

Supplementary Table 1:**Institutions and Principal Investigators in the Drug-Induced Liver Injury Network*****Clinical Centers, Locations, Years funded, Principal Investigator(s):***

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University of California, San Francisco (UCSF), CA: 2003-2013. Timothy Davern

University of Connecticut, Framingham, CT: 2003-2007. Herbert Bonkovsky.

University of Michigan, Ann Arbor, MI: 2003-2020. Robert J. Fontana.,

University of North Carolina (UNC), Chapel Hill, NC. Paul Watkins, Paul Hayashi.

University of Southern California (USC), Los Angeles, CA: 2012-2020. Andrew Stolz

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Einstein Healthcare Network, Philadelphia, PA; 2013-2020. Victor J. Navarro

University of Pennsylvania, Philadelphia (UPenn), PA: 2008-2013. Raj Reddy

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**Supplementary Table 2:
Categorization of Implicated Agents by Product Labels**

Group	Green Tea in Name	Green Tea in Label	Commercial Names (number of instances, if not 1)	Concentration Of GTE Per Serving
1	Yes	Yes	Green Tea Extract (n=6)	300-600 mg
			TeGreen (n=2)	400 mg
2	Yes	Yes	Green Tea Fat Buster (n=6)	400 mg
			Mega T: Green Tea (n=2)	Not Given
			Green Tea Fat Metabolizer	400
3	No	Yes	SLIMQUICK (n=5)	Not Given
			Hydroxycut (n=2)	Not Given
			Animal Cuts	Not Given
			Bodyform High Octane Thermogenic	Not Given
			Dexatrim Max	Not Given
			Energy Fizz Sticks	Not Given
			Estroven: Strength/Energy	Not Given
			Herbalife: Herbal Tea Concentrate	Not Given
			Leanmode	250 mg
			Megamen Powered Ripped Vitapack Program	Not Given
			Ortho Multi Greens	50 mg
			Quick Loss Diet Spray w/ Hoodia	Not Given
			Ripped Juice Rev PEA	Not Given
			Super Plus Weight Loss Enhancer	Not Given
			Thermofit	Not Given
			Up Your Gas: Energy Booster	Not Given
Xyngular-Core 4-Accelerate	Not Given			
Zeal	Not Given			

Supplementary Table 3

**Comparison of Green Tea- versus Other Herbal and Dietary Supplement (HDS)-
versus Conventional Drug-Associated Liver Injury**

Feature	Green Tea (n=40)	Other HDS (n=202)	Drugs (n=1142)	p value
Age	39.5 (17-69)	40.6 (20-81)	52.8 (1.7-88)	<0.001
Female Sex*	73%	36%	62%	<0.001
Race*: White	72%	73%	79%	<0.001
Black	8%	10%	13%	
Asian	3%	6%	3%	
Other/Multiple	18%	11%	5%	
Latino/Hispanic*	36%	19%	9%	<0.001
Time to Onset (days)	72 (15-448)	67 (1-1891)	39 (1-7046)	<0.001
Initial ALT (U/L)	1621 (396-4185)	403 (31-9108)	467 (6-15065)	<0.001
Initial Alk P (U/L)	155 (80-550)	155 (38-1427)	220 (35-1963)	<0.001
Initial bilirubin (mg/dL)	7.0 (0.4-30.1)	8.5 (0.3-45.7)	4.2 (0.2-48.4)	<0.001
ANA or SMA positivity	46%	37%	45%	0.07
Eosinophilia (≥5%)	3%	11%	15%	0.04
Enzyme pattern				<0.001
Hepatocellular	95%	53%	53%	
Mixed	5%	25%	23%	
Cholestatic	0%	22%	24%	
Severity Score				<0.001
1 (Mild, anicteric)	13%	13%	26%	
2 (Moderate, jaund)	20%	18%	21%	
3 (Moderate, hosp)	33%	41%	29%	
4 (Severe, INR ≥ 1.5)	28%	21%	18%	
5 (Fatal, transplant)	8%	7%	7%	
Liver Transplant	8%	6%	3%	0.07
Chronicity	3%	12%	18%	0.03
	Green Tea	Other HDS	Drugs	p value

All results are median (range) or proportion. * Numbers differ slightly from total because of duplicate enrollments of the same patient (n=7) and missing data. Abbreviations: HDS, herbal and dietary supplements; ALT, alanine aminotransferase; Alk P, alkaline phosphatase; jaund, jaundice (bilirubin ≥2.5 mg/dL); hosp, hospitalized for liver injury.

