REVIEW ARTICLE

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Safety of Green Tea Extracts

A Systematic Review by the US Pharmacopeia

Dandapantula N. Sarma,[1] *Marilyn L. Barrett*,[2] *Mary L. Chavez*,[2] *Paula Gardiner*,[2] *Richard Ko*,[2] *Gail B. Mahady*,[2] *Robin J. Marles*,[2] *Linda S. Pellicore*,[2] *Gabriel I. Giancaspro*[1] and *Tieraona Low Dog*[2]

1 US Pharmacopeia, Rockville, Maryland, USA
2 US Pharmacopeia Dietary Supplements Information Expert Committee, Rockville, Maryland, USA

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Abstract

Green tea [*Camellia sinensis* (L.) Kuntze] is the fourth most commonly used dietary supplement in the US. Recently, regulatory agencies in France and Spain suspended market authorization of a weight-loss product containing green tea extract because of hepatotoxicity concerns. This was followed by publication of adverse event case reports involving green tea products. In response, the US Pharmacopeia (USP) Dietary Supplement Information Expert Committee (DSI EC) systematically reviewed the safety information for green tea products in order to re-evaluate the current safety class to which these products are assigned. DSI EC searched PubMed (January 1966–June 2007) and EMBASE (January 1988–June 2007) for clinical case reports and animal pharmacological or toxicological information. Reports were also obtained from a diverse range of other sources, including published reviews, the US FDA MedWatch programme, USP's MEDMARX® adverse event reporting system, the Australian Therapeutic Goods Administration, the UK Medicines and Healthcare products Regulatory Agency, and Health Canada's Canadian Adverse Drug Reaction Monitoring Program. Case reports pertaining to liver damage were evaluated according to the Naranjo causality algorithm scale. In addition, the Committee analysed information concerning historical use, regulatory status, and current extent of use of green tea products. A total of 216 case reports on green tea products were analysed,

including 34 reports concerning liver damage. Twenty-seven reports pertaining to liver damage were categorized as possible causality and seven as probable causality. Clinical pharmacokinetic and animal toxicological information indicated that consumption of green tea concentrated extracts on an empty stomach is more likely to lead to adverse effects than consumption in the fed state. Based on this safety review, the DSI EC determined that when dietary supplement products containing green tea extracts are used and formulated appropriately the Committee is unaware of significant safety issues that would prohibit monograph development, provided a caution statement is included in the labelling section. Following this decision, USP's DSI ECs may develop monographs for green tea extracts, and USP may offer its verification programmes related to that dietary ingredient.

The US Pharmacopeia (USP) is a nonprofit, standards-setting organization for foods and drugs, and the USP-National Formulary (USP-NF) are recognized in the US Federal Food, Drug and Cosmetic Act (FFDCA) as official compendia of the US.[1,2] Since its founding by an independent group of practitioners in 1820, USP has been an independent, science-based public health organization. USP documentary standards and reference materials (also termed official USP Reference Standards or Compendial Reference Materials) are recognized not only in the US but also in approximately 130 nations worldwide. USP's standards-setting body is the Council of Experts, which has five Expert Committees devoted to creating official standards for dietary supplements. USP has also established verification programmes to assist manufacturers in assuring the public that they are making good quality dietary supplements and dietary supplement ingredients.[3]

The US Dietary Supplement Health and Education Act of 1994 (DSHEA) amendments to FFDCA do not require federal premarketing approval of dietary supplements. DSHEA does, however, stipulate that if a dietary supplement is (i) covered by the specifications (tests, procedures and acceptance criteria of a monograph) of an official compendium (USP-NF); (ii) is represented as conforming to the specifications of an official compendium (USP-NF); but (iii) fails to so conform, the supplement is considered to be misbranded within the meaning of FFDCA [§403(s)(2)(D)]. This affords legal recognition to USP-NF standards for dietary supplements. Thus, the US Congress allows dietary supplement manufacturers the option of citing USP quality standards on their label; however, for those manufacturers that claim to conform, it creates the possibility of US FDA enforcement via the misbranding provisions of the Act.

