reports of drug-induced liver injury in a reference hospital of Zulia state, Venezuela]. [Article in Spanish] Invest Clin. 2015;56(1):3-12.

Miksad R, de Lédinghen V, McDougall C, Fiel I, Rosenberg H. Hepatic hydrothorax associated with vitamin a toxicity. J Clin Gastroenterol. 2002;34(3):275-9.

Millonig G, Stadlmann S, Vogel W. Herbal hepatotoxicity: acute hepatitis caused by a Noni preparation (Morinda citrifolia). Eur J Gastroenterol Hepatol. 2005;17(4):445-7.

Mimidis KP, Papadopoulos VP, Baltatzidis G, Giatromanolaki A, Sivridis E, Kartalis G. Severe acute cholestasis caused by *Teucrium polium*. J Gastrointestin Liver Dis. 2009;18(3):387-8.

Minuk GY, Kelly JK, Hwang WS. Vitamin A hepatotoxicity in multiple family members. Hepatology. 1988;8(2):272-5.

Molinari M, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, Nashan B, Peltekian K. Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl. 2006;12(12):1892-5.

Moro PA, Cassetti F, Giugliano G, Falce MT, Mazzanti G, Menniti-Ippolito F, Raschetti R, Santuccio C. Hepatitis from Greater celandine (*Chelidonium majus L.):* review of literature and report of a new case. J Ethnopharmacol. 2009;124(2):328-32.

Mostefa-Kara N, Pauwels A; Pines E, Biour M, et al. Fatal hepatitis after herbal tea. Lancet 1992;340(8820):674.

Mounajjed T, Graham RP, Sanderson SO, Smyrk TC. Clinical associations of hepatic stellate cell (HSC) hyperplasia. Virchows Arch. 2014;465(1):57-65

Mrzljak A, Kosuta I, Skrtic A, Kanizaj TF, Vrhovac R. Drug-induced liver injury associated with noni (*Morinda citrifolia*) juice and phenobarbital. Case Rep Gastroenterol 2013;7:19-24.

Munoz SJ, Fariello R, Maddrey WC. Submassive hepatic necrosis associated with the use of progabide: a GABA receptor agonist. Dig Dis Sci. 1988;33(3):375-80.

Muqeet Adnan M, Khan M, Hashmi S, Hamza M, AbdulMujeeb S, Amer S. Black cohosh and liver toxicity: is there a relationship? Case Rep Gastrointest Med. 2014;2014:860614.

Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. Am J Gastroenterol. 1996;91(7):1436-8.

Nadir A, Reddy D, Van Thiel DH. Cascara sagrada-induced intrahepatic cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity. Am J Gastroenterol 2000;95(12):3634-7.

Nakasone ES, Tokeshi J. A Serendipitous Find: A Case of Cholangiocarcinoma Identified Incidentally After Acute Liver Injury Due to Cascara sagrada Ingestion. Hawaii J Med Public Health. 2015;74(6):200-2.

Nam SW, Baek JT, Lee DS, Kang SB, Ahn BM, Chung KW. A case of acute cholestatic hepatitis associated with the seeds of Psoralea corylifolia (Boh-Gol-Zhee). Clin Toxicol (Phila). 2005;43(6):589-91.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. (a)

Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. Dig Dis Sci. 2013b;58(9):2682-90. (b)

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis. 2014;34(2):172-93. (a)

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, Seeff LB, Serrano J, Sherker AH, Stolz A, Talwalkar J, Vega M, Vuppalanchi R.

Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014;60(4):1399-408. (b)

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis. 2013a;17(4):715-35.

Neergheen-Bhujun VS. Underestimating the toxicological challenges associated with the use of herbal medicinal products in developing countries. Biomed Res Int. 2013;2013:804086.

Neff GW, Reddy KR, Durazo FA, Meyer D, Marrero R, Kaplowitz N. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. J Hepatol. 2004;41(6):1062-4.

Nencini C, Galluzzi P, Pippi F, Menchiari A, Micheli L. Hepatotoxicity of *Teucrium chamaedrys L*. decoction: role of difference in the harvesting area and preparation method. Indian J Pharmacol. 2014;46(2):181-4.

Ng V, Tran TT, Sundaram V. An unexpected cause of an infiltrative liver mass. Gastroenterology. 2014;147(2):e12-3.

Nisbet BC, O'Connor RE. Black cohosh-induced hepatitis. Del Med J. 2007;79(11):441-4.

Nortadas R, Barata J. Fulminant hepatitis during self-medication with conjugated linoleic acid.

Ann Hepatol. 2012;11(2):265-7.

Nowack R, Nowak B. Herbal teas interfere with cyclosporin levels in renal transplant patients. Nephrol Dial Transplant. 2005;20(11):2554-6.

O'Donnell J. Polar hysteria: an expression of hypervitaminosis A. Am J Ther. 2004;11(6):507-16.

O'hara M, Kiefer D, Farrell K, Kemper K et al. A review of 12 commonly used medicinal herbs. Arch Fam Med 1998;7(6):523-536.

Ortiz Cansado A, Crespo Valadés E, Morales Blanco P, *Sáenz de Santamaría J, González Campillejo JM, Ruiz Téllez T. [Veno-occlusive liver disease due to intake of Senecio vulgaris tea].* [Article in Spanish] Gastroenterol Hepatol. 1995;18(8):413-6.

Ossendza RA, Grandval P, Chinoune F, Rocher F, Chapel F, Bernardini D. [Acute cholestatic hepatitis due to glucosamine forte].[Article in French]. Gastroenterol Clin Biol. 2007;31(4):449-50.

Patel DN, Low WL, Tan LL, Tan MM, Zhang Q, Low MY, Chan CL, Koh HL. Adverse events associated with the use of complementary medicine and health supplements: an analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. Clin Toxicol (Phila). 2012;50(6):481-9.

Patel SS, Beer S, Kearney DL, Phillips G, Carter BA. Green tea extract: a potential cause of acute liver failure. World Gastroenterol. 2013;19(31):5174-7.

Pauwels A, Thierman-Duffaud D, Azanowsky JM, Loiseau D, Biour M, Levy VG. [Acute hepatitis caused by wild germander. Hepatotoxicity of herbal remedies. Two cases]. [Article in French] Gastroenterol Clin Biol. 1992;16(1):92-5.

PDR Staff. Physicians' Desk Reference, 70th Edition. PDR Network, 2016.

Pedrós C, Cereza G, García N, Laporte JR. [Liver toxicity of *Camellia sinensis* dried etanolic extract]. [Article in Spanish] Med Clin (Barc). 2003;121(15):598-9.

Pérez Alvarez J, Sáez-Royuela F, Gento Peña E, López Morante A, Velasco Osés A, Martín Lorente J. [Acute hepatitis due to ingestion of *Teucrium chamaedrys* infusions]. [Article in Spanish] Gastroenterol Hepatol. 2001;24(5):240-3.

Picciotto A, Campo N, Brizzolara R, Giusto R, et al. Chronic Hepatitis induced by Jin Bu Huan. J Hepatol 1998;28(1):156-7.

Pierard S, Coche JC, Lanthier P, Dekoninck X, Lanthier N, Rahier J, Geubel AP. Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution. Eur J Gastroenterol Hepatol. 2009;21(8):941-5.

Pillukat MH, Bester C, Hensel A, Lechtenberg M, Petereit F, Beckebaum S, Müller KM, Schmidt HH. Concentrated green tea extract induces severe acute hepatitis in a

63-year-old woman--a case report with pharmaceutical analysis. J Ethnopharmacol. 2014;155(1):165-70.

Pittler MH, Ernst E. Systematic review: hepatotoxic events associated with herbal medicinal products.
Aliment Pharmacol Ther. 2003;18(5):451-71.

Polymeros D, Kamberoglou D, Tzias V. Acute cholestatic hepatitis caused by *Teucrium polium* (golden germander) with transient appearance of antimitochondrial antibody. J Clin Gastroenterol. 2002;34(1):100-1.

Poon WT, Chau TL, Lai CK, Tse KY, Chan YC, Leung KS, Chan YW. Hepatitis induced by *Teucrium viscidum*. Clin Toxicol (Phila). 2008;46(9):819-22.

Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. Br J Clin Pharmacol. 2013;75(3):603-18.

Rabe C, Musch A, Schirmacher P, Kruis W, Hoffmann R. Acute hepatitis induced by an aloe vera preparation: A case report. World J Gastroenterol 2005; 11: 303-4.

Rader JI, Calvert RJ, Hathcock JN. Hepatic toxicity of unmodified and time-release preparations of niacin. Am J Med. 1992;92(1):77-81.

Rahimi R, Abdollahi M. An update on the ability of St. John's wort to affect the metabolism of other drugs. Expert Opin Drug Metab Toxicol. 2012;8(6):691-708.

Rahnema CD, Crosnoe LE, Kim ED. Designer steroids - over-the-counter supplements and their androgenic component: review of an increasing problem. Andrology. 2015;3(2):150-5.

Ramanathan VS, Hensley G, French S, Eysselein V, Chung D, Reicher S, Pham B. Hypervitaminosis A inducing intra-hepatic cholestasis--a rare case report. Exp Mol Pathol. 2010;88(2):324-5.

Ramanathan VS, Mitropoulos E, Shlopov B, Eysselein V, Chung D, Reicher S, Pham BV. An Enzyte'ing' case of acute hepatitis. J Clin Gastroenterol. 2011;45(9):834-5.

Ramos R, Mascarenhas J, Duarte P, Vicente C, Casteleiro C. Conjugated linoleic acid-induced toxic hepatitis: first case report. Dig Dis Sci. 2009;54(5):1141-3.