Supplementary Table 4
Sixteen Products Linked to Green Tea induced Liver Injury
with Chemical Analysis, HLA and DILIN Causality Score Results

#	Name	# Active Ingredients	Catechins/ Serving (mg)	ECGC/ Serving (mg)	# HLA-B*35:01	Causality Score
1	TeGreen 97	1	111.5	56.3	1	1
7	Green Tea Fat Burner	16	125.6	85.2	2	1
8	SLIMQUICK Ultra	23	6.6	3.8	1	1
14	Hydroxycut	16	52.8	31	1	3
15	SLIMQUICK	23	109.6	67	1	3
16	Quick Loss Diet Spray with Hoodia	7	0	0	0	3
18	SLIMQUICK and SLIMQUICK with Hoodia	23 22	91.1 117.8	59.7 71.5	1	2
19	Super Plus Weight Loss Enhancer	7	116.2	116.2	1	3
20	Green Tea Extract	1	384.1	219	1	3
21	Xyngular-Core 4 Accelerate	8	314	120.5	2	2
22	Vi-Slim Metab-Awake tablets	9	38.2	23.1	1	3
26	Animal Cuts	39	265.4	167.2	0	3
28	Green Tea Fat Burner	16	44.4	1.6	1	2
35	TeGreen 97	1	114.4	85.6	1	3
36	Ortho Multi Greens	40	13.5	5.2	0	3

Abbreviations: #, case number; # Active Ingredients, number of active ingredients on label; # HLA-B*35:01, number of B*35:01 alleles present with 1 = heterozygosity and 2 = homozygosity; Causality Score, likelihood score with 1 = definite, 2 = highly likely and 3 = probable.

Green Tea Case Summaries

Concise clinical summaries of 12 cases of green tea induced liver injury are provided in this supplementary appendix.

The cases were selected to demonstrate the distinctive characteristics of the injury using cases with the more complete data, serial laboratory results and adequate follow up when possible.

Included among the 12 cases are some adjudicated as definite (#1, #7 and #8), with recurrence upon re-exposure, (#5 & #8, #25 & #27 and, by history, #1), with severe course (#5, #25, #27, #33), necessitating liver transplant (#3, #15), homozygous for B*35:01 (#7, #21, #33) and cases without B*35:01 (#26). Cases are presented in a formulaic manner focusing upon exclusion of other causes of liver disease and documentation of the course and outcome. If available, results of chemical analysis of the herbal supplements taken for catechins and EGCG are provided expressed as mg per serving.

The 12 cases include very convincing examples of green tea induced liver injury as well as cases in which the association can only be considered “probable”. In all cases the causality score was assigned based only on the clinical history and routine laboratory data, before chemical analysis or HLA typing results were available. Causality scores of 1 were considered as definite (>95% likelihood), 2 as highly likely (75%-95% likelihood), and 3 as probable (50%-74% likelihood). Cases were scored for severity as 1+ (mild) if serum enzyme elevations arose without jaundice or hyperbilirubinemia (total bilirubin < 2.5 mg/dL); as 2+ (moderate) if jaundice was present but the patient was not hospitalized; as 3+ (moderate-hospitalized) if jaundice was present and the patient was hospitalized for liver injury; as 4+ (severe) if jaundice was present and INR was 1.5 or greater; and as 5+ (fatal) if the patient died due to liver disease or underwent liver transplantation within 6 months of onset.

Abbreviations: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; HDS, herbal and dietary supplements; ANA, anti-nuclear antibody; SMA, smooth muscle antibody; AMA, mitochondrial antibody; HLA, human leukocyte antigen; GT, green tea; GTE, green tea extract; CT, computerized tomography; MRI, magnetic resonance imaging; R ratio, the initial ALT divided by initial Alk P, both expressed as multiples of the local upper limit of the normal range. R ratios of >5 are interpreted as hepatocellular, < 2 as cholestatic, and 2 to 5 as “mixed” hepatocellular-cholestatic; EGCG, epigallocatechin gallate.

No	Implicated Agent Abbreviated name	B*35:01 Status	Severity Score	Causality Score	Recur [Other]	Chemical Analysis
1	TeGreen	1	3	1	1	1
3	Up Your Gas Energy	1	5	3		
5	Dexatrim Max	1	4	3	1 [8]	
7	GT Fat Burner	2	3	1		1
8	SLIMQUICK Fat Burner	1	2	1	1 [5]	1
15	SLIMQUICK Fat Burner	1	5	3		1
20	GT Extract	1	3	3		1
21	Core-4 Accelerator	2	3	2		1
25	Hydroxycut	1	4	3	1 [27]	
26	Animal Cuts	0	3	3		1
27	BF Fat Burning Powder	1	4	2	1 [25]	
33	GT Fat Burner	2	4	2		

For B*35:01 status, 1 = 1 copy, heterozygous, 2 = 2 copies, homozygous, 0 = not present,

For severity score, 1 = mild, anicteric, 2 = moderate jaundiced, 3 = moderate, jaundiced and hospitalized, 4 = severe, jaundiced and INR > 1.5, 5 = fatal or liver transplant

For causality score, 1 = definite, 2 = highly likely, 3 = probable

For Recur Other, 1 = recurrence with re-exposure, [#] the other case number of the two patients with two episodes of liver injury

