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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Herbalife. [Updated 2018 Apr 11].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Herbalife

Updated: April 11, 2018.

OVERVIEW

Introduction

Herbalife is weight management and nutritional supplement manufacturer that markets herbal and dietary supplements (HDS) for a wide range of conditions, including weight loss, digestive health, heart health, personal care, energy and fitness, general health, wellbeing, and boosting of energy and immunity. There have been many reports of acute, clinically apparent liver injury in persons taking Herbalife products, but the link to the HDS product has often been controversial. The specific ingredients in the various Herbalife products that might cause liver injury have not been identified.

Background

Herbalife is a for-profit, publically traded company (Herbalife International of America, Inc., Torrance CA) that produces an array of multi-ingredient herbal and nutritional supplements (MINS). The products are not sold in conventional stores or nutrition outlets, but by independent distributors or via the internet. The constituents of the various Herbalife products vary but are largely proteins, amino acids, vitamins, minerals and selected botanicals such as aloe vera, green tea, ginseng, gingko, guarana, valerian, lavender, saw palmetto, echinacea, astragalus, ginger, hops, bilberry, vegetable and fruit extracts and many others. The ingredients and their concentrations in some of the products have been modified over time. Some of the more common products sold are listed in the Table below with a partial listing of their ingredients as provided in the product label. Because the products are considered nutritional supplements, they are not subject to the usual efficacy and safety evaluation given to medications. However, all nutritional supplements are subject to rules regarding purity and good manufacturing practices. Nutritional supplements are not recommended for specific medical conditions, but can be advertised as being supportive of general health, wellness and weight reduction. These multiingredient products appear to be generally safe and well tolerated, but prospective studies of their efficacy, tolerance and safety have not been published.

Selected Herbalife Products (April 2018)

Product Name	Condition	Major Listed Ingredients
Formula 1 Shake Mix: Healthy Meal	Weight control	Soy protein, fructose, cellulose powder, corn bran, guar gum, minerals, rice fiber, soy lecithin, canola oil, carrageenan, medium chain triglycerides, citrus pectin, psyllium husk powder, ginger root powder, proteases of Aspergillus, honey powder, ascorbic acid, dl-alpha tocopherol, papaya fruit, carotene, pantothenate, bromelain, papain powder, folic acid, pyridoxine, thiamine, riboflavin, cholecalciferol, cyanocobalamin and several minerals.

Selected Herbalife Products continued from previous page.

