

## Liver Injury from Herbal, Dietary, and Weight Loss Supplements: a Review

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### Abstract

Herbal and dietary supplement usage has increased steadily over the past several years in the United States. Among the non-bodybuilding herbal and dietary supplements, weight loss supplements were among the most common type of HDS implicated in liver injury. While drug induced liver injury is rare, its consequences are significant and on the rise. The purpose of this review is to highlight case reports of weight loss products such as Hydroxycut and OxyElite Pro as one form of HDS that have hepatotoxic potential and to characterize its clinical effects as well as pattern of liver injury. We also propose future strategies in the identification and study of potentially hepatotoxic compounds in an effort to outline a diagnostic approach for identifying any drug induced liver injury.

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### Introduction

The use of herbal and dietary supplements (HDS) in the United States (U.S.) has steadily increased over the past several decades. In the early 1970s, the prevalence of dietary supplement use was 28% and 38% among adult men and women, respectively.<sup>1</sup> More recent data from The National Health and Nutrition Examination Survey (NHANES) 2003–2006 have revealed a dramatic rise in usage, with approximately 50% of all Americans and 70% of adults  $\geq 71$  y reporting dietary supplement use.<sup>2</sup>

Direct causality to liver injury is difficult to establish with HDS, as they are comprised of a variety of different

**Keywords:** Drug induced liver injury; Herbal and dietary supplements; Weight loss supplements.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug induced liver injury; DILIN, Drug Induced Liver Injury Network; DSHEA, Dietary Supplement Health and Education Act; EGCG, epigallocatechin gallate; FDA, Food and Drug Administration; HCA, hydroxycitric acid; HDS, herbal and dietary supplements; HEV, hepatitis E virus; HPLC, high performance liquid chromatography; IgM, immunoglobulin M; INR, international normalization ratio; M&V, Maria & Victorino; NHANES, The National Health and Nutrition Examination Survey; OEP, OxyElite Pro; PT, prothrombin time; RUCAM, Roussel Uclaf Causality Assessment Model; TCMs, traditional Chinese medicines; ULN, upper limit of normal; UPLC-QTOF-MS, ultra performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry.

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compounds that may change over time, are prone to contamination or adulteration, and can be used with other agents, including conventional medications. The purpose of this review is to highlight the hepatotoxic potential of HDS weight loss products and to discuss the available case reports on liver injury due to such products. Through this qualitative analysis, we aim to provide insight to the clinician who is faced with a patient with suspected liver injury from HDS and to the investigator who is focused on HDS research.

### HDS induced liver injury in the U.S. and abroad

HDS usage is occasionally associated with liver injury, potentially leading to acute liver failure. However, direct causality is difficult to confirm, and the total impact of liver injury from HDS on the U.S. population is unknown. That being said, the U.S. Drug Induced Liver Injury Network (DILIN) has reported that the proportion of cases on liver injury attributed to HDS has increased over the past 10 years.<sup>3</sup>

Although there is still much to be learned about the epidemiology of drug and dietary supplement induced liver injury in the Western World, data from two population based studies published in France and Iceland provide some insight. Sgro *et al.* investigated a region in France where its inhabitants were likely to obtain their medical care locally, thus ensuring a truer estimate of incident liver injury. Data collected over 3 years revealed an annual incidence rate of drug induced liver injury (DILI) of 13.9 per 100,000 inhabitants. When extrapolated to the country of France, this data predicted more than 8,000 cases of DILI annually. However, only 400 to 500 such cases were reported, suggesting that DILI was largely underestimated in the general population.<sup>4</sup>

In 2013, a study based on the Icelandic population revealed an incidence of DILI of 19.1 per 100,000 inhabitants per year.<sup>5</sup> This is a higher estimate than that of the French study, and several distinctions between the two studies are worth noting. The Icelandic study was published 10 years after the 2002 French study and, therefore, included new drugs, such as biological agents, that have a significant impact on the incidence of DILI. In addition, the Iceland study incorporated inpatients and outpatients, whereas the French publication only included outpatients. While both of these studies attempted to estimate the true incidence of DILI within a population, their results may be difficult to generalize given the homogeneity of the populations studied.

Since prescriptions are monitored centrally in Iceland, the Iceland study was able to estimate the risk of liver injury from specific medications. Eight medications (amoxicillin/clavulanate, diclofenac, azathioprine, infliximab, nitrofurantoin, isotretinoin, atorvastatin, and doxycycline) were

implicated in the majority of injury events. Interestingly, 16% of liver injury cases were attributed to HDS, and the commonly implicated hepatotoxic ingredient *Camellia sinesis* (green tea extract) was noted in several instances.

