Hepatotoxicity from green tea: a review of the literature and two unpublished cases

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REVIEW ARTICLE

Hepatotoxicity from green tea: a review of the literature and two unpublished cases

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Abstract
Purpose To review the current literature on suspected green tea-related hepatic reactions and to describe two new cases reported within the framework of the Italian surveillance system of natural health products.
Results A literature search of publication between 1999 and October 2008 retrieved 34 cases of hepatitis. Histological examination of the liver revealed inflammatory reactions, cholestasis, occasional steatosis, and necrosis. A positive dechallenge was reported in 29 cases. There was one reported death. A positive rechallenge occurred in seven cases (20%). In the two new cases, the causality assessment was judged as "possible" according to the RUCAM score.
Conclusions Our analysis of the published case reports suggests a causal association between green tea and liver damage. The hepatotoxicity is probably due to (-)-epigallocatechin gallate or its metabolites which, under particular conditions related to the patient's metabolism, can induce oxidative stress in the liver. In a few cases, toxicity related to concomitant medications could also be involved.

Keywords Green tea · *Camellia sinensis* · Catechins · Epigallocatechin gallate · Hepatotoxicity · Herbal supplements

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Introduction

The consumption of tea originated in China and Southeast Asia thousands of years ago and was thereafter introduced progressively all around the world. Historically, green tea has been lauded for various beneficial health effects, and more recently its biological activities have been investigated. Tea is obtained from the leaves of *Camellia sinensis* (L.) Kuntze (Fam. Theaceae). Its composition varies with climate, season, horticultural practices, variety and age of the plant, and manner in which the leaves have been processed. There are several commercial kinds of tea, of which the main ones are green, black, and oolong tea. To obtain green tea, fresh leaves are stabilized by dry heating or steaming to inactivate the enzymes, then rolled, dried rapidly, and more or less roasted. To obtain black tea, leaves are allowed to wilt for about 20 h, rolled, fermented in a humid atmosphere, then dried with hot air; black tea represents 80% of the world market. Oolong tea is only partially fermented [1].

The main chemical components of unfermented tea are polyphenols (up to 20% and more of the dry weight), of which the main ones are catechins, mainly (-)-epigallocatechin gallate (EGCG, 5–12%) and (-)-epicatechin gallate (ECG, 1–5%) [1]. Tea is also a good source of methylxanthines, primarily in the form of caffeine (2–5%), with smaller quantities of theobromine and theophylline. Fermentation

induces changes in the composition; in addition to the development of the aroma, following the formation of volatile products, polyphenols undergo oxidation.

Some studies have shown that green tea consumption is associated with a reduced risk of cardiovascular diseases, degenerative diseases, and cancer [2–4]. The potential health benefits associated with tea consumption have been partially attributed to the antioxidative properties of polyphenols, particularly to catechins, among which EGCG is the most effective. Green tea seems to also have anti-diabetic and anti-obesity properties [5]. On the basis of its potential anti-obesity effect, green tea has been marketed during recent years as a herbal supplement for the control of body weight. Unfortunately, some reports of adverse effects, mainly hepatitis, associated to the consumption of green tea preparations have been published. In April 2003, the manufacturer of Exolise (Arkopharma, Carros, France), a green tea extract containing high EGCG levels and marketed as a weight loss supplement, withdrew this product from the market owing to 13 cases of liver damage due to its consumption [www.afssaps.sante.fr]. The same product was also removed from the Spanish market because of other hepatotoxicity cases. Since then, much attention has been given to the possible hepatotoxic effects of green tea. Despite the withdrawal of Exolise from the market, other green tea-based herbal supplements have been marketed, and reports of hepatotoxicity from green tea are increasing.

In this paper, we present a review of the current literature on suspected hepatotoxicity due to the consumption of green tea along with two new cases reported within the surveillance system of natural health products active in Italy [6].