Product Name	Condition	Major Listed Ingredients
Formula 2 Multivitamin Complex	Healthy diet	Vitamins A, C, D, E, B6 and B12; thiamine, riboflavin, niacin, folate, biotin and pantothenic acid; calcium, iron, iodine, magnesium zinc, selenium, copper, manganese and chromium; potassium, vanadium, lycopene, and proprietary"herbal blend"
Formula 3 Cell Activator	Healthy diet	Alpha lipoic acid (150 mg), aloe vera concentrate (52 mg), shiitake mushroom (15 mg), pomegranate rind extract (11 mg), Rhodiola root extract (10 mg), dried pine bark extract (2 mg), resveratrol (0.9 mg)
Prolessa Duo	Weight control	Safflower, palm and oat oils; glucose syrup, sodium caseinate, silicon dioxide, ascorbyl palmitate, phosphates, soy lecithin, tocopherols, natural flavors
Total Control	Weight control	Ginger root, green tea leaf, oolong tea leaf, black tea leaf, and pomegranate rind powder extracts
Cell-U-Loss	Weight control	Corn silk (134 mg), parsley herb (10 mg), dandelion leaf (10 mg) and asparagus root extracts (5 mg); sodium, potassium, calcium and magnesium
Tri-shield	Heart health	Vitamin E (2 IU), Neptune Krill Oil (300 mg), Omega-3 fatty acids (45 mg).
Core Complex with CoQ10 Plus	Heart health	Vitamin D (600 IU), E (18 IU), B6 (4 mg) and B12 (12 mg), marine lipid complex (fish oil: 1.5 g), phytosterol esters (1.3 g), omega-3 fatty acids (717 mg), Neptune Krill Oil (300 mg), hawthorn fruit extract (30 mg), coenzyme Q10 (100 mg)
Herbalifeline	Heart health	Vitamin E (8 IU), marine lipid complex (fish oil: 758 mg), Omega-3 fatty acids (from fish Oil: 336 mg)
Niteworks Powder Mix	Heart health	Vitamin C (500 mg), vitamin E (200 IU), folate (400 mcg), calcium (66 mg), proprietary protein blend (L-arginine, L-citruline: 5.2 g), L-taurine (300 mg), lemon balm extract (50 mg), alpha lipoic acid (10 mg)
Mega Garlic Plus	Heart health	Vitamin C (70 mg), calcium (44 mg), phosphorus (34 mg), garlic power (600 mg)
CoQ10 Plus Softgel	Heart health	Vitamin D (600 IU), coenzyme Q10 (100 mg), docosahexaenoic acid (from Algal oil: 100 mg), Hawthorn fruit extract (30 mg)
Xtra-Cal Advanced	Women's health	Vitamin D (134 IU), calcium (334 mg), magnesium (67 mg), zinc (2.5 mg), copper (.33 mg), manganese (.33 mg), boron (167 mg), herbal blend (20 mg) [tumeric root and rose hips powder]
Woman's Choice	Women's health	Soy isoflavone (150 mg), kudzu extract (75 mg), chaste berry extract (40 mg)
Triple Berry Complex	Women's health	Cranberry Powder (510 mg), bilberry extract (51 mg), blueberry powder (51 mg)
Tang Kuei Plus	Women's health	Vitamin C (8 mg), Tang Kuei root extract (200 mg), passion flower extract (30 mg)
Ultimate Prostate Formula	Men's health	Vitamin E (12.5 IU), selenium (12.5 mcg), saw palmetto lipid extract (160 mg), pumpkin seed oil (50 mg), lycopene (tomato extract: 0.5 mg)
Male Factor 1000	Men's health	Vitamin C (50 mg), calcium carbonate (96 mg), male factor blend (380 mg): [Green Oat, Nettle Leaf, Sea Buckthorn Juice, Clycine, Dextrose, Asian Ginseng, Eleuthero Extract]
Prelox Blue	Male sexual performance enhancer	Protein (2 g), L-arginine, aspartic acid, L-taurine, pycnogenol (dried pine bark extract)
Ultimate Prostate Formula	Prostate health	Vitamin E (12.5 IU), selenium (12.5 mcg), saw palmetto lipid extract (160 mg), pumpkin seed oil (50 mg), lycopene (tomato extract: 0.5 mg)
Kid's Shakes	Children's health	Soy protein, fructose, sugar, maize dextrin, whey protein. Vitamins A, C, D, E, B6, B12, calcium, iron, thiamine, riboflavin, folate, biotin, pantothenic acid, phosphorus, magnesium, zinc
Multivites	Children's health	Vitamins A (2500 IU), C, D, E, B6 and B12, thiamine, riboflavin, niacin, folate, biotin, pantothenic acid, calcium, iron, magnesium, zinc

Selected Herbalife Products continued from previous page.

Product Name	Condition	Major Listed Ingredients
Kindermins	Children's health	Vitamin A (1500 IU), C, D, E, B6 and B12, thiamine, riboflavin, niacin, folate, biotin, pantothenic acid, calcium, iron (7.5 mg), magnesium, zinc
Joint Support Advanced	Joint health	Selenium (23.3 mcg), copper (0.33 mg), manganese (0.67 mg), glucosamine (500 mg), Scutellaria baicalensis extract (160 mg)
Ocular Defense Formula	Ocular health	Vitamin A (1250 IU), C (80 mg), and E (7.5 IU), selenium (22.5 mcg), copper (0.45 mg), lutein (6 mg).
Active Fiber Complex	Digestive health	Sugarcane fiber, maize dextrin, maltodextrin, citrus fiber, soy fiber, inulin, carboxymethycellulose, silicon dioxide (total 5 g of fiber)
Herbal Aloe Powder & Concentrate	Digestive health	Aloe vera concentrate (inner leaf)
Florafiber	Digestive health	Cellulose powder, microcrystalline cellulose, dicalcium phosphate, stearic acid, apple pectin, psyllium seed, lactobacillus acidophilus
21 day Herbal Cleansing Program	Digestive health	Calcium (150 mg), herbal blend of milk thistle extract, insulin, beet root, lactobacillus acidophilus, hesperidin complex, apple pectin, lemon pectin, chamomile extract
Garden 7 Phytonutrient Supplement	Immune health	Vitamin A (1676 IU) and C (65 mg), calcium, riboflavin, garlic, carrot, broccoli and spinach powder, Hesperidin, quercetin, grape skin and cranberry extract, allicin, lycopene, lutein, zeaxanthin
RoseGuard	Environmental toxin defense	Vitamin A (2500 IU), C (30 mg) and E (15 IU), calcium (33 mg), Astragalus root (510 mg), rosemary leaf (210 mg) and turmeric root (80 mg) extracts.
Schizandra Plus	Immune support	Vitamin A (2500 IU), C (40 mg), E (20 IU) and B6 (10 mg); calcium (16 mg) and selenium (35 mcg). Schizandra extract (120 mg)
Best Defense	Immune boosting	Vitamin C (1000 mg), zinc (7.5 mg), and herbal blend of Echinacea purpurea, Echinacea angustifolia, Astragalus, Schisandra, ginger and maltodextrin.
Relax Now	Stress	Jujube (seed: 250 mg), ashwagandha (root: 100 mg) and passionflower extracts (aerial part: 75 mg).
Sleep Now	Stress	Calcium (144 mg) and blend of herbs including passionflower, valerian, hops, wild lettuce, cinnamon, orange peel, lavender (flower) and amla extract
H3O Fitness Drink	Energy and fitness	Vitamins A, C, and E, calcium and magnesium with trehalose dehydrate and sugar (12 g)
Liftoff	Energy and fitness	Vitamins C (60 mg), B6 (6 mg) and B12 (12 mcg); thiamine (3 mg), riboflavin (1.7 mg), niacin (20 mg), biotin (300 mg), and pantothenic acid (20 mg), sodium, potassium and an energy blend (393 mg) of L-taurine, Panax ginseng root, caffeine, Ginkgo biloba extract, guarana extract and inositol.
N-R-G Nature's Raw Guarana Tea or Tablets	Energy and fitness	Calcium (202 mg) and guarana seed blend (800 mg).
Green Tea	Hydration	Green tea extract (25 mg of caffeine) for brewing tea
Herbalife 24 Formula 1 Sport	Nutrition for Athletes	Vitamins A, C, D, E, B6 and B12; calcium, iron; thiamine, riboflavin, niacin, folate, pantothenic acid, phosphorus, magnesium, zinc, copper and chromium with milk protein concentrate, fructose, sugar and sunflower oil.