For Chemical Analysis, 1 = catechins found, 0 = catechins not identified,

For all results, blank = none or not done

Green Tea Case #1

A 38-year-old Hispanic woman developed fatigue, nausea and abdominal pain beginning 16 days after starting a weight loss regimen called “The Right Approach”. The regimen consisted of 3 products: “TeGreen” (green tea extract: 500 mg twice daily), “Cortitrol” (*Magnolia officinalis*, *Epimedium koreanum*, L-Theanine, Beta-Sitosterol, and phosphatidyl serine) and “Crave Ease” (Chromium, Glucosol, and Vanadium). She stopped the supplements but developed itching, dark urine and jaundice. She was otherwise healthy, took no prescription medications, did not drink alcohol, and had no risk factors for viral hepatitis. A year previously she had a similar episode of liver injury while taking the same products, but their role was not recognized, and she underwent cholecystectomy. A liver biopsy showed acute hepatitis without fibrosis. She eventually recovered and liver tests were normal in follow up. When she presented the second time, 26 days after stopping the regimen, serum bilirubin was 6.7 mg/dL, ALT 1166 U/L, AST 977 U/L, and alkaline phosphatase 182 U/L, (R ratio = 15.5: hepatocellular). Serum albumin was 3.8 g/dL and INR 1.2. Tests for hepatitis A, B, C and E were negative as were ANA, SMA and AMA. CT scans of the abdomen showed no evidence of biliary obstruction. Over the next few days, bilirubin rose to 9.0 mg/dL and INR to 1.24 (Table). Thereafter, she began to improve spontaneously on no specific therapy. In follow up, 6 and 9 months after onset, she was asymptomatic, and liver tests were normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
Pre	Pre	31	104	0.7	1.10	Normal
0	Pre	<i>The Right Approach started (Green tea: 1000 mg daily)</i>				
16 days	0	<i>Nausea and bloating: The Right Approach stopped</i>				
42 days	26 days	1166	182	6.7	1.20	Admission
	28 days	1123	212	9.0		
	29 days	810	158	6.5	1.24	
	33 days	877	165	2.8	1.02	Discharge
	38 days	978	165	1.8		
	2 months	69	122	1.2	1.14	
	4 months	40	96	0.7		
	6 months	25	85	1.0		Normal
	9 months	20	82	1.0		Normal
Local normal values		< 50	< 125	< 1.2	< 1.20	

This patient decided to restart the supplements that were suspected to have caused liver injury before and became symptomatic 2 weeks later. In view of the history of recurrence, the liver injury was judged to be definitely due to green tea. Chemical analysis of TeGreen demonstrated catechins (111.5 mg) and ECGC [56.3 mg]. HLA typing showed that she was heterozygous for HLA-B*35:01. The severity score was 3+ (jaundice and hospitalization) and chronicity score none.

Green Tea Case #3

A 49-year-old Caucasian woman developed fatigue after taking an over-the-counter supplement called “Up You Gas Energy Booster” for 2 years. She stopped the supplement, but fatigue worsened, and she developed nausea, anorexia, dark urine and jaundice. The listed ingredients of “Up Your Gas” were niacin (15 mg), vitamin B12 (250 mcg), and an “Herbal Energy Blend” (750 mg) consisting of green tea leaf extract (GTE) as well as 7 other herbs: guarana seed, kola nut, *Panax ginseng*, ginkgo leaf, acai leaf, black pepper and royal jelly. She had mild asthma for which she used an inhaler and gastrointestinal reflux for which she took esomeprazole chronically. She had no history of liver disease, drug allergies or risk factors for viral hepatitis. She drank an average of 1 drink per day regularly but had no history of alcohol related illnesses or complications. On presentation, serum bilirubin was 13.0 mg/dL, ALT 1100 U/L, AST 1491 U/L, and alkaline phosphatase 334 U/L (R ratio = 10.4: hepatocellular). The INR was 1.7 and albumin 3.2 g/dL. She was admitted for evaluation. Tests for hepatitis A, B, C and E were negative. ANA was weakly positive (1:40) but SMA and AMA were negative. CT and MRI scans of the abdomen showed a heterogeneous liver but no evidence of biliary obstruction. Over the next few weeks, her bilirubin rose to 23.8 mg/dL and INR to above 2.0 (Table). She was treated with prednisone without clear benefit. She developed ascites and evidence of hepatic failure and was transferred to a tertiary referral center where she underwent liver transplantation. The explant showed sub-massive necrosis and moderate cholestasis, minimal steatosis, and no fibrosis.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
2 years	19 days	1100	334	13.0	1.7	Admission
	25 days	835	326	17.8	1.8	
	38 days	366	260	18.0	2.2	
	56 days	224	418	20.5	2.2	Transferred
	65 days	209	402	23.8	2.4	
	80 days	220	437	17.7	2.3	
	95 days	17	118	28.0	5.4	
		Liver Transplantation				
	112 days	57	119	1.3	0.9	Discharged
Local normal values		< 40	< 115	< 1.2	< 1.20	

This patient developed an acute hepatitis that evolved into subacute hepatic failure with no clear-cut cause other than exposure to a dietary supplement containing green tea. The history, clinical course and liver histology did not support a diagnosis of alcoholic liver disease. Despite the long latency, this case was judged as probably due to green tea. The product was not available for chemical analysis. HLA typing showed heterozygosity for HLA-B*35:01. The severity score was 5+ (liver transplant).