Raschi E, De Ponti F. Drug- and herb-induced liver injury: Progress, current challenges and emerging signals of post-marketing risk. World J Hepatol. 2015;7(13):1761-71.

Rashid NN, Grant J. Hydroxycut hepatotoxicity. Med J Aust. 2010;192(3):173-4.

Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. Gastroenterology. 1985;88(4):1050-4.

Rifai K, Flemming P, Manns MP, Trautwein C. [Severe drug hepatitis caused by *Chelidonium*].[Article in German] Internist (Berl). 2006;47(7):749-51.

Roeder E. Medicinal plants in China containing pyrrolizidine alkaloids. Pharmazie 2000; 55(10): 711-26.

Rohilla R, Garg T, Goyal AK, Rath G. Herbal and polymeric approaches for liver-targeting drug delivery: novel strategies and their significance. Drug Deliv. 2016;23(5):1645-61.

Roselle H, Ekatan A, Tzeng J, Sapienza M, Kocher J. Symptomatic hepatitis associated with the use of herbal red yeast rice. Ann Intern Med. 2008;149(7):516-7.

Roytman MM, Pörzgen P, Lee CL, Huddleston L, Kuo TT, Bryant-Greenwood P, Wong LL, Tsai N. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. Am J Gastroenterol. 2014;109(8):1296-8.

Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. Ann Intern Med. 2001;135(1):68-9.

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 2004;10(8):1018-23.

Safi KH, Filbrun AG, Nasr SZ. Hypervitaminosis A causing hypercalcemia in cystic fibrosis. Case report and focused review. Ann Am Thorac Soc. 2014;11(8):1244-7.

Sanchez W, Maple JT, Burgart LJ, Kamath PS. Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. Mayo Clin Proc. 2006;81(4):541-4.

Sansone RA, Sansone LA. Carrot man: a case of excessive beta-carotene ingestion. Int J Eat Disord. 2012;45(6):816-8.

Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts: a systematic review by the US Pharmacopeia. Drug Saf. 2008;31(6):469-84.

Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by *Teucrium polium L*.: report of two cases and review of the literature. Eur J Gastroenterol Hepatol. 2007;19(6):507-11.

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis. 2003;7(2):453-73.

Schoepfer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, Zimmermann A, Oneta CM. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J Hepatol. 2007;47(4):521-6.

Scott BA, Troppmann C, Rossaro L. Hepatotoxicity associated with a dietary supplement. Ann Intern Med. 2003g;138(8):W-W49.

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology. 2015;148(3):517-532

Semwal RB, Semwal DK, Vermaak I, Viljoen A. A comprehensive scientific overview of Garcinia cambogia. Fitoterapia. 2015;102:134-48.

Seybold U, Landauer N, Hillebrand S, Goebel FD. Senna-induced hepatitis in a poor metabolizer.
Ann Intern Med. 2004;141(8):650-1.

Sezer RG, Bozaykut A. Pediatric hepatotoxicity associated with polygermander (*teucrium polium*). Clin Toxicol (Phila). 2012 ;50(2):153.

Shad JA, Chinn CG, Brann OS. Acute hepatitis after ingestion of herbs. South Med J 1999;92(11):1095-97.

Shah NL, Zacharias I, Khettry U, Afdhal N, Gordon FD. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. Clin Gastroenterol Hepatol. 2008;6(2):255-8.

Sharma T, Wong L, Tsai N, Wong RD. Hydroxycut(®) (herbal weight loss supplement) induced hepatotoxicity: a case report and review of literature. Hawaii Med J. 2010;69(8):188-90.

Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. Arch Intern Med 1997;157(8):913-9.

Sheth A, Khurana R, Khurana V. Potential liver damage associated with over-the-counter vitamin supplements. J Am Diet Assoc. 2008;108(9):1536-7.

Shim M, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. Dig Dis Sci. 2009;54(2):406-8.

Shipley A, Berkowitz B, Rivero C. Designer steroids: Hide and Seek. The Washington Post. 10/18/2005. http://www.washingtonpost.com/wp-dyn/content/graphic/2005/10/18/GR2005101800648.html. Accessed 11/30/15.

Skoulidis F, Alexander GJ, Davies SE. Ma huang associated acute liver failure requiring liver transplantation. Eur J Gastroenterol Hepatol. 2005;17(5):581-4.

Smith A, Dillon J. Acute liver injury associated with the use of herbal preparations containing glucosamine: three case studies. BMJ Case Rep. 2009;2009. pii: bcr02.2009.1603.

Smith BC, Desmond PV. Acute hepatitis induced by ingestion of the herbal medication chaparral. Aust N Z J Med. 1993;23(5):526.

Soni MG, Burdock GA, Preuss HG, Stohs SJ, Ohia SE, Bagchi D. Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt. Food Chem Toxicol. 2004;42(9):1513-29.

Sonmez A, Yilmaz MI, Mas R, Ozcan A, Celasun B, Dogru T, Taslipinar A, Kocar IH. Subacute cholestatic hepatitis likely related to the use of senna for chronic constipation. Acta Gastroenterol Belg. 2005;68(3):385-7.

Stadlbauer V, Weiss S, Payer F, Stauber RE. Herbal does not at all mean innocuous: the sixth case of hepatotoxicity associated with morinda citrifolia (noni). Am J Gastroenterol. 2008;103(9):2406-7.

Stadlbauer V, Fickert P, Lackner C, Schmerlaib J, Krisper P, Trauner M, Stauber RE. Hepatotoxicity of NONI juice: report of two cases. World J Gastroenterol. 2005;11(30):4758-60.

Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy *Teucrium polium L*. Eur J Gastroenterol Hepatol. 2006;18(6):681-3.

Stedman C. Herbal toxicity. Semin Liver Dis 2002;22(2):195-206.

Steenkamp V, Stewart MJ, Zuckerman M. Detection of poisoning by Impila (*Callilepis laureola*) in a mother and child. Hum Exp Toxicol. 1999;18(10):594-7.

Stephens C, López-Nevot MÁ, Ruiz-Cabello F, Ulzurrun E, Soriano G, Romero-Gómez M, Moreno-Casares A, Lucena MI, Andrade RJ. HLA alleles influence the clinical signature of amoxicillin-clavulanate hepatotoxicity. PLoS One. 2013 9;8(7):e68111.

Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. Ann Intern Med. 2005;142(6):477-8.

Stickel F, Baumüller HM, Seitz K, Vasilakis D, Seitz G, Seitz HK, Schuppan D. Hepatitis induced by Kava (*Piper methysticum rhizoma*). J Hepatol. 2003;39(1):62-7.

Stickel F, Droz S, Patsenker E, Bögli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with Bacillus subtilis. J Hepatol. 2009;50(1):111-7.

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int. 2011;31(5):595-605.

Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hepatol. 2005;43(5):901-10.

Stickel F, Pöschl G, Seitz HK, Waldherr R, Hahn EG, Schuppan D. Acute hepatitis induced by Greater Celandine (Chelidonium majus). Scand J Gastroenterol. 2003;38(5):565-8.

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol. 2015;89(6):851-65.

Stillman AE, Huxtable RJ, Fox D, Hart M, Bergeson P. Pyrrolizidine (*Senecio*) poisoning in Arizona: severe liver damage due to herbal teas. Ariz Med. 1977;34(8):545-6.

Stohs SJ, Ray SD. A review and evaluation of the efficacy and safety of Cissus quadrangularis extracts. Phytother Res. 2013;27(8):1107-14.

Stohs SJ, Preuss HG, Ohia SE, Kaats GR, Keen CL, Williams LD, Burdock GA. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. World J Gastroenterol. 2009;15(32):4087-9.

Strahl S, Ehret V, Dahm HH, Maier KP. [Necrotizing hepatitis after taking herbal remedies]. [Article in German] Dtsch Med Wochenschr. 1998;123(47):1410-4.

Strasser M, Stadlmayr A, Haufe H, Stickel F, Ferenci P, Patsch W, Feldman A, Weghuber D, Datz C, Aigner E. Natural course of subjects with elevated liver tests and normal liver histology. Liver Int. 2015 Aug 10. [Epub ahead of print]

Suk KT, Kim DJ, Kim CH, Park SH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroneterol 2012;107:1380-1387.

Sullivan JB Jr, Rumack BH, Thomas H Jr, Peterson RG, Bryson P. Pennyroyal oil poisoning and hepatotoxicity. JAMA 1979;242:2873-4.

Takegoshi K, Tohyama T, Okuda K, Suzuki K, Ohta G. A case of Venoplant-induced hepatic injury.
Gastroenterol Jpn. 1986;21(1):62-5.

Takikawa H, Takamori Y, Kumagi T, Onji M, Watanabe M, Shibuya A, Hisamochi A, Kumashiro R, Ito T, Mitsumoto Y, Nakamura A, Sakaguchi T. Assessment of 287 Japanese cases of drug induced liver injury by the diagnostic scale of the International Consensus Meeting. Hepatol Res. 2003;27(3):192-195.

Tandon BN, Tandon HD, Tandon RK, Narndranathan M, Joshi YK. An epidemic of veno-occlusive disease of liver in central India. Lancet. 1976;2(7980):271-2.

Teschke R. Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review. Menopause. 2010a;17(2):426-40. (a)

Teschke R. Kava hepatotoxicity--a clinical review. Ann Hepatol. 2010;9(3):251-65. (b)

Teschke R. Traditional Chinese Medicine Induced Liver Injury. J Clin Transl Hepatol. 2014;2(2):80-94.

Teschke R, Schulze J. Suspected herbal hepatotoxicity: requirements for appropriate causality assessment by the US Pharmacopeia. Drug Saf. 2012;35(12):1091-7. (a)

Teschke R, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. World J Gastroenterol. 2013;19(19):2864-82. (a)

Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. World J Hepatol. 2013;5(7):353-63. (b)

Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. Eur J Gastroenterol Hepatol. 2013;25(9):1093-8. (c)

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32(10):1543-56. (b)

Teschke R, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: a structured causality assessment. Ann Hepatol. 2009;8(3):258-66.