Hepatotoxicity

The initial reports of liver injury attributed to Herbalife were from Spain and Israel, with subsequent case series from Latin America, Switzerland, Iceland and the United States. At least 50 instances of clinically apparent liver injury have been described in persons taking Herbalife products. The typical latency has ranged from 1 month to

more than a year, the average being 2 to 9 months. The onset is usually insidious with fatigue, nausea, abdominal discomfort, followed by dark urine and jaundice. The pattern of serum enzyme elevations is usually hepatocellular with marked elevations in ALT, but only modest increases in alkaline phosphatase. Occasional cases with a mixed pattern of injury have been described and some cases have been called "cholestatic", largely on the basis of liver histology rather than serum enzyme elevations. Immunoallergic features and autoimmune markers were not common. Resolution occurred upon withdrawal and several instances of relapse with restarting a Herbalife product have been described, although details of the rechallenge are rarely given, largely because the rechallenge was not intentional but a result of the patient restarting the medication on their own and without medical supervision. Liver histology has been variable, but usually shows acute hepatitis with cholestatic features. At least one instance with changes of sinusoidal obstruction syndrome has been described.

A major difficulty in assessing cases of liver injury possibly due to a Herbalife product is that most patients are taking more than one preparation (some as many as 12) and each product contains multiple nutritional supplements and botanicals. Some of the products contain green tea and others aloe vera, but the concentrations of these herbals are not always clear and they appear to have decreased in recent years. Because of the many components in these multi-ingredient nutritional supplements, it is difficult to attribute the liver injury to any specific substance listed on the product labels. The components of the products change and green tea is no longer listed as a constituent of the core products. The number of cases of liver injury attributable to Herbalife products appears to have decreased since their introduction.

Likelihood score: A (well established cause of clinically apparent liver injury).

Mechanism of Injury

The liver injury attributed to Herbalife products remains unexplained. There was no clear commonality in the products themselves, much less their constituents. Some products contained green tea or aloe vera extracts, both which have been implicated in other forms of HDS liver injury.

Outcome and Management

The liver injury that has been attributed to Herbalife products has usually been mild-to-moderate in severity and self-limited in course, resolving in 1 to 2 months of stopping the preparations. Rare instances of acute liver failure and even progressive fibrosis and cirrhosis have been reported, but are uncommon and not always completely well documented. Nevertheless, in patients presenting with acute or chronic, unexplained liver injury, all HDS products should be discontinued and the case reported to federal registries. It is also helpful to carefully define what products were being taken and at what doses and for how long. Retrieval of the actual product or products can also be helpful as progress is being made in the identification of ingredients by advanced chemical and biochemical methods.

Drug Class: Herbal and Dietary Supplements, Nutritional Supplements, Multi-Ingredient

CASE REPORT

Case 1. Acute hepatitis after use of several Herbalife Products.