Green Tea Case #5

A 42-year-old Caucasian woman with a history of diabetes developed fatigue, nausea, poor appetite, rash, itching and jaundice 3 months after starting a weight loss product called “Dexatrim Max”, labelled as having green tea and oolong tea extract, ginseng, caffeine and 3-acetyl-7-oxo-dehydroepiandrosterone. In the previous week she also started amoxicillin for a sinus infection and pravastatin for hyperlipidemia. Drugs taken chronically included metformin, glimepiride, insulin, hydroxyzine, pseudoephedrine, magnesium, and a vitamin B complex. She had no history of liver disease or drug allergies, did not drink alcohol, and had no risk factors for viral hepatitis. Serum bilirubin was 9.1 mg/dL, ALT 2826 U/L, AST 1933 U/L, and alkaline phosphatase 153 U/L (R ratio = 44.8: hepatocellular). Serum albumin was 3.4 g/dL and INR 1.07. All medications were stopped, and she was admitted to the hospital. Tests for hepatitis A, B, C and E were negative. ANA and AMA were negative and SMA only weakly positive (1:20). Abdominal ultrasound showed evidence of fatty liver and CT scan showed mild dilation of the extrahepatic bile duct, but a subsequent MRI was normal. Over the next two weeks, serum bilirubin rose to 27.0 mg/dL and INR to 1.52. A liver biopsy showed acute lobular hepatitis, but no plasma cells or significant steatosis or fibrosis. Skin biopsy showed non-specific inflammation. She was monitored on no treatment and, after 3 weeks, began to improve. In follow up 7 months after onset, she was without symptoms and all liver tests were normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0		<i>Dexatrim Max started</i>				
3 months	0	2826	153	9.1		All medications stopped
	2 days	2272	142	16.7	1.07	MRI
	7 days	1726	194	23.2	1.23	Liver biopsy
	10 days	1172	128	25.1	1.45	
	14 days	1053	155	27.0	1.42	
	15 days	890	157	23.5	1.52	
4 months	22 days	624	197	19.1	1.11	
	36 days	383	85	3.8	1.05	
	44 days	172	75	2.5	1.03	
5 months	50 days	68	70	1.8	1.06	
	57 days	40	69	1.0	1.05	
10 months	7 months	16	47	0.8	0.88	Normal
Local normal values		< 50	< 125	<1.2	<1.20	

This case was adjudicated as highly likely due to Dexatrim and as probably due to green tea. The product was not available for chemical analysis. HLA testing showed heterozygosity for B*35:01. The severity score was 4+ (severe) and chronicity none.

Green Tea Case #8

Approximately 4 years later, at age 46, the woman described above as Patient #5 began taking another green tea-containing weight loss product (“SLIMQUICK Ultra Fat Burner”). Within 2 weeks she developed fever, chills, fatigue, nausea and itching. She had no recent risk factors for viral hepatitis and drank alcohol only occasionally. She was taking metformin for diabetes and cetirizine for allergic rhinitis. She had received a few days of amoxicillin with clavulanate and ibuprofen when she saw her physician because of fever. She returned with worsening symptoms and was found to have a serum bilirubin of 0.8 mg/dL, ALT 1018 U/L, AST 1122 U/L, and alkaline phosphatase 107 U/L (R ratio = 22.6: hepatocellular). The serum albumin was 3.4 and initial INR 1.46. Tests for hepatitis A, B, C and E were negative. SMA was weakly positive (1:40) but ANA was negative. An abdominal CT scan showed no evidence of biliary dilation. Over the next two weeks, her symptoms worsened, and she became jaundiced with peak bilirubin of 13.8 mg/dL. She was not hospitalized and did not undergo liver biopsy or receive corticosteroids. Over the next few weeks, her symptoms resolved, and liver tests improved and were normal when tested 7 months later.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Weight loss agent started</i>				
7 days	0	<i>Weight loss agent stopped</i>				
	7 days	1018	107	0.8		
	14 days	1521				
	18 days	1198	210	8.3		
1 month	20 days			12.8	1.46	
	22 days	632	203	13.8	1.24	
	28 days	365	213	7.5	1.10	
	41 days	68	79	7.5	1.10	
8 months	7 months	18	47	0.6	1.12	Normal
Local normal values		< 40	< 125	<1.2	<1.20	

This patient had a recurrence of liver injury after re-exposure to a different weight loss product that contained green tea extract. The time to onset of the second episode was shorter than the first (7-14 days vs 3 months), but the clinical features were similar with a marked hepatocellular pattern of enzyme elevations, slight increases in INR and peak bilirubin of 13.8 mg/dL, but ultimate complete recovery. Because of the positive re-challenge history, this case was adjudicated as definite green tea related liver injury. The course of injury was considered unlikely to be due to amoxicillin or clavulanate. Chemical analysis of the product revealed catechins [6.6 mg] and ECGC (3.8 mg). She was heterozygous for HLA-B*35:01. The severity score was 2+ (jaundiced but not hospitalized) and chronicity none.