Teschke R, Schwarzenboeck A, Hennermann KH. Causality assessment in hepatotoxicity by drugs and dietary supplements. Br J Clin Pharmacol. 2008;66(6):758-66.

Theiler R, Wirth HP, Flury R, Hanck A, Michel BA. [Chronic vitamin A poisoning with musculoskeletal symptoms and morphological changes of the liver: a case report]. [Article in German] Schweiz Med Wochenschr. 1993;123(51-52):2405-12.

Thomasson HR, Crabb DW, Edenberg HJ, Li TK. Alcohol and aldehyde dehydrogenase polymorphisms and alcoholism. Behav Genet. 1993;23(2):131-6.

Urban TJ, Daly AK, Aithal GP. Genetic basis of drug-induced liver injury: present and future.
Semin Liver Dis. 2014;34(2):123-33.

van de Meerendonk HW[1], van Hunsel FP, van der Wiel HE. [Autoimmune hepatitis induced by *Actaea racemosa*. Side affects of an herb extract]. [Article in Dutch] Ned Tijdschr Geneeskd. 2009;153(6):246-9.

Vanderperren B, Rizzo M, Angenot L, Haufroid V, Jadoul M, Hantson P. Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. Ann Pharmacother. 2005;39(7-8):1353-7.

Vannacci A, Lapi F, Gallo E, Vietri M, Toti M, Menniti-Ippolito F, Raschetti R, Firenzuoli F, Mugelli A. A case of hepatitis associated with long-term use of *Cimicifuga racemosa*. Altern Ther Health Med. 2009;15(3):62-3.

Vassiliadis T, Anagnostis P, Patsiaoura K, Giouleme O, Katsinelos P, Mpoumponaris A, Eugenidis N. Valeriana hepatotoxicity. Sleep Med. 2009;10(8):935.

Vilar JH, García M, Cabrera P. [Veno-occlusive liver disease induced by *Senecio vulgaris* toxicity]. [Article in Spanish] Gastroenterol Hepatol. 2000;23(6):285-6.

Vivekanandarajah A, Ni S, Waked A. Acute hepatitis in a woman following excessive ingestion of an energy drink: a case report. J Med Case Rep. 2011;22;5:227.

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. 2014;171(4):404-15.

Vuppalanchi R, Navarro V, Vega M, Bonkovsky HL, Seeff L, Serrano J; Drug-Induced Liver Injury Network (DILIN). Herbal dietary supplement associated hepatotoxicity: an upcoming workshop and need for research. Gastroenterology. 2015;148(3):480-2.

Wainwright J, Sconland MM, Candy HA. Toxicity of *Callilepis laureola*. S Afr Med J 1977; 52(8): 313-5.

Watson AR, Coovadia HM, Bhoola KD. The clinical syndrome of Impila (*Callilepis laureola*) poisoning in children. S Afr Med J 1979;55(8):290-2.

Weinstein DH, Twaddell WS, Raufman JP, Philosophe B, Mindikoglu AL. SlimQuick™ - associated hepatotoxicity in a woman with alpha-1 antitrypsin heterozygosity. World J Hepatol. 2012 27;4(4):154-7.

West, B.J., Jensen, C.J., Westendorf, J., and White, L.D. A safety review of noni fruit juice. *J Food Sci* 2007;71(8):R100-R106.

West, B.J., Jensen, C.J., and Westendorf, J. Noni juice is not hepatotoxic. *World J Gastroenterol 2006;*12(22):3616-9.

Weston CF, Cooper BT, Davies JD, Levine DF. Veno-occlusive disease of the liver secondary to ingestion of comfrey. Br Med J (Clin Res Ed). 1987;295(6591):183.

Whiting PW, Clouston A, Kerlin P.Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust. 2002;177(8):440-3.

Whitsett M, Marzio DH, Rossi S. SlimQuick™-Associated Hepatotoxicity Resulting in Fulminant Liver Failure and Orthotopic Liver Transplantation. ACG Case Rep J. 2014;1(4):220-2.

Woolf GM, Petrovic LM, Rojter SE, Wainwright S, et al. Acute hepatitis associated with the Chinese herbal product jin bu huan. Ann Intern Med 1994;121(10):729-35.

World Health Organization (WHO). The use of the WHO-UMC system for standardized case causality assessment. http://who-umc.org/Graphics/24734.pdf. Accessed 9/8/15.

Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. Arch Intern Med. 2005;165(12):1363-9.

Yang HN, Kim DJ, Kim YM, Kim BH, Sohn KM, Choi MJ, Choi YH. Aloe-induced toxic hepatitis. J Korean Med Sci 2010; 25: 492-5.

Yang L, Aronsohn A, Hart J, Jensen D .Herbal hepatoxicity from Chinese skullcap: A case report. World J Hepatol. 2012;4(7):231-3.

Yang XX, Hu ZP, Duan W, Zhu YZ, Zhou SF. Drug-herb interactions: eliminating toxicity with hard drug design. Curr Pharm Des. 2006;12(35):4649-64.

Yeong ML, Swinburn B, Kennedy M, Nicholson G. Hepatic veno-occlusive disease associated with comfrey ingestion. J Gastroenterol Hepatol 1990;5(2):211-4.

Yuan L, Kaplowitz N. Mechanisms of drug-induced liver injury. Clin Liver Dis. 2013;17(4):507-18,

Yu K, Geng X, Chen M, Zhang J, Wang B, Ilic K, Tong W. High daily dose and being a substrate of cytochrome P450 enzymes are two important predictors of drug-induced liver injury. Drug Metab Dispos. 2014 Apr;42(4):744-50

Yu EL, Sivagnanam M, Ellis L, et al. Acute hepatotoxicity after ingestion of Morinda citrifolia (noni berry) juice in a 14-year-old boy. J Pediatr Gastroenterol Nutr 2011; 52:222–224.

Yuce B, Gulberg V, Diebold J, Gerbes AL. Hepatitis induced by Noni juice from Morinda citrifolia: a rare cause of hepatotoxicity or the tip of the iceberg? Digestion. 2006;73(2-3):167-70.

Zheng EX, Navarro VJ. Liver Injury from Herbal, Dietary, and Weight Loss Supplements: a Review.
J Clin Transl Hepatol. 2015;3(2):93-8.

Zhou Y, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21,789 patients. Eur J Gastroenterol Hepatol. 2013;25(7):825-9.

Zhou SF, Xue CC, Yu XQ, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. Ther Drug Monit. 2007;29(6):687-710.

Table 1. Selected liver injuries briefly defined

Type of Liver Injury	Definition
Elevated liver enzymes Elevated bilirubin	Two- or three-fold + or greater increase in* Alkaline transferase (ALT); Alkaline phosphatase (ALP) Two-fold or greater increase in: Bilirubin in the presence of increased ALT and ALP
Jaundice	Yellowish pigmentation of the skin and whites of eyes along with possible darker urine (due to high bilirubin levels)
Hepatitis (acute or chronic)	Inflammation of the liver
Cholestasis	Impaired bile flow
Steatosis (Fatty liver disease)	Excessive accumulation of fat in the liver cells
Fibrosis	Excessive connective tissues builds up in the liver
Veno-occlusive disease	Connective tissue and collagen block hepatic veins
Cirrhosis	Liver tissue becomes scarred and loses function
Necrosis	Death of liver tissue

Acute liver failure	Rapid (1-12 weeks) liver dysfunction in a patient without prior known liver disease
Chronic liver disease or failure	Liver disease for over 6 months resulting in gradual loss of liver function to the point of failure
Hepatic encephalopathy	Liver failure contributing to confusion, altered consciousness level, and coma
Liver transplant	Diseased liver (or portion) is replaced with a healthy liver (or portion). Follows acute liver failure or end-stage liver disease.
Death (CDC, 2013)	18,146 due to alcoholic liver disease** 18,281 not due to alcohol (chronic liver disease and cirrhosis)

FDA-b, 2009; *Teschke, 2013-a, and **http://www.cdc.gov/nchs/fastats/liver-disease.htm (2013)

See American College of Gastroenterology for the latest diagnostic recommendations

Table 2. Most common causes of liver transplant in the United States

Medical Condition	Percent	Estimated number of 6,000 liver transplants a year
Hepatitis C virus	30	1,800
Alcoholic liver disease	18	1,080
Idiopathic/autoimmune	12	720
Primary biliary cirrhosis	10	600
Primary sclerosing cholangitis	8	480
Acute liver failure	7	420
Hepatitis B virus	6	360
Metabolic liver disease (inborn errors of metabolism)	3	180
Cancer	3	180
Other	3	180

Source: Luu, 2014

Table 3. Herb Induced Liver Injuries Reported in PubMed*

Common Name	Scientific Name	Suggested Active Compounds	Uses	Herbal Induced Liver Injury (HILI)	References
Aloe Vera	*Aloe barbadensis*	Anthraquinones	Laxative, gastric problems, aging, general well being	Elevated ALT and AST, jaundice, acute hepatitis	Belfrage, 2008 Bottenberg, 2007 Curciarello, 2008 Kanat, 2006 Lee, 2014 Rabe, 2005 Yang, 2010
Arrowroot Juice	*Maranta arundinacea*, but several plants serve as sources including *Zamia*	Unknown	Treating diarrhea (10 ml 3x/day) (Cooke, 2000)	Hepatitis in two cases in Korea (source of arrowroot may be different, possibly kuzu)	Kim, 2009

	integrifolia, - Pueraria lobata (kuzu in Japan)				
Black Cohosh	*Actaea racemosa*	Triterpenes glycosides and polyphenols	Menopause, hot flashes	Acute hepatitis, necrosis, fibrosis, encephalopathy, liver transplant and death The Dietary Supplement Information Expert Committee determined that black cohosh products should be labeled to include a cautionary statement (Mahady, 2008)	Chow, 2008 Cohen,2004 Enbom, 2014 Guzman, 209 Joy, 2008 Levitsky, 2005 Lontos, 2003 Lynch, 2006 Muqeet, 2014 Nisbet, 2007 Pierard,2009 Van de Meerendonk, 2009 Vannacci, 2009 Whiting, 2002