Seventeen cases of hepatotoxicity related to Tealine [7–9] were not included in our review. The consumption of Tealine, a body weight supplement containing *Teucrium chamaedrys* (germander) and green tea powdered leaves, was reported to be hepatotoxic in the early 1990s, but the adverse reactions were subsequently attributed to the germander.

Methods

In order to collect literature reports on green tea hepatotoxicity, we carried out a systematic search of case reports on the Medline database. The references of all retrieved papers were then carefully investigated. The keywords for liver damage were: hepatotoxicity, liver injury, hepatitis, hepatic failure, hepatic necrosis, hepatic fibrosis, cirrhosis, cholestasis, and veno-occlusive disease. Each term was matched with *Camellia sinensis*, green tea, polyphenols, catechins, EGCG, epigallocatechin gallate, EGC, and other broad keywords, such as herbal medicine, alternative medicine, plant extracts, dietary supplements, herbal drug, and medicinal plants. No temporal limits were given to the search; articles in English, French, Italian, Spanish, and German were considered.

Two new cases were collected within the Italian surveillance system of suspected adverse reactions to natural health products. The system was set up by the Italian National Institute of Health (Istituto Superiore di Sanità) in April 2002 to identify and compile suspected adverse reactions to any kind of natural health product (medicinal plants, dietary supplements, among others) that are not included in the National pharmacovigilance system.

The causality assessment on the two new cases was performed according to the RUCAM method [10]. This method is considered to be the most appropriate approach for evaluating the role of a substance in the development of adverse reactions to drugs; it has been standardized for drug-induced liver injuries.

Results

Thirty-four cases of hepatitis following the consumption of preparations containing green tea were retrieved from Medline between 1999 and October 2008 [11–35] (Table 1). Six cases were men (27–45 years old) and 28 women (19–69 years old). In 15 patients, herbal preparations containing only green tea (nine of the 15 subjects took Exolise) were used; in the others, multicomponent preparations had been ingested. All supplements were used as weight loss products.

Laboratory tests showed high values of transaminases (values up to 140-fold higher than normal), alkaline phosphatase levels that varied from normal to 8.3-fold higher than the normal values, gamma glutamyl transpeptidase levels up up to 394 U/L, and bilirubin levels up to 25-fold above the normal values. According to the RUCAM scale, liver injury in the 32 assessable cases was classified as hepatocellular (62.50%), cholestatic (18.75%), or mixed (18.75%) (Table 1) [10].

The time of onset of the reaction varied between 4 days and 4 years; however, onset was ≤4 weeks in 25% of the cases and ≤3 months in 70% (Table 1). The histological examination, when performed, showed inflammatory reactions, cholestasis, sometimes steatosis, and necrosis (Table 1). Serum analysis confirmed negative viral serology for active hepatitis A, B, and C in all patients. An autoimmune reaction was also generally excluded by the measurement of non-organ specific autoantibody serum levels.

Risk factors related to the age were present only in five of 34 subjects. Alcoholism was generally excluded. In 15 cases, the consumption of other medications (both synthetic and herbal drugs) was reported; in seven cases, no other medication was declared.

Table 1 Clinical data of the events associated with green tea and composition of the dietary supplements