### The definition of liver injury

In 1989, an international consensus meeting established the definition of liver injury as an increase of more than twice the upper limit of normal (ULN) in the serum levels of alanine aminotransferase (ALT) or conjugated bilirubin or a combined increase in the levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin, with one of these being more than twice the ULN.<sup>6</sup> During the same meeting, patterns of liver injury were described, with a predominant initial elevation of ALT associated with hepatocellular injury. Cholestatic injury was linked to a predominant elevation of ALP. Furthermore, the R ratio (the ratio of the ULN of ALT to the ULN of ALP) was used to quantify these patterns of injury; where  $R > 5$  indicated a hepatocellular pattern,  $R < 2$  indicated a cholestatic pattern, and an R value in between revealed a mixed pattern.

More contemporary definitions of liver injury allowed for significantly higher liver enzyme levels. In 2001, the definition of liver injury was proposed as an ALT level of more than three times the ULN and a total bilirubin level of more than twice the ULN.<sup>7</sup> While these values can be used by clinicians as a guide in identifying liver injury, they are intended to be used in the drug development process and in the investigation of potentially hepatotoxic medications.

A distinction must be made between elevated liver tests that reflect injury and other tests that reflect impaired function, a more ominous consequence of hepatotoxicity. Whereas liver injury can be detected with liver enzyme tests and their relationship to one another, serum albumin, conjugated bilirubin, and coagulation tests (prothrombin time, PT; international normalization ratio, INR) are indicators of liver function. Typically, but not uniformly, the degree of liver injury parallels the degree of impaired liver function.

### The diagnosis of liver injury

Diagnosing liver injury as a result of HDS begins with a thorough history of the substances ingested, particularly since patients may be asymptomatic, not forthcoming with a history of their use, or exhibit subtle symptoms at the initial time of presentation.

Exclusion of other causes of injury, such as viral hepatitis, autoimmune etiologies, anatomic malformations, and metabolic disturbances, must be performed. In particular, hepatitis E virus (HEV) should be ruled out in the diagnosis of DILI. A study from the DILIN revealed that out of 318 suspected cases of DILI, nine patients tested positive for anti-HEV immunoglobulin M (IgM), where acute hepatitis E was the most likely diagnosis in seven patients and was a possible primary diagnosis for two patients. These results indicated that infection with HEV may explain a small proportion of cases of suspected DILI and patients should be tested accordingly.<sup>8</sup>

Although the diagnosis of DILI relies on the initial history and clinical presentation, efforts have been made to objectify data and assess causality. The Roussel Uclaf Causality Assessment Model (RUCAM) and Maria & Victorino (M&V) scale have been developed for such purposes.<sup>9,10</sup> A validated

causality algorithm,<sup>11</sup> the RUCAM scale is used universally in the clinical setting.

Arguably, consensus expert opinion, as used by the DILIN, is the de facto gold standard in the U.S. for assessing the causal association between a drug or HDS and liver injury. A study comparing the DILIN causality assessment approach and RUCAM revealed that the former was more likely to generate a score supportive of DILI, although significant interobserver variability was found for both approaches.<sup>12</sup>

Unfortunately, none of the conventional causality assessment approaches are perfectly suited to accurately assess HDS associated liver injury. For example, the variable composition of HDS and the potential for adulteration and contamination are not accounted for in any causality assessment approach.

The diagnosis of DILI due to a particular HDS can be in question at times, but a positive rechallenge test can be used to confidently establish and confirm a given diagnosis.<sup>13,14</sup> Unfortunately, due to the obviously harmful risks to the patient, this is an approach that has largely been abandoned, except in cases of unintentional rechallenge.

### Obesity and weight loss in the U.S.

According to the DILIN study in the U.S., HDS are a common cause of liver injury and, relative to prescribed drugs, HDS-related hepatotoxicity is on the rise.<sup>15</sup> From 2004 to 2013, 136 patients were enrolled and found to have liver injury due to HDS, of which 45 had liver injury due to bodybuilding HDS and 85 had liver injury due to nonbodybuilding HDS. Among the nonbodybuilding HDS, weight loss supplements were among the most common type implicated in injury.<sup>16</sup>

Rates of obesity have increased over the past several decades, with its prevalence reported as 32.2% among adult men and 35.5% among adult women in 2007-2008.<sup>17</sup> Likewise, there is a concomitant increase in the popularity of weight loss products, with an estimated total revenue of 60 billion dollars in 2013.<sup>18</sup> Conventionally recommended means of weight loss include lifestyle adjustments that decrease caloric intake and increase physical activity. However, alternative methods of weight loss have become increasingly popular, with the use of weight loss supplementation comprising a large part.