[Modified from: Chen GC, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, et al. Acute liver injury induced by weight-loss herbal supplements. World J Hepatol 2010; 2: 410-5. PubMed Citation]

A 37 year old woman developed nausea, epigastric pain and jaundice approximately 2 months after starting several Herbalife dietary supplements for weight loss. The supplements mentioned included Formula One Shake Mix, [Formula Two] Multivitamin Complex, [Formula Three] Cell Activator, Cell-U-loss, Herbal Concentrate Original and Total Control Formula. She had no previous history of liver disease and denied alcohol and drug

abuse. On presentation one month after onset of symptoms, she was jaundiced, but had no fever, rash or signs of chronic liver disease. Laboratory tests showed marked elevations in ALT (2068 U/L) and AST (2199 U/L) with minimal increase in alkaline phosphatase (185 U/L) and a total bilirubin of 15.3 mg/dL. She was admitted for evaluation. Tests for hepatitis A, B, C, E, EBV and cytomegalovirus were negative as were routine autoantibodies. Immunoglobulin levels were normal. An abdominal CT scan showed no evidence of biliary obstruction. A liver biopsy showed an acute hepatocellular injury with bridging fibrosis. Once the supplements were stopped, she improved slowly and was discharged one week later without evidence of worsening liver disease, hepatic encephalopathy or hypoglycemia (Table). Subsequently, her symptoms resolved and laboratory tests had returned to normal or near normal levels when she was seen two months later.

Key Points

Medication:	Multiple Herbalife products
Pattern:	Hepatocellular (R=39)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 months
Recovery:	approximately 2 months
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
3 months	0	2068	185	15.3	Admitted. INR normal
	8 days	1501	183	29.9	Discharged
5 months	2 months	43	65	1.1	Outpatient clinic
Normal Values		**<35**	**<126**	**<1.2**	

Comment

A case of drug induced liver injury in a woman in a weight loss program using multiple Herbalife products. No other possible cause of liver injury was identified. The agent responsible in the numerous dietary supplements that she was taking could not be identified. The injury was distinctly hepatocellular and viral-hepatitis like and resembled the typical injury associated with green tea. She worsened for the first week after stopping the nutritional supplements but improved thereafter, and all tests were normal or near normal two months later.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Herbalife®

DRUG CLASS

Herbal and Dietary Supplements

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Herbalife	Not Applicable	Herbal Mixture	Not Applicable

ANNOTATED BIBLIOGRAPHY

References updated: 11 April 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott 1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; Herbalife products are not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS] mentions that there have been 6 published reports of 34 cases of liver injury attributed to Herbalife products from Argentina, Iceland, Israel, Spain and Switzerland, usually with a hepatocellular pattern of injury and some cases being severe and causing cirrhosis or need for liver transplantation; the patients were taking up to 17 different Herbalife products and the specific substances responsible were unknown).

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: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, but the specific botanical substances implicated were not listed).

Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, et al. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. J Hepatol 2007; 47: 514-20. PubMed PMID: 17692424.

(Description of 12 cases of liver injury attributed to Herbalife products in Israel identified by a Ministry of Health investigation: 11 women, 1 man, ages 32-78 years, onset after 2-35 months [mean=11 months], typically with a hepatocellular pattern of enzyme elevations [mean peak bilirubin 9.1 mg/dL, ALT 1481 U/L, Alk P 282 U/L], 1 with ANA resolving on recovery; 11 patients recovered, one died of hepatitis B reactivation, 3 redeveloped liver injury upon reexposure).

Schoepfer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, Zimmermann A, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J Hepatol 2007; 47: 521-6. PubMed PMID: 17692989.

(Description of 10 cases of liver injury attributed to Herbalife weight loss products identified in a survey of Swiss hospitals: 4 men and 6 women, ages 30-69 years, with onset after 2-144 months [median=5 months], typically with a hepatocellular pattern of enzyme elevations and 9 with jaundice [bilirubin 0.4-28.2 mg/dL, ALT 4-50 times ULN, Alk P 1.1-6.5 times ULN], 2 with recurrence on rechallenge, 3 requiring liver transplant, 1 with sinusoidal obstruction syndrome, 1 with cirrhosis).

Stickel F. Slimming at all costs: Herbalife-induced liver injury. J Hepatol 2007; 47: 444-6. PubMed PMID: 17692988.

(Editorial in response to Schoepfer [2007] and Elinay [2007] discussing the difficulties in assigning causality and identifying the toxic component, many patients take multiple herbal products and each one may include multiple components, and the product may also contain contaminants or a botanical that is not on the label).

Duque JM, Ferreiro J, Salgueiro E, Manso G. [Hepatotoxicity associated with the consumption of herbal slimming products]. Med Clin (Barc) 2007; 128: 238-9. Spanish. PubMed PMID: 17335732.