First author of publication, year	Sex, age (years)	Herbal product composition (Brand name)	Time (duration of treatment in weeks)	AST/ALT (U/L)[a]	ALP (U/L)[a]	γ-GT (U/L)[a]	Bilirubin[a]	Liver injury	Histology	Other medications	Recovery time[b]	Dechallenge/ rechallenge
Our cases	f, 81	Green tea dry aqueous extract (90% EGCG) (Epinerve Sifi, Catania, Italy)	4	1996/2368	NR	NR	21.8 mg/dL	HEP	NR	Simvastatin, butizide and kalium canrenoate, travoprost	12	+/No
	f, 72		12	>700	NR	NR	18 mg/dL	HEP	Cholestatic hepatitis, granulomatous cholangitis	Luteinofta (Sooft, Montegiorgio, Ascoli Piceno, Italy)	8	+/No
Shim, 2008 [11]	m, 28	Green tea extract; *Garcinia cambogia*, *Gymnema silvestre*, Soy phospholipids, *Rhodiola rosea*, *Withania somnifera*, other ingredients (Hydroxycut, Iovate Health Sciences Research, Mississauga, Canada)	12	1049/2272	152	NR	18.1 mg/dL	HEP	NP	Paracetamol, aspirin	1.3	+/NR
Bjornsson, 2007 [12]	f, 60	Green tea, *Betula alba* and *Ilex paraguariensis* extract, *Coleus forskohlii* (Cuur Scandinavian Clinical Nutrition, Stockholm, Sweden)	8	62N/73N	8.3N	NR	7.6N	MIX	NR	Enalapril	8	+/NR
	f, 56		12	8N/41N	4.7N	NR	1N	MIX	NR	Diclofenac	5	+/NR
	f, 64		5	77N/89N	1.4N	NR	25N	HEP	NR	Omeprazol	12	+/NR
	f, 35		11	55N/95N	1.8N	NR	25N	HEP	NR	Simvastatin, Metoprolol, Hydroxyzin, Losartan	8	+/NR
	m, 40		20	33N/25N	2.7N	NR	25N	MIX	Centrilobular hepatocytes drop out with bridging necrosis, heavy inflammatory reaction	None	12	+/NR
Federico, 2007 [13]	f, 51	Green tea infusion (NR)	260	4-5N	>200	~200	NR	COL	Mild cholestasis	Estrogen and progestogen	9	+/+
	f, 20		NR	~ 60	>250	~70	NR	COL	NR	NR	9	+/No
Molinari, 2006 [14]	f, 44	Green tea extract, Vitamin E, wheat germ oil, soy oil, beeswax, glycerol esters of fatty acids (NR)	26	2393/3583	NR	112	275 μmol/L	HEP	Hepatocellular necrosis, mixed inflammatory infiltrates. The patient underwent orthotopic liver transplant	Progestogen	NR	NR/No

Table 1 (continued)

First author of publication, year	Sex, age (years)	Herbal product composition (Brand name)	Time (duration of treatment in weeks)	AST/ALT (U/L)[a]	ALP (U/L)[a]	γ-GT (U/L)[a]	Bilirubin[a]	Liver injury	Histology	Other medications	Recovery time[b]	Dechallenge/ rechallenge
Javaid, 2006 [15]	f, 46	Green tea infusion (NR)	31	1188/1100	194	NR	211 μmol/L	HEP	NR	NR	NR	NR/NR
Martinez-Sierra, 2006 [16]	f, 26	Green tea (75%), *Menta piperita* (25%) infusion (Té verde Hacendado, Mercadona, Valencia, Spain)	18	1813/3314	NR	NR	6.5 mg/dL	HEP	Toxic liver disease	NR	9	+/+
Jimenez-Saenz, 2006 [17]	m, 45	Green tea infusion (NR)	18	1037/1613	310	394	119 μg/dL	HEP	NP	None	8	+/+
Bonkovsky, 2006 [18]	f, 37	Green tea extract (Tegreen 97: polyphenols 97%, cathechins 64%), *Magnolia officinalis*, *Epimedium koreanum* and *Lagerstroemia speciosa* extract, calcium, chromium, L-Theanine, β-sitosterol, vanadium (The Right Approach Complex, Pharmanex, Provo, UT, USA)	18	1783/1788	238	NR	200 μmol/L	HEP	Marked interface necrosis, mild lobular inflammation	NR	26	+/+
Mathieu, 2005 [19]	f, 52	Green tea, *Citrus aurantium*, *Citrus paradisi*, *Cynara scolymus*, *Petroselinum sativum* extracts (X-elles)	1.2	2.5N/6.5N	2N	2N	9N	COL	Portal inflammation, mild cholestasis, mixed centrolobular inflammatory infiltrates, necrosis	None	13	+/No
Gloro, 2005 [20]	f, 48	Green tea extract (AR25: EGCG 25%), caffeine (19%) (Exolise, Arkopharma, Carros, France)	8	140N/102N	N	3.3N	473.2 μmol/L	HEP	Mixed portal inflammatory infiltrates, necrotic and steatosic lobular hepatocytes	Bronz'age, paracetamol	NR	NR/No
Abu el Wafa, 2005 [21]	f, 35	See Gloro, 2005 [20] (Exolise, Arkopharma, Carros, France)	1.2	1191/2885	182	NR	19.47 mg/dL	HEP	NP	None	8	+/No
Stevens, 2005 [22]	m, 27	Green tea extract (cathechins 70%, EGCG 45%); *Garcinia cambogia*, *Gymnema silvestre*, *Salix*	5	1808/3131	171	NR	133 μmol/L	HEP	NR	None	4	+/No