In a survey conducted in 2008 among 3,500 U.S. adults, 33.9% of those who made a serious weight loss attempt reported using a dietary supplement.<sup>19</sup> Additionally, users as well as nonusers of dietary supplements held the belief that these products are regulated by the Food and Drug Administration (FDA), and that they are safer than over-the-counter or prescription medications. The results of this study highlighted two significant points: the use of dietary supplements as an alternative or complementary form of weight loss is common and users perceive them to be safe.

While HDS are marketed as natural products and ostensibly safe, they are regulated under the auspices of the 1994 Dietary Supplement Health and Education Act (DSHEA), quite differently from drugs by the FDA. Under DSHEA, dietary supplements are not held to the same standards as prescription drugs and can be marketed without clinical safety studies (<http://www.fda.gov/RegulatoryInformation/default.htm>).

### Dietary supplements for weight loss

In 2002, products marketed for weight loss under the Hydroxycut label were launched for consumption. Shortly after their release, reports of death due to cardiac and cerebrovascular events in previously healthy patients taking Hydroxycut products were reported.<sup>20</sup> The adverse events were thought to be due to ephedra, a cardiovascular stimulant, and by the end of 2004, dietary supplements containing ephedra were removed from the market. However, usage of Hydroxycut continued as modified products were ephedra free.

After the final ban of ephedra, another popular weight loss dietary supplement, Oxyelite Pro (OEP), became available on the market. In contrast to Hydroxycut, OEP did not contain ephedra. While current formulations of Hydroxycut and OEP are no longer manufactured with ephedra, they are still comprised of multiple ingredients, some with suspected hepatotoxic potential. Although infrequent, these products have been implicated in cases of mild hepatitis to severe liver failure requiring transplantation. There is no convention for the classification of HDS and weight loss supplements. Moreover, some products could be marketed for multiple uses. As such, a product sold for weight loss could also be advertised for other purposes, such as performance enhancement.

In this review, we define weight loss products as dietary supplements that are marketed for the purpose of weight reduction, "fat burning" or "increasing metabolism". Using Ovid MEDLINE search, we used the following terms, "weight loss supplements" "liver injury" and "hepatotoxicity" to identify clinical case reports of liver injury due to HDS used for weight loss.

### Case reports of liver injury due to HDS marketed for weight loss

In 2009, the FDA issued a warning after 23 cases of severe liver injury were purportedly due to products sold under the Hydroxycut label. A particular product formulation was recalled shortly thereafter. The first case report published described two men, aged less than 35 who had both taken Hydroxycut at the recommended dose and presented several weeks after commencing use with fatigue and jaundice.<sup>21</sup> They did not have evidence of viral or autoimmune hepatitis (exclusion of hepatitis E was not reported) and denied use of acetaminophen or other drugs or herbal supplements. While there were many similar characteristics between the two cases upon presentation, one striking difference was the pattern of liver injury. The first case had a hepatocellular pattern of injury (ALT 3131, alkaline phosphatase 171, R>5), whereas a cholestatic pattern was observed in the second case (ALT 43, alkaline phosphatase 530, R<2). The quality of these cases is limited by the lack of formal causality assessment, as hepatotoxicity due to Hydroxycut was assumed by the temporal relationship of supplement ingestion and development of symptoms.

In a larger case series, eight patients with liver injury from Hydroxycut products were described.<sup>22</sup> Three of the eight required liver transplantation, with the most common presenting symptoms being nausea, vomiting, abdominal pain, and fatigue. All eight patients exhibited a hepatocellular pattern of injury (R > 5). Six published case reports since 2007 described clinical characteristics of hepatotoxicity from Hydroxycut

products.<sup>23-27</sup> Of the nine patients described, seven had severe hepatocellular injury.

Roystman et al. reported eight previously healthy individuals who developed liver injury as a result of a newly formulated OEP that contained the compound aegeline.<sup>28</sup> Six out of the eight patients had taken the old formulation and then subsequently the new form of aegeline containing OEP. Patients who developed liver injury typically had a hepatocellular pattern of injury, with severity and need for liver transplantation correlating directly to the degree of INR elevation. Due to liver injury cases associated with the new OEP formulation, the FDA banned the sales of this supplement and other aegeline containing supplements.<sup>29</sup>

Foley et al. described OEP-associated liver injury in seven active duty service members.<sup>30</sup> Other causes of possible liver injury, specifically autoimmune and viral hepatitis, acetaminophen toxicity, and alcohol, were ruled out in these cases. In this case series, formal causality assessment was not performed. Assessments of hepatotoxicity reports due to OEP must be viewed with caution, as several patients had also taken other dietary supplements, such as RoxyLean, C4 Extreme, and Jack 3D.