(Description of 3 cases of liver injury arising during use of Herbalife products from Spain, 3 women ages 49-54 years, with onset after 1, 6 and 36 months of starting the products [bilirubin 0.7, 0.8 and 26.7 mg/dL, ALT 138, 505 and 1890 U/L, Alk P 112, 166 and 425 U/L], resolving upon stopping in all three).

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008; 23: 366-73. PubMed PMID: 18318821.

(Review of hepatotoxicity of herbal medications focusing upon those used for weight loss including nitroso-fenfluramine, usnic acid, ephedra, germander, skullcap, green tea and Herbalife products).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry. Rev Esp Enferm Dig 2008; 100: 688-95. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to a Spanish registry between 1994 and 2006, 13 [2%] were attributed to herbal remedies, but no Herbalife product was implicated).

Chao S, Anders M, Turbay M, Olaiz E, Mc Cormack L, Mastai R. [Toxic hepatitis by consumption of Herbalife products: a case report]. Acta Gastroenterol Latinoam 2008; 38: 274-7. Spanish. PubMed PMID: 19157382.

(63 year old Argentinean woman developed jaundice and pruritus 2.5 months after starting Herbalife products [peak bilirubin 17.5 mg/dL, ALT 847 U/L, Alk P 3 times ULN], resolving within 5 months of stopping).

Manso G, López-Rivas L, Duque JM, Salgueiro E. Spanish reports of hepatotoxicity associated with Herbalife products. J Hepatol 2008; 49: 289-90; author reply 290-1. PubMed PMID: 18571274.

(Discussion of 4 cases of Herbalife hepatotoxicity from Spain [3 reported by Duque 2007], 2 occurring in sisters, suggesting a genetic propensity and an idiosyncratic drug reaction).

Ignarro L, Heber D, Henig YS, Bejar E. Herbalife nutritional products and liver injury revisited. J Hepatol 2008; 49: 291-3; author reply 293-4. PubMed PMID: 18550201.

(Comment on publications on Herbalife hepatotoxicity [Elinav and Schoepfer 2007] from the sponsor, questioning whether their product was involved, because the product has been used safely and without reports of liver injury by millions).

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: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, 2 cases being attributed to Herbalife products).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; specific discussion of green tea, Hydroxycut, Herbalife and traditional Chinese herbal medicines).

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: 111-7. PubMed PMID: 19010564.

(78 year old man and 50 year old woman developed jaundice having used Herbalife products for 3 and 1 years [bilirubin 35.7 and 4.9 mg/dL, ALT 2339 and 128 U/L, Alk P 168 and 597 U/L, ANA 1:1280 and 1:160], ultimately resolving after stopping the commercial products, one with concurrent prednisolone and one with ursodiol therapy; testing of 4 samples of Herbalife products revealed growth of bacillus subtilis).

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 2009; 18: 1039-47. PubMed PMID: 19650152.

(Review of 778 spontaneous reports of adverse reactions to herbal products to a Swedish Registry found 31 with increased liver enzymes, 26 with elevated aminotransferase levels, 22 with mixed liver reaction and 12 with hepatitis; agents implicated in causing liver injury included valerian, ginseng, green tea, and aloe vera; no mention of Herbalife products).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to HDS, including several herbal mixtures, usnic acid, Ma Huang, black cohosh, and Hydroxycut; Herbalife products were not mentioned).

Chen GC, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, et al. Acute liver injury induced by weight-loss herbal supplements. World J Hepatol 2010; 2: 410-5. PubMed PMID: 21173910.

(Description of 3 women, ages 31, 37 and 53 years, taking Hydroxycut [n=1] or Herbalife [n=2] products for weight loss who developed jaundice 3, 4 and 12 months after starting [bilirubin 15.3, 29.9, and 18.2 mg/dL, ALT 1227, 2068 and 983 U/L, Alk P 268, 185 and 292 U/L], resolving within 2-3 months of stopping: Case 1).

Appelhans K, Smith C, Bejar E, Henig YS. Revisiting acute liver injury associated with herbalife products. World J Hepatol 2011; 3: 275-7. PubMed PMID: 22059112.

(Letter in response to Chen [2010] arguing that the two cases attributed to Herbalife products were inadequately documented and that the previously reported studies showing Bacillus subtilis contamination in Herbalife products [Stickel 2009] were poorly documented and inadequately controlled).

Stiefelhagen P. ["Doing something good" for the body? Definitely not! Liver damage caused by food supplements]. MMW Fortschr Med 2010; 152: 21. German. PubMed PMID: 21174361.

(News report on liver injury due to nutritional supplements such as Herbalife products [at least 22 cases being reported between 1998 and 2004] and Hydroxycut products).