		spp.and *Paullinia cupana* extract, calcium, chromium, potassium, glucomannan, α-lipoic acid, L-carnitine, caffeine, gelatin, silica, cellulose (Hydroxycut, Iovate Health Sciences Research, Mississauga, Canada)										
	m, 30		0.6	59/45	530	NR	133 μmol/L	COL	Cholestasis, portal inflammation	None	8	+/No
Porcel, 2005 [23]	f, 53	Green tea leaves, *Ananas sativus* powder, citric acid, maltodextrine, magnesium stearate, silicium dioxide (Fitofruits grasas acumuladas)	2	927/1259	187	NR	91.4 mmol/L	HEP	NP	NR	5	+/No
Garcia-Moran, 2004 [24]	f, 25	Green tea leaves micronized powder (caffeine >2%) (Camilina Arkocapsulas Arkopharma, Carros, France)	8	1943/2398	164	63	19.9 mg/dL	HEP	NP	Orthosifon - Arkocapsulas (Arkopharma, Carros, France)	8	+/No
Lau, 2004 [25]	f, 42	Green tea leaves, *Gynostemma pentaphyllum*, Aloe sp. juice, *Raphanus sativus* semen, *Crataegus* sp fruit[c] (Slim 10)	18	NR	NR	NR	NR	–	Sub-massive hepatocellular necrosis. Post mortem: extensive areas of dense fibrotic tissue	NR	death	death
Dueñas Sadornil, 2004 [26]	f, 35	See Gloro, 2005 [20] (Exolise, Arkopharma, Carros, France)	5	1108/1558	430	162	18.9 mg/dL	MIX	NP	NR	4	+/No
Peyrin-Biroulet, 2004 [27]	f, 56	Green tea hydroalcholic extract, *Cassia* sp. (Mincifit, Arkopharma, Carros, France)	2	33N/54N	N	3N	80 μmol/L	HEP	NP – Rech: cholestasis, mild necrosis, steatosis of 20% hepatocytes	None	8	+/+[e]
Vial, 2003 [28]	f, 46	See Gloro, 2005 [20] (Exolise, Arkopharma, Carros, France)	13	61N/75N	2N	8.5N	508 μmol/L	HEP	NP	Thyroxine, benfluorex, chromocarb diethylamine, Phapax (Lehning, Sainte-Barbe, France) Bioptimum stress (Boiron, Sainte-Foy-lès-	8	+/+

Table 1 (continued)