Green Tea Case #7

A 34-year-old Hispanic woman developed nausea, anorexia and epigastric pain, followed by dark urine and jaundice 6 weeks after starting a weight loss agent called “Green Tea Fat Burner.” The product included green tea extract (400 mg), caffeine (160 mg) and a proprietary mixture that included *Yerba Maté*, bladderwrack, Cayenne, Eleuthero, Ginger, Gotu Kola and Licorice (*Glycyrrhiza glabra*) and was taken twice daily. She had no history of liver disease and no other major medical conditions except for previous cholecystectomy. She did not drink alcohol, was taking no prescription medications and had no known drug allergies. She had a tattoo a year before but had no other specific risk factors for viral hepatitis. When seen 12 days after onset of symptoms and stopping the supplement, serum bilirubin was 7.9 mg/dL, ALT 1592 U/L, AST 1447 U/L, and alkaline phosphatase 141 U/L (R ratio= 36.5: hepatocellular). Serum albumin was 4.3 mg/dL and initial INR 1.10. She was hospitalized for six days (Table). Blood alcohol and acetaminophen levels were negative. Tests for hepatitis A, B, C and E were negative as were ANA, SMA and AMA. An abdominal CT scan showed no evidence of biliary dilation. After serum bilirubin peaked at 9.7 mg/dL, liver tests began to improve, and she was discharged on no specific therapy. In follow up at 3 and 6 months after onset, she had no symptoms and liver tests were normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Green Tea Fat Burner started</i>				
~ 6 weeks	0	<i>Symptoms of nausea; weight loss agent stopped</i>				
	12 days	1592	141	7.9	1.1	Hospitalized
2 months	14 days	1270	102	9.7	1.1	Biopsy
	18 days	1437	129	6.8	1.1	Discharged
	27 days	972	115	3.7		
	3 months	15	82	0.5		
	6 months	16	67	0.8	1.01	
Local normal values		< 40	< 125	<1.2	<1.20	

This patient had moderately severe acute liver injury arising after 6 weeks of exposure to a multi-ingredient dietary supplement containing green tea extract with multiple other ingredients. The liver injury was judged as definitely due to the dietary supplement and definitely due to green tea. Chemical analysis revealed the presence of catechins (125.6 mg) and ECGC (85.2 mg) in the product. HLA typing showed that she was homozygous for HLA-B*35:01. Severity was scored as 3+ (jaundiced and hospitalized) and chronicity as none.

Green Tea Case #15

A 27-year-old Hispanic woman developed nausea, fatigue and right upper quadrant pain followed by jaundice within a few weeks of starting two weight loss agents called “SLIMQUICK Ultra Fat Burner” and “Ripped Fuel Extreme, Ephedra-Free”, both of which listed green tea extract as a component but without their concentrations. She was otherwise healthy, had no history of liver disease, drug allergies or risk factors for viral hepatitis and rarely drank alcohol. Two weeks previously she had a dental procedure and received a few days of amoxicillin, codeine with acetaminophen and prochlorperazine. On presentation, serum bilirubin was 5.4 mg/dL, ALT 1384 U/L, AST 1478 U/L, and alkaline phosphatase 131 U/L (R ratio = 30.2: hepatocellular). The INR was 2.2 and albumin 3.0 g/dL. She was admitted for evaluation (Table). Tests for hepatitis A, B, C and E were negative as were ANA, SMA and AMA. Initially, ultrasound of the abdomen was normal. Over the next two weeks, however, she steadily worsened, developing ascites and hepatic encephalopathy, with bilirubin rising to 21.1 mg/dL and INR to 5.6 (Table). She was treated with prednisone but without clear benefit. Two weeks after presentation, she underwent liver transplantation. She quickly recovered and was discharged 2 weeks later with liver test results that were near normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
~ 1 month	2 days	1384	131	5.4	2.2	Admission, US normal
	4 days	1587	132	8.4	1.5	
	6 days	1662	123	18.2	3.6	Ascites on US
	8 days	1155	116	19.5	3.8	Liver biopsy
	12 days	732	132	20.1	5.8	Worsening ascites
	14 days	447	116	16.1	5.6	
	15 days	<i>Liver Transplantation (Bilirubin 21.1 mg/dL)</i>				
	33 days	36	118	1.7	1.1	Discharged
Local normal values		< 50	< 105	< 1.2	< 1.20	

This patient developed acute liver failure within a month of starting two weight loss supplements that both listed green tea extract on product labels. This case was judged to be probably due to the dietary supplements and probably due specifically to green tea extract. Chemical analysis of the SLIMQUICK product verified the presence of catechins (109.6 mg) and ECGC (67 mg). HLA typing showed heterozygosity of HLA-B*35:01. The severity score was 5+ (liver transplant).