Black Cohosh Note: In 2008, a significant number of hepatotoxic cases (approximately 30) came to the attention of the Dietary Supplement Information Expert Committee of the US Pharmacopeia's Council of Experts. Their review stated that black cohosh products should be sold with a cautionary statement indicating that hepatotoxicity is possible (Mahady, 2008). A previous 2002 review required no such statement showing that sometimes a significant period of time must pass for a sufficient number of cases to surface before action is taken. Thirteen additional cases were reported in 2009 (Mahady, 2009), and another review is provided by Teschke, 2010a.					
Cascara	*Cascara sagrada*	Anthracene glycoside	Laxative	Fibrosis, hepatitis	Jacobsen, 2009 Nadir, 2000
Chaparral	*Larrea divaricata*	Nordihydroguaiaretic acid (NDGA)	Cancer (melanoma), bronchitis, colds, rheumatic pain, stomach pain, and chicken pox.	Hepatitis, liver toxicity, liver failure. 13 cases of hepatitis reported to FDA between1992-94. Removed from the GRAS list in 1970.	Alderman, 1994 Batchelor, 1995 CDC, 1992 Gordon, 1995 Katz, 1990 Kauma, 2004 Shad, 1999 Sheikh, 1997 Smith, 1993
Chinese Herbs (single herbs only as herb combinations were excluded)					

Fo-ti (called Shou Wu Pian when combined with other herbs)	*Polygonum Multiflorum*	Anthraquinones	Hair growth, gray hair prevention, restore youthful vigor, prostatitis, constipation, erectile dysfunction, cancer.	18 cases of jaundice. Hepatitis (numerous cases of hepatitis reported with Shou Wu Pian)	Banarova, 2012 Dong, 2013
Celandine (Greater celandine)	*Chelidonium majus L.*	Isoquinoline alkaloids	Externally for skin conditions (warts, eczema); internally for liver, gallstones, irritable bowel syndrome	Cholestatic hepatitis	Crijns, 2002 Hardeman, 2012 Moro, 2009 Rifai,2006 Stickel, 2006 Strahl, 1998
Comfrey	*Symphytum officinale* *Symphytum asperum*	Pyrrolizidine alkaloids*	Internally for blunt injuries (bruises, sprains, and broken bones), digestive tract problems (ulcers, diarrhea, inflammation), rheumatism and	Veno-occlusive disease, tends to lack symptoms of jaundice or increased liver enzymes	Bach, 1989 Ridker, 1985 Weston, 1987 Yeong, 1990

			pleuritis. Externally as a gargle for gum disease, pharyngitis, and strep throat.		
Comfrey Notes: The sale fo comfrey is banned in Canada and Germany, but not the United States (Stickle, 2005)					
Germander	Teucrium chamaedrys L Teucrium polium Teucrium viscidum	Diterpenes	Weight loss, gout, digestive aid, fever. Most of those affected were ingesting 600 - 1600 mg/day for 2 months (Stickle, 2005).	Hepatitis, liver transplant, and death. Total of 52+ cases. Includes the 26 hepatitis cases in France where germander was banned in 1992 (Castot,1992). Most recovered, but there were two cirrhosis cases, 1 liver transplant and 1 death (Gori, 2011).	Ben Yahia, 1993 Castot, 1992 Dao, 1993 Diaz,1992 Dourakis, 2002 Goksu, 2012 Gori, 2011 Laliberte, 1996 Larrey, 1992 Legoux, 1992 Mattei, 1995 Mattei, 1992 Mazokopakis, 2004

					Mimidis, 2009 Mostefa-Kara,1992 Nencini, 2014 Pauwels, 1992 Perez, 2001 Polymeros, 2002 Poon, 2008 Savvidou, 2007 Sezer, 2012 Starakis, 2006
Gota Kolu	*Centella asiatica*	Pentacyclic triterpenic saponosides	Weight loss	4 cases of hepatitis with 2 positive rechallenges	Dantuluri 2011 Jorge 2005
Green Tea Extract	*Camellia sinensis*	Catechins - epigallocatechin-3-gallate (EGCG)	Weight loss	Hepatitis, 2 liver transplants. 34 reports - 27 cases possible, 7 probable (Sarma, 2008).	Abu, 2005 Bonkovsky, 2006 Garcia-Cortes, 2008 (3) Gloro, 2005 (LT)

					Molinari, 2006 (LT) Patel, 2013 Pedros, 2003 Pillukat, 2014 Sarma, 2008 (27)
Green Tea Extract: See Hydroxycut and other dietary supplements containing green tea extract. Exolise®, a weight loss supplement, was withdrawn from the market in France and Spain due to hepatotoxicity (Weinstein, 2012).				19 cases (2 listed here) were summarized by Mazzaniti (2015) with 11 possible cases and 8 probable (CIOMS /RUCAM). Four were beverage based. All recovered except 2 with declining labs, and the 4 liver transplants were patients taking multiple ingredients. Ten cases were primarily green	

	tea/extract. 44 yr female with acute liver failure followed by transplant taking 720 mg/day for weight loss (Molinari, 2006) Two cases of green tea drinks: 1) 51 yr female drinking unknown cups/day for 5 years with elevated enzymes and positive rechallenge (Federico, 2007), 2) 45 yr male drinking 6 cups a day for 4 months with hepatitis and positive	

				rechallenge (Jimenez-Saenz, 2006)	
Groundsel	*Senecio vulgaris* *Senecio longilobus*	Pyrrolizidine alkaloids	Traditional medicinal teas in Mexico, Jamaica, Afghanistan, India. Constipation, colic, epilepsy, worms. Not recommended for internal use due to its toxic and carcinogenic pyrrolizidine alkaloids.	Ascites, hepatitis, veno-occlusive liver disease, infant death	Fox, 1978 Oritz, 1995 Stillman,1977 (D) Vilar, 2000
Impila	*Callilepis laureola*	Atractylside	Traditional Zulu remedy that means “good health.” Ward off evil spirits in children. About 44% of deaths in children under 10 years (Wainwright,1977).	Hypoglycemia and prolonged prothrombin times are universal symptoms. Leucocytosis (80%), acidic breathing (73%), convulsions (52%), coma (40%),	Steenkamp, 1999 Wainwright, 1977 Watson, 1979

				diarrhea or vomiting (40%), jaundice (13%), elevated enzymes (Watson, 1979). Acute liver and renal failure. Acute fatal hepatocellular necrosis, especially in children. Death.	
Jin Bu Huan (JBH)	*Lycopodium serratum*	Levo-tetrahydropalmatine; Pyrrolizidine alkaloids	Traditional Chinese Medicine used as a sedative sleeping aid, analgesic, and for indigestion.	Acute hepatitis, life threatening bradycardia, respiratory distress, liver damage.	Brent, 1999 Horowitz, 1996 Picciotto, 1998 Woolf,1994
Kava	*Piper methysticum*	Kava lactones (kava pyrones)	Anxiety and insomnia. Traditional use as a cultural beverage in Polynesia. A review of	Acute hepatitis necrotizing hepatitis, cholestatic hepatitis, lobular hepatitis,	Brauer 2003 Bujanda 2002 CDC, 2002 Christi ,2009

			kava cases is provided by Teschke, 2010b.	fulmitant hepatic failure, liver transplant, death. Consuming alcohol with kava may be a triggering factor.	Escher, 2001 Gow, 2003 Humberston, 2003 Kraft, 2001 Russmann, 2001 Stickel, 2003 Strahl, 1998
Pennyroyal (American or European)	*Mentha pulegium*	Pulegone	Oil or tea leaves used in Hispanic cultures to treat colic, stimulate menses, & induce abortion.	Rapid onset. Elevated liver enzymes, liver necrosis, coma, death (especially in infants & young women)	Anderson, 1996 (3) Bakerink, 1996 (D) Sullivan, 1979 (D)
Rattlebox	*Crotalaria sessiliflora* *Crotalaria longirostrata*	Pyrrolizidine alkaloids	Chinese remedy for cancer. Seeds sometimes accidently mixed with foods in India, China, South America, and other	Chronic diarrhea, cirrhosis, liver necrosis, biliary hyperplasia, fibrosis, veno-occlusive disease, hepatomegaly, death	Guan, 2006 Lyford, 1976 Ng,2014 Tandon,1976

	Crotalaria (species)		countries. Teas in Mexico.		
Saw palmetto	*Serenoa repens*	Estrogenic and antiandrogenic effects (Jibrin, 2006)	Benign prostate enlargement	58 yr male with elevated enyzmes and enlarged liver and history of Gilbert's syndrome taking 900 mg of dried extract + 660 mg of berry powder. Symptoms decreased when stopping supplement.	Lapi, 2010
Senna	*Cassia angustifolia*	Menthofuran Anthraquinones	Laxative	Hepatitis, liver necrosis. Positive re-exposure (Beuers 1991)	Beuers, 1991 Seybold, 2004 Sonmez, 2005 Vanderperren, 2005
Skullcap	*Scutellaria*	Cytotoxic flavonoids	Anxiety, insomnia	Hepatitis, liver failure	Estes, 2003 (LT)

	lateriflora			and death	Hullar,1999 (LT,D)
Thistle (Blue, glue, pine or Mediterranean thistle)	*Atractylis gummifera*	Diterpenoid glucosides	Stomach aches and stomach ulcers. Common cause of accidental poisoning in Mediterranean children eating plants. Thistle looks like wild artichoke and the root is like a chewing gum	Severe hepatitis, necrosis, liver failure, liver transplant, death	Caravaca, 1985 Catanzano, 1969 Georgiou, 1988 (D) Lemaigre, 1975 Hamouda, 2004 Hamouda, 2000
Usnic acid	*Usnea lichens (fungi & algae)*	Usnic acid extracted from lichens	Traditional Chinese antimicrobial agent (Guo, 2008). Weight loss – popular ingredient in fat burner formulations that increase metabolism and thermogenesis.	Liver transplant. FDA received 21 of liver toxicity from dietary supplements containing usnic acid (Guo, 2008). See dietary supplements LipoKinetix and UCP-1.	Durazo, 2004 LT

Valerian	*Valeriana officinalis L.*	Valeric acid	Anxiety, insomnia	Acute hepatitis, hepatomegaly (no jaundice), liver Fibrosis	Cohen, 2008 Vassiliades, 2009
Add a DSILI case report not on the list or make comments/corrections					
New herb	*New*	New	New	New	New

*These case reports are compiled from published papers in the scientific literature. Commercial formulations may have changed.