First author of publication, year	Sex, age (years)	Herbal product composition (Brand name)	Time (duration of treatment in weeks)	AST/ALT (U/L)[a]	ALP (U/L)[a]	γ-GT (U/L)[a]	Bilirubin[a]	Liver injury	Histology	Other medications	Recovery time[b]	Dechallenge/ rechallenge
										Lyon, France)		
Pedros, 2003 [29]	f, 35	See Gloro, 2005 [20] (Exolise, Arkopharma, Carros, France)	5	976/1558	340	162	18.9 mg/dL	MIX	NP	NR	NR	+/No
	f, 34		Several	NR	NR	NR	NR	–	NR	Moxifloxacin	NR	NR/No
	f, 69		5	3N/4N	1.5N	10N	NR	COL	NP	NR	NR	+/No
	f, 29		6.5	1023/1674	260	65	18 mg/dL	HEP	NR	NR	NR	+/No
Bajaj, 2003 [30]	m, 44	As in Stevens, 2005 [22] + *Ephedra sinica* extract (Hydroxycut Iovate Health Sciences Research, Mississauga, Canada)	16	2046/3600	NR	NR	3.5 mg/dL	HEP	Mild periportal fibrosis, periportal and parenchymatous inflammatory infiltrates	Fluticasone, albuterol	13	+/No
Kanda, 2003a [31]	f, 52	Green tea, *Gynostemma pentaphyllum*, *Nelumbo* sp., *Chrysanthemum* sp., *Lycium barbarum*, *Crataegus monogyna*, *Citrus aurantium*, *Cassia mimosoides*, *Raphanus sativus*, beer yeast, Blc Golden tang, raifukushi[d] (Be-petite)	9	1539/1920	414	NR	3.7 mg/dL	MIX	Dramatic portal inflammation with characteristic fibrosis	NR	18	+/No
Kanda, 2003b [32]	f, 31	Green tea leaves, *Gynostemma pentaphyllum*, barbaloin, total saponin, polyphenol[d](Onshidou-genbi-kounou)	4	9310/8820	438	381	1.6 mg/dL	HEP	NR	NR	26	+/No
Thiolet, 2002 [33]	f, 39	Green tea (7%), Oolong tea, *Cassia angustifolia* leaves, *Momordica grosvenori*, *Malva verticillata* (Ooloon tea fine tonic)	2	1.9N/3.9N	1.4N	2N	NR	COL	NP	Levonorgestrel, ethinylestradiol	13	+/No
Seddik, 2001 [34]	f, 50	See Gloro, 2005 [20] (Exolise, Arkopharma, Carros, France)	4	31N/40N	1.5N	5.8N	129 μmol/L	HEP	Marked periportal hepatocytes necrosis, lobular inflammatory infiltrates, marked centrolobular cholestasis	Tiocolchicosid, tetrazepam	9	+/No

Gavilan, 1999 [35]	f, 19	Green tea powdered leaves (Arkocapsulas, Arkopharma, Carros, France)	8	1130/1110	NR	NR	11 mg/dL	HEP	Necrosis of hepatocytes, mixed inflammatory infiltrates	Herbal tea: *Cassia angustifolia*, *Fucus vesiculosus*, *Mentha piperita*, *Equisetum arvense*	10	+/+

f, Female; m, male; AST/ALT, aspartate aminotransferase/alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma glutamyl transpeptidase; NR, not reported; No, not done; NP, not performed; HEP, hepatocellular; COL, cholestatic; MIX, mixed; -, not evaluable; ECGC, (-)-epigallocatechin gallate

[a] x N, x times the upper normal value

[b] Recovery time (weeks)

[c] Capsules were adulterated with N-nitrosofenfluramine

[d] Adulteration with N-nitrofenfluramine is hypothesized

[e] Rechallenge was performed with Dynasvelte (*Camellia sinensis* + *Coffea arabica* + chromium)

In 29 cases, the reaction ameliorated when consumption of the herbal product ceased (positive dechallenge), in four cases the dechallenge was not reported. The recovery generally required from 4 to 13 weeks; one death was also registered. A positive rechallenge occurred in seven cases [13, 16–18, 27, 28, 35].

In the following sections we describe two new cases reported within the Italian surveillance system of natural health products.