Green Tea Case #20

A 69-year-old Caucasian woman developed fatigue and nausea followed by dark urine and jaundice 3 months after starting 3 over-the-counter herbal products - green tea extract [500 mg twice daily], turmeric root [400 mg once daily] and a product called “Super Nails” which had 20 active ingredients including horsetail, oat straw and rice bran and multiple vitamins, minerals and amino acids. She used multiple other dietary supplements on a regular basis including bilberry, biotin, calcium, chromium, CoQ-10, DHEA, echinacea, feverfew, flax seed oil, folate, ginger root, glucosamine with chondroitin and methyl sulfonyl methane (MSM), lysine, lecithin, selenium, vitamin D, vitamin E, and zinc. Prescription medications included simvastatin, naproxen and cetirizine which she had taken for several years. She had no history of liver disease, drug allergies or risk factors for viral hepatitis, and drank alcohol socially, averaging less than one drink daily. At presentation, serum bilirubin was 12.0 mg/dL, ALT 2097 U/L, AST 2655 U/L, and alkaline phosphatase 550 U/L (R ratio = 14.2: hepatocellular). Serum albumin was 3.9 g/dL and INR 1.00. She was admitted for evaluation and monitoring (Table). Testing for hepatitis A, B, C and E was negative as were ANA, SMA and AMA. Liver ultrasound was normal except for gallbladder wall thickening. A liver biopsy showed acute hepatitis with mild cholestasis but minimal fibrosis and steatosis. After worsening for 2 weeks, she began to recover without specific therapy and had normal liver tests when seen 6 months later.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Started green tea extract (1000 mg bid) and turmeric root</i>				
107 days	0	<i>Stopped both supplements</i>				
	2 days	2097	550	12.0	1.00	Admission
	7 days	1758	537	20.6	1.10	
	9 days	1282	513	22.8	1.10	Liver biopsy
	16 days	785	578	29.8	1.10	
4 months	22 days	577	588	22.0	1.00	
	29 days	445	482	9.4	0.90	
	36 days	193	268	5.4	0.90	
	43 days	67	165	3.6	0.90	
6 months	79 days	17	90	1.0	1.00	
9 months	6 months	15	94	0.6	0.90	
Local normal values		< 40	< 125	< 1.2	<1.20	

This patient had moderately severe acute liver injury after taking green tea extract for 3 months. The liver injury was judged as probably due to the green tea extract. Chemical analysis of the implicated product revealed catechins (384 mg) and ECGC (219 mg). HLA testing showed that she was heterozygous for HLA-B*35:01. Severity was scored as 3+ (jaundice and hospitalization) and chronicity as none.

Green Tea Case #21

A 43-year-old Caucasian man developed nausea, abdominal pain, dark urine and jaundice 7 weeks after starting an over-the-counter commercial product called “Xyngular Core-4 Accelerate” which was advertised as boosting energy and promoting weight loss. The supplement was taken twice daily and contained 8 ingredients including unspecified amounts of green tea, guarana, oolong tea, Kola nut and cayenne pepper in addition to vitamin B12, calcium and chromium. He also took vitamin D, vitamin B complex, and omega-3 fatty acids (fish oil) regularly. He had no history of liver disease, drug allergies or other medical conditions and was taking no prescription medications. He had a remote history of excessive alcohol use but had limited intake to 2 drinks per day for the previous 2 years. On presentation, 3 weeks after stopping the supplement, serum bilirubin was 1.6 mg/dL, ALT 2701 U/L, AST 1792 U/L, and alkaline phosphatase 391 U/L (R ratio = 14.4: hepatocellular). Serum albumin was 3.4 g/dL and INR 1.25. He was admitted for further evaluation (Table). Tests for acute hepatitis A, B, C and E were negative as were ANA, SMA and AMA. Liver ultrasound and abdominal CT were normal except for gallbladder wall thickening and MRCP was normal. A liver biopsy showed an acute hepatitis with moderate cholestasis and moderate lobular, periportal and portal inflammation, and mild fibrosis. After an initial worsening with bilirubin rising to 19.8 mg/dL, he began to recover spontaneously and when seen one year later, all liver tests were normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Started “Xyngular Core-4 Accelerator” twice daily</i>				
41 days	0	<i>Stopped commercial product</i>				
2 months	24 days	2701	391	11.6	1.25	Admission
	27 days	1971	309	14.6	1.20	Liver biopsy
	31 days	1512	308	19.8	1.30	
	32 days	1178	255	18.4	1.20	Discharged
	40 days	417	197	6.5		
4 months	47 days	147	155	3.9	1.00	
	12 months	36	126	0.7	1.10	Normal
Local normal values		< 65	< 135	< 1.2	<1.20	

This patient had moderately severe acute liver injury arising after 7 weeks of exposure to unknown daily doses of green tea extract. The liver injury was judged to be highly likely due to the dietary supplement and specifically to green tea. Chemical analysis of the product revealed catechins (314 mg) and ECGC (20 mg). HLA typing showed that he was homozygous for HLA-B*35:01. Severity was scored as 3+ (jaundiced and hospitalized) and chronicity as none.