Jóhannsson M, Ormarsdóttir S, Olafsson S. [Hepatotoxicity associated with the use of Herbalife]. Laeknabladid 2010; 96: 167-72. Icelandic. PubMed PMID: 20197595.

(Description of 5 cases of liver injury attributed to Herbalife products from Iceland; 4 women and 1 man, ages 29-78 years with onset after 1-7 months of use [bilirubin 1.3 to 15.6 mg/dL, ALT 456 to 2637 U/L, Alk P 149 to 712 U/L], all recovering upon stopping).

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011; 31: 595-605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from HDS focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, noni juice, Chinese herbs, vitamin A and anabolic steroids).

Appelhans K, Goldstein LI. Revisiting liver injury associated with dietary supplements. Liver Int 2011; 31: 1239-40. PubMed PMID: 21745293.

(Letter in response to review article by Stickel [2011] stating that Herbalife has cooperated with 25 regulatory agencies investigating possible hepatotoxicity of their products and none subsequently took any actions; reply by authors mentions that numerous case reports have established a causal role of Herbalife products with liver injury).

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: 1080-7. PubMed PMID: 21751292.

(Update on cases of liver injury reported to the Spanish Pharmacovigilance Database between 2003-2010 identified 20 cases of liver injury possibly due to Herbalife products; 16 in women, mean age 45 years, 12 hospitalized [bilirubin 0.6 to 33.3 mg/dL, ALT 88 to 3269 U/L, Alk P 112 to 1034 U/L]; one patient developed cirrhosis, the others recovered; 1 to 9 different Herbalife products were implicated and no single ingredient appeared common to most cases).

Appelhans K, Frankos V, Shao A. Misconceptions regarding the association between Herbalife products and liver-related case reports in Spain. Pharmacoepidemiol Drug Saf 2012; 21: 333-4; author reply 335. PubMed PMID: 22407600.

(Letter in response to Manso [2011] from the sponsor arguing that the causality process used was faulty and that application of WHO criteria would weaken the scoring of cases to conditional or only possibly related to the Herbalife products).

Larrey D, Faure S. Herbal medicine hepatotoxicity: a new step with development of specific biomarkers. J Hepatol 2011; 54: 599-601. PubMed PMID: 21167851.

(Editorial on the problem of hepatotoxicity of herbal medications, the difficulties of causality assessment, variability of the products, possibly of contamination, lack of rigorous regulations and need for biomarkers for hepatic injury).

Appelhans K, Frankos V. Herbal medicine hepatotoxicity revisited. J Hepatol 2012; 56: 504-5. Reply by authors. PubMed PMID: 21782760.

(Letter in response to Larrey [2011] from the sponsor arguing that Herbalife products are carefully assessed for purity and that the green tea extracts used have never been implicated in causing liver injury; authors reply that idiosyncratic liver injury occurs with many medications of proven purity).

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: 324-5. PubMed PMID: 19944093.

(46 year old man who had been taking Herbalife products including multivitamins for 12 years developed jaundice and pruritus [bilirubin 11.2 mg/dL, ALT 68 U/L, Alk P 193 U/L], with a liver biopsy showing fat vacuoles in stellate cells suggestive of vitamin A toxicity; stopping the dietary supplements and avoiding excess vitamin A was followed by resolution of the liver injury).

Bejar E, Smith CR, Appelhans K, Henig YS. Correcting a misrepresentation of hypervitaminosis A attributed to Herbalife product consumption. Exp Mol Pathol 2011; 90: 320-1; author reply 322. PubMed PMID: 21315714.

(Letter in response to Ramanathan [2010] from the sponsor of Herbalife arguing that the calculation of the total vitamin A in the products taken was incorrect [3417 instead to 5082 IU daily] and within the upper limits of tolerance for vitamin A).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012; 32: 1543-56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements including 19 publications on green tea, 13 on Herbalife and 6 on Hydroxycut products).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury mentions that Herbalife products have been associated with at least 34 published cases of liver injury, the pattern of injury being hepatocellular in most cases, severity ranging from mild-to-severe and fatal, and most case being scored as only probable although a few had recurrence upon rechallenge).

Appelhans K, Najeeullah R, Frankos V. Letter: retrospective reviews of liver-related case reports allegedly associated with Herbalife present insufficient and inaccurate data. Aliment Pharmacol Ther 2013; 37: 753-4. PubMed PMID: 23458533.

(Letter in response to Bunchorntavakul [2013] from the sponsor arguing that their review article was inaccurate in regard to Herbalife products, because the authors did not adequately assess whether the reported cases were sufficiently documented).