Case 1

An 81-year-old Italian woman was admitted to the hospital for severe asthenia, jaundice, pale feces, dark urine, nausea, and vomiting. A toxic acute hepatitis was diagnosed. Results from the abdominal ultrasonography excluded alterations of the hepatic parenchyma, intra- and extrahepatic bile-duct dilatation, and pancreatic alterations. The results of the laboratory tests were: alanine aminotransferase (ALT), 2368 U/L; aspartate aminotransferase (AST), 1996 U/L; prothrombin time/international normalized ratio (PT/INR), 47%/1.51; total bilirubin, 21.80 mg/dL; direct bilirubin, 12.10 mg/dL (Table 1). The patient stated that she had taken one tablet per day of the herbal product Epinerve (SIFI, Catania, Italy), which is made from a dry aqueous extract of green tea containing 90% of EGCG, for 1 month. The herbal product had been prescribed by her ophthalmologist to treat glaucoma. The patient had also been taking simvastatin 20 mg one tablet/day; butizide + kalium canrenoate, one tablet on alternate days, for several years; travoprost eye drops, one drop/eye twice a day, for 2 years. The herbal supplement was stopped, and the patient's clinical condition improved. After 3 months of follow-up the patient completely recovered.

According to RUCAM, the liver injury has been classified as "hepatocellular". The RUCAM score was 4, so the relationship is "possible".

Case 2

A 72-year-old Italian woman was admitted to the hospital with symptoms of acute jaundice. Laboratory tests showed high values of bilirubin (total bilirubin 18 mg/dL), of the cholestasis index, and of transaminases (AST and ALT > 700 U/L) (Table 1). Serologic and virologic markers for hepatic viruses were all negative. Blood samples were negative for antibodies against cytomegalovirus and Epstein–Barr virus. Autoantibodies anti-nucleus, anti-mitochondrion, and anti-smooth muscle results were negative. Values of α1-antitrypsin and ceruloplasmin were in the normal range. The results from abdominal echography and magnetic resonance imaging of biliary ways excluded an

obstruction of the biliary tract. A hepatic biopsy identified a cholestatic hepatitis and a granulomatous cholangitis.

The medical history of the patient at admission did not reveal risk factors for hepatitis; it only revealed a weak hypertension that did not require pharmacological treatment. The woman mentioned that she had been taking two dietary supplements: Epinerve (SIFI, Catania, Italy) two tablets/day and Luteinofta (SOOFT, Montegiorgio, Ascoli Piceno, Italy) one tablet/day, for 3 months. The products were prescribed by an ophthalmologist to treat glaucoma. Luteinofta contains lutein 10 mg/tablet and vitamin E 12 mg/tablet; the composition of Epinerve has been described above.

During hospitalization, the patient was treated with ursodesossicholic acid 10 mg/kg and glutathione (GSH) intravenously; the levels of liver enzymes progressively decreased, and they were in the normal range at discharge. At the 1-year follow-up, the parameters were unchanged.

According to RUCAM, the liver injury has been classified as "hepatocellular". The RUCAM score was 5, so the relationship is "possible".

Discussion

Tea is the most consumed beverage in the world, aside from water. Green tea has gained attention of both consumers and researchers in the last few years for its potential health benefits. Because of its wide-spread and long use, it is considered to be safe. Nevertheless, several cases of hepatotoxicity following the consumption of dietary supplements containing green tea have been reported.

In few of the cases reviewed here, the hepatotoxic reaction may have been related to concomitant medications, i.e. when green tea was associated with diclofenac [12] or paracetamol [11, 20], since hepatotoxicity has been reported for these drugs [36–38]. Three other patients were also taking progestogens [13, 14, 33], which has been associated with some cases of toxic hepatitis [39, 40]. In the fatal case [25], the product was adulterated with *n*-nitrosofenfluramine, an analog of fenfluramine with hepatotoxic effects that has also been found in other slimming products [41]. With the exception of these seven cases, the other 27 cases (80%) accredited green tea as the main cause for the hepatic damage. In fact, the reported hepatotoxic reactions showed a temporal relationship between the consumption of green tea preparations and the onset of the effects: 70% of the patients had been taking green tea for a period of between 1 week and 3 months, and this time period can be considered to be "suggestive" in the causality assessment according to RUCAM. The dechallenge was always positive. Risk factors and non-drug-related causes were generally excluded. Furthermore, in seven cases the rechallenge was positive. In our view, the published evidence from case reports suggests a causal association between green tea and hepatotoxicity. The most convincing finding is represented by the seven cases (20%) of positive rechallenge.