Hydroxycut and OEP encompass different types of weight loss products. For example, Hydroxycut is available in the form of pills, powders, teas, shakes, and protein bars. Based on the published case reports, it was unclear which particular product or products were consumed; and, therefore, it was difficult to assess the exact dosage of supplements taken in most patients.

Overall, the weight loss supplements Hydroxycut and OEP predominately caused an elevation of liver enzymes with a hepatocellular pattern of injury upon initial presentation. Patients with hepatotoxicity due to these supplements most frequently presented with nausea, vomiting, jaundice, and abdominal pain. Table 1 summarizes clinical and laboratory features of each discussed case report in this review.

### Ingredients in weight loss supplements with hepatotoxic potential

Although products marketed under the Hydroxycut and OEP labels have been highlighted above, the lack of standard nomenclature in the dietary supplement industry as well as the ubiquity of products available to the public make it likely that many more products are marketed and/or used for weight loss. Thus, the task of identifying weight loss products is, in and of itself, a problem that confounds clinicians and researchers.

Among those products discussed in this review, several contain ingredients that have been suggested to cause liver injury. Hydroxycut products contain herbs such as green tea (*Camellia sinensis*) and *Garcinia cambogia*, ingredients that have been implicated in hepatotoxicity (Table 2). Green tea extract contains polyphenols, which include catechins and flavonols. Despite the theoretical antioxidant benefits of catechins, they have been found to cause cytotoxicity through mitochondrial membrane destruction and induction of reactive oxygen species formation.<sup>31</sup> More specifically, epigallocatechin gallate (EGCG), the main constituent of green tea extract, has been associated with dose dependent hepatotoxicity. With an increase in oxidative stress, moderate to severe hepatic necrosis has been observed in mice receiving high doses of EGCG.<sup>32</sup> Another important pharmacokinetic feature of catechins, as shown in dogs, is the increased risk for

**Table 1. Characteristics of weight loss supplements as described in case reports**

Weight loss supplement	N	Clinical features	Predominant pattern of injury	Underwent transplantation
Hydroxycut				
Stevens et al.	2	Fatigue, jaundice	Hepatocellular and cholestatic	0
Fong et al.	8	Nausea, vomiting, abdominal pain	Hepatocellular	3
Jones	1	Nausea, vomiting, and jaundice	Hepatocellular	0
Shim	1	Fatigue, jaundice	Hepatocellular	0
Laczek	3	Malaise, jaundice	Hepatocellular	0
Dara	2	Nausea, vomiting, fatigue, abdominal pain	Hepatocellular	0
Kaswala	1	Nausea, vomiting, abdominal pain, jaundice	Hepatocellular	0
OxyElite Pro				
Roystman et al.	8	Nausea, fatigue, abdominal pain, jaundice	Hepatocellular	2
Foley et al.	7	Nausea, vomiting, jaundice, abdominal pain	Hepatocellular	1

toxicity in the fasted state as compared to the fed state.<sup>33</sup> This is important because most patients taking catechin containing products may be fasting during the course of weight loss, thus predisposing these individuals to increased catechin levels and higher toxicity risk.

*G. cambogia*, a fruit found in Asia and Africa, contains the active ingredient hydroxycitric acid (HCA), which is frequently added to weight loss products because of its ability to inhibit the conversion of carbohydrates to fat.<sup>34</sup> Although the hepatotoxic potential of *G. cambogia* is controversial, it has been linked to hepatic fibrosis, inflammation, and oxidative stress.<sup>35</sup>

Although not in current formulations of Hydroxycut and OEP, usnic acid is a popular ingredient found in other weight loss products and has been labeled as the active component of fat burners. Usnic acid-induced hepatotoxicity may result from oxidative stress by inhibiting mitochondrial oxidative phosphorylation, thereby causing an increase in reactive oxygen species.<sup>36</sup>

In the OEP series by Roystman et al., aegeline, a compound featured in the newly reformulated OEP, was suspected to cause liver injury. Recognizing the limitations of the RUCAM/CIOMS scale that was used for adjudication of causality, the authors suggested a strong association between the use of the aegeline-containing OEP formulation with hepatotoxicity. Extracted from the plant *Aegle marmelos*, aegeline is thought to have an antiadipogenic effect by inducing lipolysis in adipocytes.<sup>37</sup> However, the mechanism of hepatotoxicity remains unknown and unproven.