Reddy KR, Bunchorntavakul C. Letter: retrospective reviews of liver-related case reports allegedly associated with Herbalife present insufficient and inaccurate data--authors' reply. Aliment Pharmacol Ther 2013; 37: 754-5. PubMed PMID: 23458534.

(Reply to Appelhans [2013] by the authors stating that the weight of the evidence is strongly in favor of a hepatotoxic potential of some of the commercial Herbalife products).

Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. Eur J Gastroenterol Hepatol 2013; 25: 1093-8. PubMed PMID: 23510966.

(Review of the literature of case series of suspected HDS related liver injury found evidence of other explanations for the liver injury in 19 of 23 publications involving 278 of 573 patients [49%] and that these other diagnoses weakened the causality assessment in most instances).

Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. World J Hepatol 2013; 5: 353-63. PubMed PMID: 23898368.

(Analysis of the published literature of outcome of rechallenge after suspected HDS hepatotoxicity identified 53 cases, 8 of which mentioned a positive rechallenge; however, documentation of the timing and results of rechallenge was frequently missing and only one case was suitably documented to judge the rechallenge using the RUCAM causality method).

Teschke R, Eickhoff A, Wolff A, Frenzel C, Schulze J. Herbal hepatotoxicity and WHO global introspection method. Ann Hepatol 2013; 12: 11-21. PubMed PMID: 23293189.

(Commentary on the WHO global introspection method for assessing causality in HDS induced liver injury, arguing the superiority of the RUCAM method because of its specificity for liver injury and attention to alternative explanations, such as hepatitis and other viral infections).

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: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 5 attributed to Herbalife products only one of which was icteric [bilirubin 0.3 to 3.6 mg/dL, ALT 223 to 859 U/L, Alk P 95 to 346 U/L], all resolving after the product was stopped).

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. Intern Emerg Med 2013; 8: 13-22. PubMed PMID: 22477279.

(Review and commentary on herbal hepatotoxicity discusses pyrrolizidine alkaloids, green tea, Echinacea, kava, usnic acid, ephedra and products made by Herbalife, Hydroxycut and LipoKinetix).

Appelhans K, Najeeullah R, Frankos V. Considerations regarding the alleged association between Herbalife products and cases of hepatotoxicity. . Intern Emerg Med 2014; 9: 599-600. PubMed PMID: 24470142.

(Letter in response to Licata [2012] from the sponsor regarding the listing of Herbalife with other products implicated in causing liver injury, arguing that there are more than 100 Herbalife products which are mostly dietary supplements and foods and no specific herbal component has been identified in their products that causes liver injury).

Licata A, Craxì A. Considerations regarding the alleged association between Herbalife products and cases of hepatotoxicity: a rebuttal. Intern Emerg Med 2014; 9 (5): 601-2. PubMed PMID: 24570131.

(Reply to Appelhans [2014] indicating that the hepatic injury is probably idiosyncratic in nature and that the possibly responsible ingredient in Herbalife products cannot be identified because of their changing nature and many ingredients).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60:1399-408. PubMed PMID: 25043597.

(Among 130 cases of HDS associated liver injury enrolled in a US prospective study between 2004 and 2013, four [3%] were attributed to Herbalife products).

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis 2013; 17: 715-35. PubMed PMID: 24099027.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment: mentions Herbalife products as being implicated in cases of acute hepatocellular injury).

Rossi S, Navarro VJ. Herbs and liver injury: a clinical perspective. Clin Gastroenterol Hepatol 2014; 12: 1069-76. PubMed PMID: 23924877.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; mentions Herbalife products as being implicated in case series of liver injury from Israel, Switzerland and Spain).

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis 2014; 34: 172-93. PubMed PMID: 24879982.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; mentions Herbalife products as having been implicated in cases of acute hepatocellular liver injury, some with a positive rechallenge).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-532. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver mentions that multi-ingredient supplements have been implicated in many cases of liver injury including proprietary agents marketed under the names Herbalife, Hydroxycut and OxyELITE Pro).

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol 2015; 89: 851-65. PubMed PMID: 25680499.

(Extensive review of liver injury due to HDS mentions that Herbalife has been implicated in 54 cases of liver injury, 7 with a positive rechallenge, but that the cause of the injury remains unknown and that few cases have been published since 2011).

Korth C. Drug-induced hepatotoxicity of select herbal therapies. J Pharm Pract 2014; 27: 567-72. PubMed PMID: 25546878.

(Review of liver injury due to selected HDS discusses the literature implicating kava, green tea, germander, pyrrolizidine alkaloids and Herbalife products).

Appelhans K, Najeeullah R, Frankos V. Deficiencies identified in dated case reports associated with Herbalife. J Pharm Pract 2015; 28: 484-5. PubMed PMID: 26272932.