In the two new cases here reported the correlation between green tea consumption and hepatotoxicity was assessed to be "possible" according to the RUCAM score. In both cases, the time of onset of the reaction was correlated to herbal drug exposure, the dechallenge was positive, the rechallenge was not performed, and age represented a risk factor. Unfortunately, non-drug-related causes (viral infections, alcoholism, etc.) can not be excluded in the first case, owing to a lack of detailed information. In the second case, non-drug-related causes can be excluded according to clinical pathology. The patient, however, had been taking a concomitant product (Luteinofta) with a compatible time of onset of the reaction, even if no hepatotoxicity has been reported for this supplement. This fact has been taken into account in the causality assessment and affected the RUCAM score.

With regard to the green tea chemical components responsible for the observed adverse reactions, it has to be noted that the tea preparations used were powdered leaves, infusions, and extracts (both aqueous and hydroalcoholic) and mostly contained standard levels of polyphenols (20–97%). These preparations differ from one another in composition: powdered leaves contain all of the tea chemical components, infusions and aqueous extracts contain mostly hydrophilic compounds, while hydroalcoholic extracts contain both hydrophilic and lipophilic components. A possible hepatotoxicity due to lipophilic components was excluded by Bun et al. on the basis of results obtained from in vivo experiments [42]. Catechins are polar substances that are soluble both in water and hydro-alcoholic vehicles, so they are contained both in aqueous and in hydro-alcoholic extracts even if their content is higher in the latter [42]. Therefore, the components responsible for hepatotoxicity are probably catechins and their gallic acid esters, particularly EGCG.

To explain how green tea catechins can induce liver injury, a number of points have to be taken into account:

1. Pharmacological, particularly pharmacokinetic, interactions between green tea components and concomitant drugs can be hypothesized, as in the cases described above that were possibly related to concomitant medications. However, green tea components seem to affect cytochrome P450 (CYP1A2, CYP2D6, CYP2C9, and CYP3A4) activity either only slightly or not at all [43, 44]. Moreover, in four of the seven cases with positive rechallenge, no concomitant medications were reported.
2. Most of the case reports of green tea hepatotoxicity involved women. Even though we must take into

account that women are the main users of herbal products, particularly those for body weight control, host genetic factors could be important in modulating susceptibility to green tea, as suggested by Jimenez-Saenz and Martinez-Sanchez [45]. In this context, Goodin et al. found that in Swiss Webster mice, females are more susceptible than males to EGCG-mediated toxicity [46].