Green Tea Case #25

A 17-year-old Hispanic, high school student developed nausea, vomiting, fatigue, dark urine and jaundice a month after he started Hydroxycut as a weight loss agent. He had no previous history of liver disease, drug allergies or risk factors for viral hepatitis. He was taking no other medications and did not drink alcohol. He denied fever, rash, abdominal pain or itching. He stopped the supplement, and when seen a week later, serum bilirubin was 22.0 mg/dL, ALT 4185 U/L, AST 3400 U/L, and alkaline phosphatase 192 U/L (R ratio = 102: hepatocellular). Serum albumin was 4.2 g/dL and initial INR 1.66. He was admitted to the hospital overnight for evaluation and later again for monitoring (Table). Tests for hepatitis A, B, C and E were negative. Serum ANA, SMA and AMA were negative and ceruloplasmin levels normal. Abdominal ultrasound and CT scans were normal. Symptoms and liver tests began to improve, but he remained jaundiced with elevated ALT levels over the next 6 weeks. A liver biopsy was not done, and he was not treated. In follow up at 3 and 11 months after onset, all tests were normal.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Hydroxycut started: 1 caplet 1-2 times daily</i>				
30	0	<i>Hydroxycut stopped</i>				
	7 days	4185	192	22.0		Hospitalized overnight
	9 days	3600	169	28.3		
	14 days	2258	143	28.2	1.66	Re-hospitalized
	18 days	1499	97	35.6	1.40	
	21 days	1167	96	34.7	1.30	Discharged
	26 days	941	119	31.0	1.20	
2 months	32 days	615		12.2	1.05	
	43 days	137	89	6.2		
4 months	3 months	15	78	1.1	1.10	
1 year	11 months	17	69	0.6		
Local normal values		< 40	< 380	<1.2	<1.20	

Hydroxycut is a popular weight loss supplement, whose composition has been modified over the years, but at the time included 16 active ingredients including extracts of both green tea and *Garcinia cambogia* in unspecified amounts. The liver injury was quite severe, but he ultimately recovered fully. This case was adjudicated as definitely due to Hydroxycut, but only probably due to green tea. The implicated product was not available for chemical analysis. HLA typing showed heterozygosity for HLA-B*35:01. The severity score was 4+ (severe) and chronicity score 0.

Green Tea Case #27

At age 22, 5 years after an initial episode of hepatitis, the same young Hispanic man as described as Case #25 began taking another weight loss product (“BodyForm High Octane Thermogenic Fat Burning Powder”). Within 3 weeks he developed abdominal pain followed by poor appetite, nausea, dark urine and jaundice. He denied fever or rash. He had no exposures to viral hepatitis and did not drink alcohol. He had received a single day of minocycline for a dental procedure. When seen by his physician, he was noticeably jaundiced and had marked elevations in liver tests, with a serum bilirubin of 12.7 mg/dL, ALT 4114 U/L, AST 2044 U/L, and alkaline phosphatase 155 U/L (R ratio = 62.9: hepatocellular). Serum albumin was 4.5 and initial INR 1.28 (Table). He was hospitalized for evaluation. Tests for hepatitis A, B, C and E and autoantibodies were again negative. Hepatic ultrasound showed a decreased echogenicity, but no evidence of biliary obstruction. A liver biopsy was not done. Again, jaundice persisted for at least 7 weeks. He recovered symptomatically, and liver tests improved, but he did not return in follow up for documentation of full recovery.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Weight loss agent started</i>				
21 days	0	<i>Weight loss agent stopped</i>				
	5 days	4114	155	12.7	1.28	
	6 days	4411	150	17.3	1.42	Hospitalized
	7 days	3800	129	17.4	1.51	Ultrasound
1 month	9 days	3932	132	25.0	1.37	
	12 days	3236	115	32.0	1.31	Discharged
	16 days	2652	111	46.0	1.15	
	20 days	1622	101	18.6	1.10	
2 months	35 days	140	80	4.4	1.12	
Local normal values		< 55	< 125	< 1.2	< 1.20	

This patient had a recurrence of liver injury after re-exposure to a different weight loss product that contained green tea extract (but not Garcinia) in an unspecified amount. The time to onset of the second episode was somewhat shorter than the first, but the clinical presentation and course were similar with 100-fold elevations in serum ALT, modest increases in alkaline phosphatase, severe injury (INR rising to 1.51 and bilirubin to 46.0 mg/dL), but with spontaneous recovery after stopping the supplement. This case was adjudicated as highly likely due to green tea. The product was not available for chemical analysis. Previous HLA typing showed heterozygosity for HLA-B*35:01. The severity score was 4+ (severe) and the chronicity score unknown.