Shaded herbs no longer sold on the internet

* Pyrrolizidine alkaloids exhibit a clear dose-dependent hepatotoxicity and are banned in Europe and North America (Stickel, 2015). PA's can be classified into saturated and unsaturated, with the latter being well-known hepatotoxic and carcinogenic compounds. They generate toxic metabolites resulting in hepatic veno-occlusive disease and/or liver cancer (Fu, 2004; Lin, 2009). Pyrrolizidine alkaloids are likely the responsible liver toxicity agents for comfrey, goundsel, Hathisunda, and Jin Bu Huan. Children in South Africa and Jamaica have developed ascites, hepatomegaly and cirrhosis after drinking 'bush tea'' (Stickle, 2005). Reviews of PA-containing plants are provided by Roeder, 2000 and Chojkier, 2003.

Table 4. Dietary Supplement Induced Liver Injury Cases Reported in PubMed and by FDA*

Common Name	Suspected Substance* (formulations often changed)	Uses	Dietary Supplement Induced Liver Injury	References
Bakuchi tablets	Psoralea corylifolia leaves with psoralens	Vitiligo	64/F with severe hepatotoxicity via elevated liver enzymes. CIOMS probable score 8	Teschke, 2009
Anabolic steroids	Illegal class III controlled substances.			
Note: Anabolic steroids. These are not legal dietary supplements so case reports are not listed. The abuse of anabolic androgenic steroids led them to being classified as controlled substances by The Anabolic Steroid Control Act of 1990 (Krishman, 2009). It is illegal to possess, manufacture, distribute or dispense them unless it is for strict medical purposes				

such as androgen deficiency, rare forms of aplastic anemia, and counteracting catabolic states such as trauma and HIV wasting (Kafrouni, 2007; Krishman, 2009). Liver injury includes peliosis hepatitis, benign or malignant neoplasms, cholestatis, and if prolonged, nephropathy (Krishman, 2009). Many anabolic steroids have been related to hepatotoxicity cases (Kafrouni, 2007; Krishnan, 2009; Shah, 2008). The Anabolic Steroid Control Act of 1990 may be too specific in listing anabolic steroids because chemists can alter a known steroid to create a new one to circumvent controlled substance laws and avoid detection thorugh standard drug screens (Rahnema, 2014). These “designer steroids” have shifted from being sold on the black market to certain body-building dietary supplements. Sport officials become aware of the new steroids, the FDA rarely bans them, and manufacturers are rarely penalized (Shipley, 2005). If the FDA does ban them and or “related substances,” a new designer steroid can be made. If the designer steroid is not on the label, the manufacturer is also violating labeling laws.				
Conjugated linoleic acid (CLA)	Conjugated linoleic acid	Weight loss	26 yr female with hepatitis 63 yr female with fulminant hepatic failure requiring transplant; 46 yr female with jaundice,	Bilal, 2015 Nortadas, 2012 Ramos, 2009

			and confirmed liver biopsy	
Euforia	Acai berry, mangosteen, Aloe vera, resveratrol, curcumin, black seed, blueberry, pomegranate, green tea, noni, goji	Anti-inflammatory and antioxidant	45 yr female with necrosis and hepatitis; 8.8% of systemic sclerosis have liver damage, but she had a positive rechallenge taking 2 ounces daily	Jimenez, 2012
Exilis	Similar to Hydroxycut – Green tea extract, *Garcinia cambogia, Gymnema sylvestre*, and others	Weight loss Other products may be on the market that mimic Hydroxycut's formulation that was removed from the market.	25 yr male with elevated enzymes, nausea, vomiting, fatigue, fulminant hepatic failure, & liver transplant. Took Exiis for two weeks.	McDonnell, 2009

Flavocoxid (Limbrel)	Proprietary blend of 2 flavonoids, baicalin and catechins derived from *Scutellaria baicalensis* (Skullcap related to liver injuries), and Acacia catechu	Medical food requiring a prescription for osteoarthritis	4 patients with elevated liver enzymes in DILIN study	Chalasani, 2012 (4)
Glucosamine &/or Glucosamine chondroitin		Osteoarthritis	28/F with jaundice, hepatitis and itching after taking glucosamine for 1 month. Elevated enzyme levels normalized after withdrawal.	Cerda, 2013

			56/F with elevated enzymes.	
			55 yr female with elevated enzymes and jaundice after 2 weeks on glucosamine.	Ebrahim, 2012
			52 yr male with elevated enzymes and itching after 3 weeks of glucosamine.	Ossendza, 2007
			64 yr male with jaundice, acute renal failure, fulminant hepatic failure, and death after taking glucosamine and chondroitin sulfate for 4 weeks.	Smith, 2009

			57 yr female with jaundice and chronic hepatitis after taking glucosamine for 4 weeks.	
Glucosamine Notes: Glucosamine can be sold as is or more commonly available in a variety of commercial preparations that combines it with chondroitin sulfate, MSM (methylsulfonylmethane), manganese ascorbate, or cartilage (shark or bovine). The glucosamine itself comes in a variety of types (eg, glucosamine sulfate, glucosamine hydrochloride, and *N*-acetylglucosamine) in tablet, capsule, powder or liquid form (Smith, 2009). One survey of 150 chronic liver disease patients showed that 15% (23/150) were taking glucosamine and/or chondroitin sulfate (Cerda, 2013).				
Green Tea Extract	*Camellia sinensis* Catechins - epigallocatechin -3-gallate (EGCG)	Weight loss	Hepatitis, 2 liver transplants. 34 reports - 27 cases possible, 7 probable (Sarma, 2008). 19 cases (2 listed here) were summarized by Mazzaniti (2015) with 11 possible cases and 8 probable	Abu, 2005 Bonkovsky, 2006 Garcia-Cortes, 2008 (3) Gloro, 2005 (LT) Molinari, 2006 (LT) Patel, 2013 Pedros, 2003 Pillukat, 2014 Sarma, 2008 (27)
Catechins are implicated in liver toxicity, but 40% (29/73) of dietary supplement products analyzed for catechins did not				

identify green tea extract on the label which is a violation of current labeling laws (Navarro, 2013a).	(CIOMS/RUCAM). Four were beverage based. All recovered except 2 with declining labs, and the 4 liver transplants were patients taking multiple ingredients. Ten cases were primarily green tea/extract. 44 yr female with acute liver failure followed by transplant taking 720 mg/day for weight loss (Molinari, 2006) Two cases of green tea drinks: 1) 51 yr female drinking unknown cups/day for 5 years with elevated	

			enzymes and positive rechallenge (Federico, 2007), 2) 45 yr male drinking 6 cups a day for 4 months with hepatitis and positive rechallenge (Jimenez-Saenz, 2006)	
Herbalife®	Numerous products with variable ingredients - pills, powders, shakes, teas, bars, etc.	Well-being, weight loss, nutritional support	63 yr F with hepatitis	Chao, 2008
Herbalife® Notes: Over 34 Herbalife® cases from at least 5 countries since 2007 have been reported (Stickel, 2011). Another review retrieved 53 cases of which 8 had a positive unintentional reexposure (Teschke, 2013b). Many ingredients			37/F with jaundice 53/F with jaundice	Chen, 2010
			3 cases of hepatotoxicity in Spain.	Duque, 2007

are in each Herbalife® product, and customers tend to take more than one product. Appelhans (2011) states numerous reasons why Chen's (2010) 3 case reports are not scientifically supported, including that Herbalife® is not a single product, and that there was insufficient information on patient histories, dosage/frequency, concomitant medications, and product ingredients. Five plus other articles defending Herbalife can be found in PubMed under Appelhan's authorship.	12 patients identified in Israeli hospitals by Ministry of Health. Hepatitis resolved in 11 patients, one succumbed to complications following liver transplant. Three experienced 2nd bout of hepatitis after rechallenge.	Elinav, 2007
	56 yr F with hepatitis and necrosis. Noni also consumed (see below)	Garrido-Gallego, 2015
	Five cases in Iceland: elevated liver enzymes and 2 with hepatitis. RUCAM = probable in 3, possible in 2. WHO criteria = certain in 1, probable in 2, possible in 2	Johansson, 2010
	A search of Spanish	Manso, 2011