**Table 2. Hepatotoxic substances found in weight loss supplements**

Ingredients	Mechanism of injury
Camellia sinesis (EGCG)	Oxidative stress
Garcinia cambogia	Oxidative stress, increased collagen deposition
Usnic Acid	Oxidative stress
Ma Huang (Ephedra)	Idiosyncratic
Aegle Marmelos	Under investigation

### Identification of toxic components in weight loss supplements & future strategies

By following a careful diagnostic approach, as outlined in this paper, a relatively confident attribution of liver injury to any given product can be achieved. However, determining which specific component within an herb or dietary supplement is responsible for liver injury remains the most important and difficult endeavor. All HDS are prone to variability, contamination, and adulteration. Furthermore, the interaction of components within a product may also contribute to hepatotoxic potential and adds to the conundrum when identifying the culprit ingredient.

Utilization of the paradigm used to study traditional Chinese medicines (TCMs) may provide a feasible approach to gather toxicity data on HDS in the U.S. Ultra performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS) is a quantitative and qualitative analysis of toxic constituents that has been applied to the quality assessment of TCMs in China.<sup>38</sup> Prior to the availability of UPLC-QTOF-MS, high performance liquid chromatography (HPLC) coupled with MS was used to analyze the quality of herbal medicines. However, UPLC-QTOF-MS has faster analytical speed and greater separation efficiency. Using UPLC-QTOF-MS, Fan et al. were able to separate and analyze the *Ilex latifolia* leaf, a substance commonly used as an herbal tea named ku-ding-cha in China. By doing so, a complex natural substance can now be analyzed in its component parts. In turn, these components can be studied for their potential therapeutic benefit and toxic potential.

While chemical analysis of TCMs is gaining traction in the Eastern hemisphere, similar concepts can be applied to the study of hepatotoxins in weight loss supplements in the U.S. and the West. Specifically, mass spectrometry technology can separate different components within each product and determine the more commonly found entities across a spectrum of weight loss products. Once commonly occurring ingredients are isolated, the toxicity of these products can be tested *in vitro* and *in vivo*, including cytotoxicity studies, genotoxicity studies, and dose escalation studies in animals. By performing these analyses, the hepatotoxic potential of each isolated substance can be determined. Furthermore,

the interaction and combination of several different ingredients can be studied in this way to assess the possibility of mixtures leading to injury.

Further application of mass spectrometric methods involves the analysis of bioactive components and their metabolites in body fluids, such as blood, plasma, urine, saliva, and bile.<sup>39</sup> Other advancements in the diagnosis of DILI include the study of biomarkers in hepatotoxicity, thereby providing further insight into pharmacodynamics and toxicological mechanisms.<sup>40</sup> Although such methods have been used in conventional medications, HDS pose unique challenges that limit the applicability of such techniques at the current time.

Finally, it should not be overlooked that a particular population of patients may be at risk for liver injury from weight loss products. Specifically, host factors, such as the body mass index and the hormonal milieu of a metabolic syndrome, may put certain patients at risk for injury. Behavioral factors, such as fasting while taking products that contain green tea extract, may also predispose to liver injury, as has been shown in the canine model. Further exploration of these factors must parallel a chemical dissection of HDS for the identification of potentially culprit ingredients. Conceivably, an interplay of chemical, host, and behavioral factors may come together to cause toxicity.

## Conclusions

HDS use in the U.S. is prevalent and increasing. Given the rising problem of obesity and the ubiquity of products sold as a sole or complementary mode of weight loss as well as the compelling reports of liver injury resulting from such supplements, hepatotoxicity from HDS must be given greater attention. Specifically, clinicians must acknowledge their hepatotoxic potential, recognize common presentations, and be able to counsel their patients accordingly. Empirical assessments from published case reports suggest that patients with liver injury due to weight loss supplements typically present with nausea, vomiting, and abdominal pain. Jaundice is not typically the presenting symptom; rather a hepatocellular pattern of injury initially without jaundice is more common. However, as injury progresses, jaundice becomes more apparent. For laboratory scientists, research must focus on identifying culprit ingredients and testing the toxicological potential of suspects alone and in combination with others. Clinical researchers must establish a more standard nomenclature for all HDS, refine the process of causality assessment, and explore the impact on host and behaviors on toxicity.

## Conflict of interest

None

## Author contributions

Writing the paper (EXZ, VJN).

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