Green Tea Case #26

A 24-year-old Hispanic man developed fatigue followed by dark urine, itching and jaundice approximately 4 months after starting regular use of an over-the-counter commercial product called “Animal Cuts” recommended to him for increase in stamina and aid in body building. He was healthy and without major medical problems and had no history of liver disease or drug allergies and no risk factors for viral hepatitis. He did not drink alcohol and was taking no other drugs or herbal products and specifically denied taking anabolic steroids. Animal Cuts is described on the internet as having 39 active ingredients including 31 botanicals, 2 minerals and 6 other nutrients. Green tea extract is listed as an ingredient, but the amount is not provided. On presentation serum bilirubin was 22.7 mg/dL, ALT 3801 U/L, AST 2538 U/L and alkaline phosphatase 190 U/L (R ratio = 47.3: hepatocellular). Serum albumin was 4.8 g/dL and INR 1.04. The supplement was stopped, and he was admitted (Table). Tests for acute hepatitis A, B, and C were negative. Liver ultrasound was normal except for gallbladder wall thickening. A liver biopsy showed acute hepatitis with periportal and lobular inflammation, confluent necrosis and no cholestasis, steatosis or fibrosis. After an initial worsening with bilirubin rising to 25.6 mg/dL, he began to recover spontaneously, and when seen in clinic several weeks later, serum ALT levels had fallen to normal and total bilirubin was 2.0 mg/dL. He did not return for further follow up.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Started Animal Pak, 1 scoop twice daily.</i>				
4 months	0	3801	190	22.7		Stopped supplement
	1 days	3024	185	23.4	1.04	Admission
	4 days	2763	169	25.0	1.01	
	5 days	2839	167	25.4	1.00	
	6 days	3148	160	25.6	1.01	Liver Biopsy
	10 days	3250	157	1.6	0.99	
	19 days	2678	167	6.6		
	49 days	49	75	2.0		Last visit
Local normal values		< 55	< 130	< 1.2	<1.20	

This patient had moderately severe acute liver injury arising after 4 months of exposure to a multi-ingredient dietary supplement that contained 31 active ingredients including green tea extract. The liver injury was judged as probably due to its green tea extract. Chemical analysis of the implicated product revealed catechins (132.7 mg) and ECGC (83.6 mg). HLA typing showed the absence of HLA-B*35:01. Severity was scored as 3+ (jaundiced and hospitalized) and chronicity as unknown. While anabolic steroid jaundice was suspected, that diagnosis was not supported by the pattern of injury, clinical course or liver histology, and green tea was still considered to be the most likely cause despite absence of HLA-B*35:01.

Green Tea Case #33

A 41-year-old Hispanic woman developed fatigue and nausea followed by weight loss and jaundice within 3 to 4 weeks of starting a weight loss product called “Green Tea Fat Burner”, a commercial product with 16 active ingredients labelled as containing 12 herbs, including green tea extract (400 mg per serving) recommended to be taken twice daily. She had a remote history of an acute hepatitis of unknown cause 8 years earlier and cholecystectomy. She had no other medical illnesses or drug allergies, took no prescription medications, did not drink alcohol, and had no known risk factors for viral hepatitis. Blood testing showed a total bilirubin of 6.3 mg/dL, ALT 2325 U/L, AST 2548 U/L and alkaline phosphatase 197 U/L (R ratio = 20.9: hepatocellular). Tests for hepatitis A, B, C and E were negative. Both ANA and AMA were negative, while SMA was weakly positive (1:20). She was initially followed as an outpatient, but with worsening symptoms and liver tests she was admitted and treated with N-acetyl cysteamine (Table). An ultrasound and CT scan of the abdomen showed hepatomegaly, but no evidence of biliary obstruction. Serum bilirubin rose to 26.7 mg/dL and INR to 1.7. A liver biopsy showed severe acute hepatitis with bridging necrosis but no fibrosis. She was not treated with corticosteroids and improved slowly. Jaundice persisted for more than a month but then resolved and at follow up at 6 months, liver tests were normal except for mild alkaline phosphatase elevations.

Time after starting	Time after Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
0	Pre	<i>Started weight loss supplement “Green Tea Fat Burner”</i>				
3 weeks	0	<i>Developed fatigue and nausea, stopped supplement</i>				
	14 days	2325	197	6.3	1.5	
	22 days	1802	144	18.3		Admitted
	26 days	1532	120	20.7	1.7	
	28 days	1440	120	20.1	1.8	Liver biopsy
	35 days	996	143	23.8	1.7	
	41 days	667	128	20.9	1.6	Discharged
	6 months	24	161	0.3	1.1	Normal
Local normal values		< 60	< 120	< 1.2	<1.20	

This patient had a severe and prolonged hepatitis arising within a month of starting a popular commercial multi-ingredient weight loss product containing green tea extract. The liver injury was judged to be highly likely due to green tea extract. The implicated product was not available for chemical analysis. HLA typing showed homozygosity for HLA-B*35:01. Severity was scored as 4+ (jaundiced, INR >1.5) and chronicity as minimal based upon the alkaline phosphatase level. The short latency and medical history of acute hepatitis of unknown cause suggests a previous episode of green tea related liver injury.