	Pharmacovigilance Centres (2003-2010) revealed 20 cases, 12 required hospitalization, 9 were jaundiced, 2 experienced positive rechallenge. Karch and Lasagna scale = 1 definite, 14 probable, 5 possible.	
	Two cases of probable cause and a fatality.	Menqual-Moreno, 2015 (2)
	Ten cases of hepatitis detected by a questionnaire sent to all Swiss hospitals (1998-2004). Liver biopsy showed hepatic necrosis, marked lymphocytic - eosinophilic infiltration, and	Schoepfer, 2007

			cholestasis in 5 patients; 1 with fulminant liver failure and transplant. CIOMS = certain in 2, probable in 7, possible in 1.	
			Two patients with hepatitis and cirrhosis respectively after ingesting bacterially (*Bacillus subtilis*) contaminated products. CIOMS = probable.	Stickel, 2009
Hydroxycut®	Numerous formulations with different ingredients: Green tea extract; *Garcinia*	Weight loss and body building (See Elixis above)	41/M with jaundice taking Newer version Hydroxycut®, SX-7 Clean Sensory	Araujo, 2015

	cambogia (hydroxycitric acid); *Ma huang* extract (ephedra) (Bajaj 2003) *Cissus quadrangularis* (toxic to animals) (Barakat, 1985); 2000 formula = hydroxagen?, guarana extract, L-carnitine, ma huang extract,			

	willow bark extract, chromium picolinate (Kockler, 2001)			
Hydroxycut® Notes: Hydroxycut® was withdrawn by its manufacturer after a May 1, 2009 warning issued by FDA for its possible role in 23 cases of hepatotoxicity reported via MedWatch (Sarma, 2010). Lobb (2009) published a review on hepatotoxicity cases related to Hydroxycut®. Hydroxycut® was named after one of its ingredients, hydroxycitric acid, an extract from *Garcinia cambogia* (Stohs, 2009). In 2009, fourteen different Hydroxycut® formulations containing up to 20 different ingredients existed. Eight of the 14 formulas contained hydroxycitric acid. Semwal (2015) provides a comprehensive review of *Garcinia cambogia*, while Stohs (2009) and Soni (2004) summarize studies			31/F with jaundice resolved within 2 weeks	Chen, 2010
			40/F on 6 pills daily with elevated liver enzymes. 33/F with jaundice	Dara, 2008
			8 patients at different medical centers; 3 required liver transplants; 1 death.	Fong, 2010
			/M Army soldier with jaundice	Jones, 2007
			23, 25, 25 yr males in the military on Hydroxycut with liver biopsies revealing acute	Laczek, 2008

supporting Hydroxycut's® and hydroxycitric acid's safety respectively. Stoh (2013) also supported the safety of *Cissus quadrangularis*.			hepatitis, steatosis, and cholestatis respectively.	
			23/M with jaundice on Hydroxycut Hardcore	Rashid, 2010
			28/M with jaundice	Shim, 2009
			27/M with jaundice 30/M with jaundice, cholestatis	Stevens, 2005
Inneov masa capilar®	Green tea extract (27-30%), grape seed catechins, taurine, & zinc gluconate.	Stop hair loss	59/F on pills for 1 month with necrosis, jaundice (probable on CIOMS/RUCAM) 31/F taking pills for 1 month with elevated enzymes (highly probable)	Fernandez, 2014
Kalms Tablets (not Calms; different product)	Skull cap, valerian (formula may have changed)	Sedative		MacGregor, 1989 (2)

LipoKinetix®	Contained norephedrine, yohimbine, 3,5-diiodothyronine, sodium usniate (See usnic acid), and caffeine.	Weight loss	7 cases of severe hepatotoxicity (20-32 yrs of age; 5 were Japanese) taking LipoKinetix® (4 on other products listed) for 10-32 days with jaundice.	Favreau, 2002 (7)
FDA removed it from market in 2001. FDA has received multiple reports of persons who developed liver injury or liver failure while using Lipokinetix (FDA, 2013-c).			32 yr female with necrosis. 32 yr female with liver transplant.	Neff, 2004
			24 yr female taking LipoKinetix® for 3 months with jaundice followed by liver transplant	Scott, 2003
Lipolyz® and Somalyz®	Fat burner Lipolyz® contained:	Fat burner Somalyz® contained: GABA (667 mg),	28 yr female bodybuilder with unresponsive encephalopathy requiring	Krishna, 2011

	Propionyl l-carnitine (500 mg), green tea extract (300 mg), usnic acid (12 mg), guggulsterone (10 mg)vitamin E (20 IU), C-Amp (2 mg)	Propionyl l-carnitine (167 mg), phosphatidylcholine (50 mg); usnic acid (4 mg), melatonin (1 mg), vitamin E (20 IU)	liver transplant after taking two fat burners for 1 month. The underlined substances could have contributed. Although no cases appear with GABA, it is possible because Progabide, a GABA drug mimetic, resulted in severe hepatic failure after 4 weeks (Munoz, 1988).	
Move Free Advanced	Skullcap Glucosamine	Osteoarthritis	2 patients with hepatotoxicity that resolved upon ceasing supplement. Probable 6 on Naranjo scale. 78 yr female with hepatitis. Positive re-exposure (Yang, 2012)	Linnebur, 2010 Yang, 2012

Niacin (3 gm, slow release)	Niacin, a B-vitamin	Prescribed for high blood cholesterol. Energy drinks do get that “buzz” (tingling from niacin).	69 yr male switched from fast to slow (timed) release niacin and experienced hepatitis	Bassan, 2012
Niacin Notes:			17 yr male with acute liver failure after taking excess niacin to deter drug test.	Ellsworth, 2014
			3 cases of niacin induced hepatitis	Mounajjed, 2014
			FDA review of niacin related to liver toxicity – adverse reactions in 6 on regular niacin, 2 on slow release, and 10 who switched from regular to slow (timed) release niacin.	Rader, 1992

			22 yr female with acute hepatitis after consuming 10 cans of energy drink daily (contained niacin)	Vivekanandarajah, 2011
OxyElite Pro®	Version 1 DMAA (1,3-dimethylamyl-amine) (See Cardiotoxicity)	Weight loss, bodybuilding	7 military patients – 5 with jaundice and 1 having a liver transplant	Foley, 2014
	Version 2 Aegeline	Weight loss, bodybuilding	Hawaii Department of Health reporting on 29 patients in Hawaii using OxyElite Pro with 12 using only OxyElite Pro. Jaundice.	Johnston, 2016
	Version 2 Aegeline	Weight loss, bodybuilding	Physician review of 8 patients (all Polynesian or Asian from Hawaii that has	Roytman, 2014

			one liver center in the state) hospitalized – 7 with jaundice, 2 with liver transplants, and 1 death. RUCAM/CIOMS scale – 7 probable, 1 highly probable.	
Pro-Lean	One capsule (to be taken once per day) contains ma-huang, guarana, kola nut, white willow bark, ginkgo biloba, bladderwrack, gotu kola, boron, ginseng, fo-ti,	Weight loss	20 yr female taking product for two weeks with jaundice, & hepatitis.	Joshi, 2007

	magnesium salicylate, folic acid, bee pollen, spirulina and ginger root, chromium vitamin B12, vanadium, caffeine, cyperus root extract, tyrosine.			
Sennomotokoun ou	11 herbs: kudzuvine root, coix seed, hawthorn fruit, wolfbeery fruit, chrysanthemmu m flower, louts	Chinese DS for weight loss. Removed from market in Japan due to adverse hepatotoxic reactions.	63 yr female with jaundice 24 yr female with jaundice 53 yr female with elevated enzymes and dark urine 120 reports of hepatotoxicity on the Japan Ministry of	Kawata, 2003

	leaves, tangle kelp, radish seeds, cassia seeds, jiogulan leaf, tea leaf extracts?		Health, Labour & Welfare website (2000-2002). Hyperthyroidism should be considered as it also contains thyroid hormones, T3. 32 reports of thyroid dysfunction.	
UCP-1	Usnic acid, L-carnitine, calcium pyruvate	Weight loss	28 yr female on UCP-1 for 3 months. Jaundice, hepatic encephalopathy, liver transplant. 38 yr male (husband of above female) taking UCP-1 for 3 months, but also on desloratidine, famotidine, and naproxen,	Sanchez, 2006

			acetaminophen/oxycodone, cyclobenzaprine, and 120 g alcohol. Jaundice.	
Venencapsan®	Horse chestnut leaf, milfoil, celandine, sweet clover, milk thistle, dandelion root.	Varicoseveins, hemorrhoids, and phlebitis	69 yr female with jaundice and elevelated enzymes, returned to normal, but jaundice returned with rechallenge.	De Smet, 1996
Venoplant	*Aesculus hippocastanum* (horse chestnut) extracts	Venous insufficiency	27 yr male with jaundice, necrosis, cholestatis	Takegoshi, 1986
Vitamin A	Recommended daily value is 5,000 IU/day. 25,000 for 6		3 Chinese men consuming fish livers. Headache, dizziness, nausea, vomiting fever, skin peeling.	Chiu, 1999

	years and 100,000 for 6 months are toxic. Children toxicity at 1500 IU/kg body weight (Penniston 2006)			
Vitamin A Notes: It has been known for more than half a century that extreme vitamin A dosages can cause severe headaches, mailase, weakness, irritability, and liver injuries. The Artic explorers and Eskimoes knew not to consume polar bear liver that averages 450,000 IU per 3 ounces. The liver of certain seals, artic foxes, wolves and many fish is also high (O'Donnell, 2004)			3 Chinese pediatric cases in New Zealand of a 2 yr female, 11 and 14 year old boys. Consumed fish livers. Headache, vomiting, abdominal pain, red, peeling rash.	Hayman, 2012
			New Zealand Chinese fisherman ingesting fish	Lonie, 1950

	livers. Headache, vomiting, peeling skin.	
	male	Castano, 2006
	60 yr male liver transplant after taking 500,000 IU daily for 4 months, then 100,000 IU for 6 months.	Cheruvattath, 2006
	Fibrosis, splenomegaly and ascites	Forouhar, 1984
	Yr male with hepatotoxicity on 25,000 IU/day	Kowalski, 1994
	41 patients with vitamin A hepatoxocity due to 25,000 to 100,000 daily; 6 died	Geubel, 1991
	52 yr female with hepatic hydrothorax. Ingested 270,000 IU daily.	Miksad, 2002
	3 family members with	Minuk, 1988

			hepatotoxicity from 20,000 to 45,000 per day for 7-10 years.	
			4 yr female with cystic fibrosis and hypervitaminosis A	Safi, 2014
			48 yr male with skin discoloration + elevated liver enzymes	Sansone, 2012
			59 yr male with cirrhosis ingesting 13,000 ug/day	Sheth, 2008
			69 yr female with hepatomegaly	Theiler, 1993
Usnic Acid	*Usnea lichens (fungi & algae)* Usnic acid extracted from		Fulminant hepatic failure requiring liver transplant Hepatic necrosis	Sanchez, 2006

	lichens			
Add a DSILI case report not on the list or make comments/corrections				
New DS	New	New	New	New

*These case reports are compiled from published papers in the scientific literature. Commercial formulations may have changed.