3. The bioavailability of catechins after oral administration is low: EGCG levels detected in plasma correspond to 0.2–2.0% of the ingested amount [47]; however, catechin plasma levels can increase under particular conditions. Isbrucker et al. found that the plasma area under the curve (AUC) for EGCG was significantly higher in fasted (205.7 ng h/mL) than in pre-fed dogs (19.8 ng h/mL) after 2 weeks dosing at 300 mg/kg per day by dietary administration [48]. The same authors did not observe adverse effects when 500 mg/kg per day EGCG were administered for 13 weeks to pre-fed dogs; conversely, this dose caused morbidity when administered to fasted dogs [48]. Other studies in healthy volunteers showed that after the administration of 800 mg Polyphenon E, a decaffeinated extract of green tea containing 60% EGCG, the plasma C_{max} of free EGCG in the fasting condition was more then fivefold higher than that obtained after administration of the same dose with food [49]. Finally, Ullman et al. showed that after repeated administrations of EGCG 800 mg/day, the C_{max} was 1682 ng/mL on day 1 and 2431 ng/mL on day 10 [50].
4. Significant uptake of EGCG by the liver has been shown under conditions intended to simulate chronic administration [51].
5. High doses of green tea extracts and catechins show toxicity after oral administration. In rats, the dietary administration of 500 mg/kg per day EGCG for 13 weeks increased bilirubin and decreased fibrinogen, while a single dose of 2000 mg/kg EGCG by the oral route was toxic [48]. The dietary administration of a green tea extract containing 55.3% catechins to rats for 90 days increased ALT, AST, and ALP levels and the liver weight at the maximum tested dose of about 3500 mg/kg [52]. Conversely, after intraperitoneal administration, low doses (50 mg/kg) of EGCG induced severe hepatic necrosis and a 20% mortality rate in mice [46]; in rats, 100 mg/kg EGCG induced an increase in plasma ALT levels, and 150 mg/kg caused the death of the animals in less than 24 h [53].
6. Although most of the potential health benefits of green tea and tea catechins have been attributed to their antioxidant properties, an increasing body of evidence suggests that polyphenols can behave as pro-oxidative agents. Experiments performed in rat liver cells showed that high concentrations of green tea extracts and of single tea phenolics are toxic; this cytotoxicity appears to be related to the gallic acid unit, and the most toxic compound was EGCG, while the least cytotoxic one was epicatechin (EC) [53, 54]. Cytotoxicity was associated with reactive oxygen species formation and depletion of GSH; GSH-depleted hepatocytes were more susceptible to EGCG cytotoxicity and ROS formation, suggesting that GSH plays a role in detoxifying this compound [53]. (-)-Epigallocatechin gallate cytotoxicity and ROS formation increased significantly by dicumarol, a NAD(P)H:quinone oxidoreductase 1 (NQO1) inhibitor, thus suggesting that *o*-quinone metabolites of EGCG cause cytotoxicity and are reductively detoxified by NQO1 [53]. Treatment with the catechol-*O*-methyltranferase inhibitor, entacapone, was also found to cause a significant increase in EGCG cytotoxicity and ROS formation, thus suggesting that hepatocyte methylation plays a role in detoxifying this compound [53]. According to Sang et al., catehol-*O*-methyltranferase can protect cells from EGCG-mediated oxidative stress and hepatotoxicity by methylation at the 4'- and 4"-hydroxyl groups, both of which are possible sites for quinone formation and redox cycling [55]. (-)-Epigallocatechin gallate has also been shown to induce oxidative stress in vivo. Sang et al. demonstrated that toxic doses of EGCG [200 and 400 mg/kg intraperitoneal (ip)] resulted in the formation of two cysteine conjugates of EGCG (EGCG-2′-cysteine and EGCG-2″-cysteine) and proposed that these conjugates arise from the formation of an EGCG quinone, which then reacts with the sulphydryl group on cysteine and likely with other cysteine-containing molecules such as GSH [56]. Moreover, treatment of lung tumor-bearing nude mice with daily injections of 40 mg/kg ip EGCG for 40 days resulted in increased expression of phosphorylated histone 2AX (a marker of DNA damage) and metallothionein (a marker of response to oxidative stress) in the liver and tumors relative to vehicle-treated mice [57].

On the basis of these results, we can conclude that the suspected hepatic reactions from green tea canlikely be ascribed to catechins, particularly to EGCG. The bioavailability of catechins is low after oral administration; however, under specific conditions, such as fasting, and after repeated administration, catechin plasma levels can rise and reach toxic levels. The hepatotoxicity can be imputed to the capability of EGCG or its metabolites to induce oxidative stress in the liver. Furthermore, taking into account that most of the reported liver injuries involve women, a gender susceptibility to green tea hepatotoxicity may be hypothesized. In some cases, an

idiosyncratic or an immune-allergic mechanism can not be excluded.

Green tea preparations are widely used for their supposed health benefits. Their efficacy has not been proved; conversely, their use is associated with adverse events, particularly with hepatotoxic reactions. A green tea-based product was withdrawn from the market after several hepatic reactions, but others are being continually introduced. Since these preparations are marketed as dietary supplements, they are generally used as self medication, i.e. beyond medical control, which increases the risk of adverse events. For all of these reasons, it appears necessary to provide detailed information to the users and to improve the active surveillance of these products.

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