(Letter in response to a review article [Korth 2014] from the sponsor arguing that many of the cases of liver injury attributed to Herbalife products were deficient, citing 10 letters to the editor from the sponsor to support the claim).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; 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: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, HDS were implicated in 145 [16%], of which 4 [0.5%] were attributed to Herbalife products).

Mengual-Moreno E, Lizarzábal-García M, Ruiz-Soler M, Silva-Suarez N, Andrade-Bellido R, Lucena-González M, Bessone F, et al. [Case reports of drug-induced liver injury in a reference hospital of Zulia state, Venezuela]. Invest Clin 2015; 56: 3-12. PubMed PMID: 25920181.

(Among 13 cases of drug induced liver injury seen at a single Venezuelan medical center during 2012-13, the most commonly implicated agents were ibuprofen [n=3], acetaminophen [n=3], isoniazid [n=2] and Herbalife products [n=2, one of which was fatal]).

Zheng EX, Navarro VJ. Liver injury from herbal, dietary, and weight loss supplements: a review. J Clin Transl Hepatol 2015; 3: 93-8. PubMed PMID: 26357638.

(Review and commentary on liver injury attributed to weight loss HDS products focusing upon Hydroxycut and OxyELITE Pro and discussing the possible hepatotoxicity of specific herbal weight loss agents, Camellia sinesis [green tea], usnic acid, Garcinia cambogia, Ma Huang [ephedra] and Aegle marmelos [aegeline]).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by Dietary Supplements: A tabular listing and clinical characteristics. Int J Mol Sci 2016; 17(4). pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products including 11 reports describing a total of 57 cases attributed to Herbalife products published between 2004 and 2015).

Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. Int J Mol Sci 2016; 17: 331. PubMed Citation (Overview of the US regulations regarding herbal and dietary supplements and role of FDA, Department of Agriculture, Federal Trade Commission and Office of Dietary Supplements of the NIH in assessment of safety of HDS products including actions taken against Hydroxycut, Lipokinetix and OxyELITE Pro when reports of liver injury appeared in postmarketing phase).

Marcus DM. Dietary supplements: What's in a name? What's in the bottle? Drug Test Anal 2016; 8 (3-4): 410-2. PubMed Citation (Commentary on regulation of HDS products concludes: "the marketing of botanical supplements is based on unfounded claims that they are safe and effective", and "there is no reason to take herbal medicines whose composition and benefits are unknown and whose risks are evident").

Rios FF, Rodrigues de Freitas LA, Codes L, Santos Junior GO, Schinoni MI, et al. Hepatoportal sclerosis related to the use of herbals and nutritional supplements. Causality or coincidence? Ann Hepatol 2016; 15: 932-8. PubMed Citation (Two women, ages 42 and 54, who were taking Herbalife products for 3 and 12 months developed abdominal discomfort, fatigue and abnormal liver tests and were found to have nodular regenerative hyperplasia, having no other risk factors except occasional use of herbal teas).

Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 449-71. PubMed PMID: 27818322.

(Summary of the US regulations on safety and efficacy of herbal and dietary supplements).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, lists at least 46 published cases of green tea associated liver injury and concludes that green tea may warrant a warning label).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic necrosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products).

de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed PMID: 27842768.

(Review of the frequency, clinical features, patterns of injury and outcomes of HDS hepatotoxicity with specific mention of anabolic steroids, black cohosh, germander, green tea, kava, pyrrolizidine alkaloids and proprietary multiingredient nutrition supplements [MINS] such as Herbalife products).

Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, et al; Drug Induced Liver Injury Network (DILIN). The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware. Drug Saf 2017; 40: 783-7. PubMed PMID: 28555362.

(A prospective, population based registry of cases of drug induced liver injury occurring in Delaware during 2014, identified 20 cases [2.7 per 100,000] overall, including 6 due to HDS products, all of which were proprietary multiingredient supplements, but none were Herbalife products).

Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology 2017; 65: 363-73. PubMed PMID: 27677775.

(Review of the problems of liver injury and HDS products and challenges for future research concludes that stronger regulations are needed to address the increasing number of cases of HDS induced liver injury, particularly those linked to use of multiingredient dietary supplements such as Herbalife products).

Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extracts consumption in adults - results of a systematic review. Regul Toxicol Pharmacol 2018 Mar 23.[Epub ahead of print] PubMed PMID: 29580974.

(Extensive review of published toxicology of green tea concludes that hepatotoxicity may occur with high doses, the safe level in adults being 338 mg of EGCG daily when taken as pills or powder and 704 mg daily in tea preparations in beverage form).