Shaded dietary supplements no longer sold on the internet

Table 5. Insufficient Evidence for DS Induced Liver Injury Case Reports

Common Name	Scientific Name	Suggested Active Compounds	Uses	Liver Injury	References
Artemisinin	Isolated from *Artemisia annua*	Amodiaquine or other possible drugs combined with this herb. A partner drug with a longer half-life is used to make the derivatives more effective.	Artemisinins (artesunate, artemether, and artemisinin), have potent anti-malarial activity, and are the first line of treatment recommended by WHO against malaria (CDC 2009). Also used against flatworms (flukes).	Severe hepatitis under prolonged amodiaquine treatment has been reported since 1985 (Guevart, 2009). A partner drug with a longer half-life is used to make the derivatives more effective.	CDC, 2009 Guevart, 2009
Bee pollen	*Apis mellifera* L.	Unknown	Immune system	33/F with elevated liver enzymes on two tablespoons	Shad, 1999

				of pure bee pollen for several months. Taking erythromycin for acne. 69 M with jaundice taking 14 tablets mixed herbs for 6 weeks (21 herbs, including black cohosh, chaparral, comfrey).	
Boh-Gol-Zhee Bu Ku Zi Pa-Go-Zhee	*Psoralea corylifolia* dried mature seeds	Unknown	Asian remedy for osteoporosis, osteomalacia, and bone fractures	44/F took 10 times the usual dose for 7 weeks and experienced liver necrosis and cholestasis	Nam, 2005
Cascara	*Cascara sagrada*	Anthracene glycoside	Laxative	77/F Japanese with jaundice taking 3-4 capsules (250 mg *Cascara sagrada* bark + 12 other herbs) for 3 days, but also on verapamil, losartan-	Nakasone, 2015

				hydrochlorothaizide, lovastatin, and metformin.	
Chaso	Chinese herbal supplement containing green tea, *cassia toreae semen,* lotus leaves, *Gynostemma pentaphyllum makino* extract, aloe, *F. crataegi fructus,* and raphanin semen.	Contained N-nitroso-fenfluramine, a known liver toxin (carcinogenic).	Weight loss	Six F aged 25-55 (Japanese) with elevated enzymes, 1 liver transplant	Adachi, 2003

Enzyte	Gingko biloba, Epimedium sagittum, Korean gingseng, Avenasativa extract, maca root, saw palmetto berry, Ptychopetalum olacoides (muira puama extract), octaconasol, L-arginine,	Unknown	Male enhancement	40/M with untreated hepatitis C secondary to intravenous drug use diagnosed with hepatitis.	Ramanathan, 2011

	Tribulus terrestris extract, pine bark, & Swedish flower pollen. Minerals such as niacin, zinc oxide, and copper				
Ephedra or Ma Huang (Chinese name)	*Ephedra sinica*	Ephedrine and pseudoephedrine	Weight loss and energy. Has thermogenic effects. Originally a nasal decongestant and bronchial asthma treatment, but discontinued (Nadir, 1996). Known for	58/F on single herb, but omeprazole drug related to hepatitis	Borum, 2001

			cardiac side-effects (see Cardiotoxicity article)		
Ephedra Note: An ephedra link to liver injury has been suggested, but it has a stronger association with cardiotoxicity (see table).				3 incidences in retrospective study of liver transplant cases 1/2001 to 10/2002, but no actual case reports: 23/F was also taking kava and died; 51/M had chronic HBV and needed a liver transplant; 21/M was also on disulfiram had a liver transplant and died.	Estes, 2003 (3)
				33/F taking Chinese herbal mixture containing Ma Huang with hepatitis. Researchers speculated that it might be another ingredient as this was the first reported case.	Nadir, 1996

				12 patients with liver injuries taking dietary supplements containing other ingredients, of which two contained usnic acid	Neff, 2004 (12 LT)
				Chinese herb mixture of 7 total herbs	Skoulidis, 2005
				9 different supplements – not all 30+ ingredients listed	
Glucosamine &/or glucosamine chondroitin			Osteoarthritis	71/F with underlying chronic hepatitis had elevated enzymes after taking glucosamine for 1year. Elevated enzyme levels normalized after withdrawal.	Cerda, 2013
				77/F with underlying chronic hepatitis with allergic skin	Cerda, 2013

				reaction. Conditions may have compromised their liver's ability to metabolize drugs and DS.	
				55/F (Japanese) with highly probable (CIOMS) for elevated enzymes and hepatitis. Refused to share supplements and only family revealed soybean extract, glucosamine, lutein (there may be others). The hyperferritinemia may have contributed to the liver injury.	Fujii, 2008
				55/F with elevated enzymes after taking mixture of	Smith, 2009

				glucosamine, black cohosh, Kalms, cod liver oil, evening primrose oil for 6 months	
Hydroxycut®	See Table 2	Green tea extract; *Garcinia cambogia* (hydroxycitric acid); *Ma huang* extract (ephedra) (Bajaj, 2003) *Cissus quadrangularis* (toxic to animals) (Barakat, 1985)	Weight loss and body building	44/M with pre-existing hepatitis A.	Bajaj, 2003
See Hydroxycut® above				23/M with liver failure due to hereditary coprophorphyria	Haimowitz, 2015

				(HCP)	
				27/M with jaundice, but also gallstones and elevated enzymes and taking other supplements: supplements (Hydroxycut, Black powder, mitotropin, xenadrine, arson, and L-glutamine powder 23)	Kaswala, 2014
				19/M with elevated liver enzymes, but liver biopsy revealed acute cholangitis (infection of bile duct treated with antibiotics)	Sharma, 2010
Lipolyz® and Somalyz®	Fat burner Lipolyz® contained: Propionyl l-carnitine (500	Fat burner Somalyz® contained: GABA (667 mg), Propionyl l-	Weight loss	28/F bodybuilder with unresponsive encephalopathy requiring liver transplant after taking two fat burners for 1 month. Several of the	Krishna, 2011

	mg), green tea extract (300 mg), usnic acid (12 mg), guggulsterone (10 mg)vitamin E (20 IU), C-Amp (2 mg)	carnitine (167 mg), phosphatidylcholine (50 mg); usnic acid (4 mg), melatonin (1 mg), vitamin E (20 IU)		underlined substances could have contributed. Although no cases appear with GABA, it is possible because Progabide, a GABA drug mimetic, resulted in severe hepatic failure after 4 weeks (Munoz, 1988).	
Mistletoe	*Viscus album*, but herbal remedy contained kelp, motherwort, skullcap, and			49 yr female with hepatitis that returned 2 years later with rechallenge, but mixed herbal remedy contained skullcap, a known liver toxin.	Harvey, 1981

	mistletoe				
Move Free Advanced	Product contains glucosamine, chondroitin, hyaluronic acid, and Uniflex proprietary extract (combination of Chinese skullcap and black catechu).		Arthritis	2 patients with hepatotoxicity (Probable on Naranjo scale)	Linnebur, 2010
Multiple dietary supplements			Well being, etc	45 yr male with jaundice taking 9 different dietary supplements for 1-4 months	Cheng, 2010

Niacin			High blood cholesterol	16 yr male with pre-existing liver transplant (twice) had hepatitis following energy drink (3 cans within 4 hours). Niacin levels unknown, but current 2015 levels at recommended daily value.	Apestegui, 2011
				56 yr male with emphysema admitted to hospital for difficulty breathing following a respiratory tract infection and possibly pneumonia. Taking only 1 gram of niacin. Liver enzymes abnormal on 7th day in hospital, followed by liver failure and death on day 10.	Fisher, 1991
Noni	*Morinda citrifolia*	One ounce of pure noni juice	Stomach cancer, improved immunity	45 yr male with elevated liver enzymes drinking unknown	Millonig, 2005

		daily (for several months)		amount of noni juice for 3 weeks. Tested positive for hepatitis A.	
				38 yr F on 2 ounces daily of noni juice (% not stated, started in January). Also on phenobarbital (LiverTox.gov), and possibly on previous pain medication (not noted) following January surgery.	Mrzljak, 2013
Noni Notes: West et al., (employed in the Research and Development Department of Tahitian Noni Juice, Prove, UT) questioned the causality of each noni juice case because of pre-existing medical conditions or DILI related drugs (West 2006, 2007). He reported that four of the five case reports appeared in Europe around the time that noni fruit juice was approved as a Novel Food by the European-Commission in 2003 (European, 2003), based on a 2002 report by the Scientific Committee on Food (European, 2002). Four of the six PubMed noni cases (67%) involved the same author, Stadlbauer, who reported these cases in				43 yr male with gliobastoma, on chemotherapy and levetiracetam (LiverTox.gov), started drinking 40 ml of noni juice for 3 weeks.	Stadlbauer, 2008
				29 yr male with previous hepatitis following paracetamol. Asthma treated	Stadlbauer, 2005

Germany or Austria (Stadlbauer, 2005; Yuce, 2005), and the 2008 case is of questionable causality due to the presence of levetiracetam, a drug listed on LiverTox.gov as associated with liver injury (Stadlbauer, 2008). No PubMed cases have occurred in Hawaii, Polynesia or Asia where noni is traditionally consumed. While some commercial noni juiced products contain 100% noni juice, the majority of these products do not, and some may contain less than 10% juice that includes other juices.	with inhalitave beta2-agonists and glucocorticoids. Also taking Chinese herbal mix containing bupleuri, pinellia, scutellaria (LiverTox.gov), codonopsis, glycyrrhizae, schizonepeta, and paeonia. Acute liver failure followed by liver transplant; 62yr female with acute hepatitis. Had chronic B-cell leukemia treated with fludarabine (LiverTox.gov).	
	14 yr boy with acute hepatotoxicity after ingesting ten 2 ounce bottles of Mind (Ultra International). Analysis revealed less than 1% noni	Yu, 2011

				fruit juice and no anthraquinones. Aloe vera (LiverTox.gov) was one of the ingredients.	
				24 yr female with hepatitis. She had multiple sclerosis and was taking beta-interferon (LiverTox.gov) for 6 weeks and noni juice for 4 weeks.	Yuce, 2006
Onshido	Rhodiola (*Rhodiola rosea*), chaste tree (*Vitex agnus castus*), Juniper (*Juniperus communis*), soy (*Glycine max*),	Contained N-nitroso-fenfluramine, a known liver toxin (carcinogenic).	Weight loss	Six F aged 27-63 with elevated enzymes and 1 death.	Adachi, 2003

	Asian ginseng (*Panax ginseng*), Japanese knotweed (*Polygonum cuspidatum*) extracts, brown seaweed (*Fucus vesiculosus*), dandelion (*Taraxacum officinale*), yerba mate (*Ilex Paraguar-iensis*), uva-ursi (*Arctostaphylos uva ursi*), phytosterols (*Glycine max*),				

	l-theanine, caffeine, vitamins D, K, B6 and B12, folate, and calcium.				
Red Yeast Rice	*Monascus purpureus* is the red mold that grows on rice (making it red)	Lovastatin, HMG-CoA (3-hydroxy-3-mehylglutaryl-coenzyme A	Lowering high blood cholesterol	62 yr female with necrosis, fibrosis and hepatitis after taking 1200 mg daily of red yeast rice for 4 months. Also on two drugs that have rare instances of liver injuries – montelukast and fluoxetine.	Roselle, 2008
Red Yeast Rice Notes: It's entirely possible that the red yeast rice contributed to the liver injuries because this product the original source of Lovastatin.					
Saw Palmetto	Prostata is a combination of zinc picolinate,	Estrogenic and antiandrogenic effects (Jibrin, 2006)	Benign prostate enlargement	65 yr male with jaundice and itching after taking Prostata for two weeks. Multiple ingredients.	Hamid, 1997

	pyridoxine, Lalanine, glutamic acid, apis mellifica pollen, silica, hydrangea extract, panex ginseng, serenoa serrulata, and pygeum africanum.				
	Serenoa repens	Excessive daily dose of 900 mg. Standard dose is 320 mg/day.		58 yr male with elevated enyzmes and enlarged liver and history of Gilbert's syndrome taking high amounts of saw palmetto	Lapi, 2010

				(900 mg of dried extract) + of berry powder (660 mg). Symptoms decreased with ceasing the supplement.	
	Supplement name or ingredients not provided	Unknown		55 yr male recovered alcoholic (15 yrs) with cholestatic hepatitis and acute pancreatitis. Liver may have already been compromised or influenced by pancreatitis.	Jibrin, 2006
SlimQuick™	24 yr female with x taking four caplets daily for 3 months. Taking tetracycline	Weinstein, 2012	Weight loss	52 yr female with jaundice, fulminant hepatic failure, and liver failure after drinking SlimQuick™ for two days while fasting. She was also taking metoprolol, a rare inducer of liver injury.	Whitsett, 2014

	known to induce liver injury even though excluded due to histopathology.			Possible DS–drug interaction.	
Vitamin A	Retinol Retinal Carotenoids	5082 IU/day consumed 5000 IU/day recommended	Vision, healthy skin and mucous membranes, reproduction, growth, and protection as an antioxidant.	46/M patient consumed Formula 1 Herbalife shake and two multivitamin tablets for 12 years. Jaundice recovery attributed to previous bile duct stricture and ceasing supplements, but a bile duct stent was inserted	Ramanathan, 2010
Add a DSILI case report not on the list or make comments/corrections					
New DS	New	New	New	New	New

*These case reports are compiled from published papers in the scientific literature. Commercial formulations may have changed.

Table 6. Comparing yearly liver transplants and deaths due to drugs and DS

Author	Liver transplant Drugs	Death Drugs		Liver Transplant DS	Death DS
Andrade 2005	0.5	1		1	0
Chalisani 2008	4	7	**vs**	0.3	0
Fontana 2014	3.1	1.3		1.1	0.14
Average	**2.4**	**3.1**		**0.8**	**0.05**

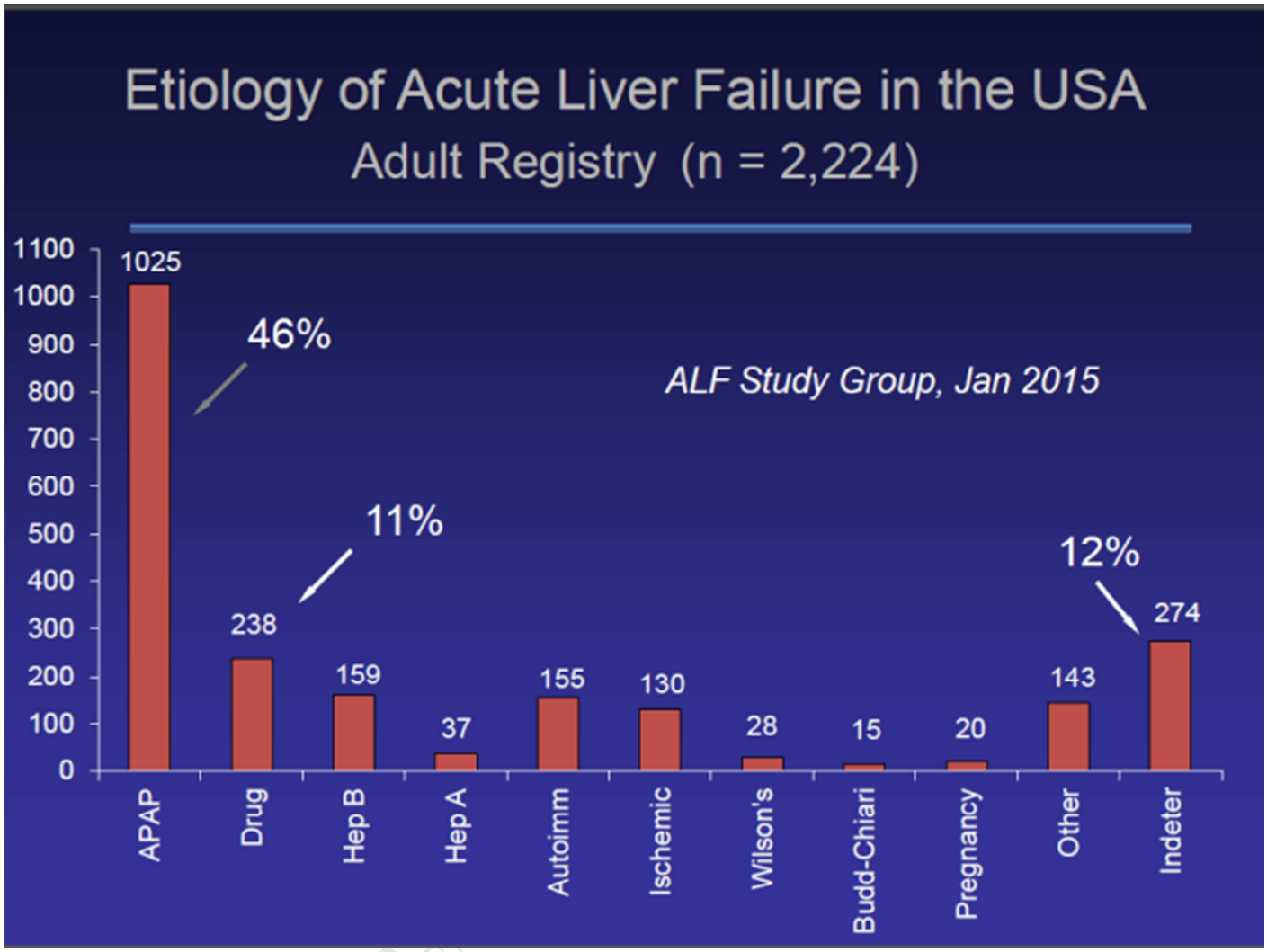

Figure 1. Etiology of acute liver failure in USA (2015) (FDA-a, 2015)

Highlights for Review

The manuscript was edited by a professional developmental editor for flow and grammar. The track changes of this edit are added, however, I made more positive changes that are not tracked, but you can see the difference.

Content was updated to include references up to June, 2016

Bullet points were added at the end of the manuscript