The USP Dietary Supplements Information Expert Committee (DSI EC) is one of five Council of Experts Dietary Supplements Expert Committees. Amongst other activities, DSI EC establishes a safety classification for dietary supplements to support a determination of acceptable safety, which may at times require a cautionary statement in labelling. In so doing, DSI EC acknowledges that some dietary supplements legally marketed in the US may not be acceptable for safe use or are acceptable only with a suitable labelling statement. Safety determinations made by DSI EC for dietary supplements other than green tea, coupled with the decision statements, are shown in table I and table II, respectively. Following a safety determination by DSI EC for a dietary ingredient, other USP Dietary Supplement Expert Committees may consider setting quality standards, and USP may consider verifying a dietary supplement and/or its ingredient. The other Dietary Supplement Expert Committees are: Dietary Supplement Bioavailability Expert Committee; Dietary Supplement Botanicals Expert Committee; Dietary Supplement General Chapters Expert Committee; and Dietary Supplement Nonbotanicals Expert Committee.

In addition to considering the history of the legal marketing of a dietary supplement in the US, DSI EC utilizes the following criteria as the Committee begins consideration of whether USP should create a monograph and/or verify a dietary supplement or dietary supplement ingredient: (i) apparent efficacy, or a presumptive belief in some beneficial activity as

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Table I. Classification of dietary supplement safety information by the US Pharmacopeia (USP) Dietary Supplements Information Expert Committee (DSI EC)[a]

Class	Definition
1	Articles for which the DSI EC is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately
1a	Articles for which the DSI EC is aware of limited human scientific data concerning safety but is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately
2	Articles for which the DSI EC is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately, provided there is a warning statement in the labelling section
3	Articles for which the DSI EC is aware of significant safety issues that would prohibit monograph development

a Articles in class 1, class 1a or class 2 would be eligible for a monograph in USP or USP-National Formulary (USP-NF) and could be admitted into the USP Dietary Supplement Verification Program. However, articles in class 2 would also require a warning statement in the labelling section. Articles in class 3 would be admitted neither to USP nor USP-NF nor the USP Dietary Supplement Verification Program because of significant safety issues. However, class assignations are not static and may be revised because of significant adverse event reports. Therefore, USP monitors adverse events reported for all dietary supplements for which monographs have been developed. In this manner, adverse event signals can prompt safety re-evaluation and possible reclassification of a dietary supplement.

evidenced by a long history of use; (ii) demand, or the extent of use by the public sector; (iii) public protection, which indicates interest by a regulatory agency; (iv) feasibility, suggesting the likelihood that the ingredient could meet compendial criteria; (v) compendial presence, demonstrated by the presence of existing monographs in other official compendia; and (vi) safety, indicated by a long history of use. If these criteria are met, DSI EC conducts extensive safety reviews of the selected dietary ingredients, analysing information from human clinical case reports, adverse event reports, animal pharmacological and toxicological data, historical use, regulatory status and global current extent of use.

Green tea-based products are the fourth most commonly used dietary supplement in the US[5] and were marketed in the US before 15 October 1994. Thus, these products do not require FDA premarketing approval. Several products are commercially available for their putative antioxidant and weight-loss activities. In February 2005, DSI EC assigned green tea a class 1a rating, indicating that only limited safety data were available and that the Committee was not aware of any significant safety issues that would prevent the inclusion of a monograph in USP-NF. However, French and Spanish recalls of a product containing green tea extract and other case reports associating the ingestion of green tea with hepatotoxicity prompted DSI EC to revisit the safety classification of green tea. DSI EC's review and conclusions are summarized in this review. The

Table II. Examples of recent dietary supplement safety information assessments by the US Pharmacopeia (USP) Dietary Supplements Information Expert Committee

Dietary supplement/ ingredient[b]	Class[a] 1	1a	2	3
Asian ginseng	√			
Cat's claw		√		
Chamomile	√			
Chaste tree (vitez agnus castus)	√			
Cranberry	√			
Echinacea angustifolia			√	
E. pallida			√	
E. purpurea			√	
Eleuthero		√		
Feverfew	√			
Garlic	√			
Ginger	√			
Ginkgo	√			
Goldenseal		√		
Hawthorn (cratageus) leaf with flower	√			
Horse chestnut	√			
Kava				√
Licorice (glycyrrhiza)			√	
Milk thistle	√			
Red clover	√			
Saw palmetto	√			
Spirulina	√			
St John's Wort			√	
Stinging nettle	√			
Valerian	√			

a See table I for class definitions.

b Standardized Common Names[4] are used throughout USP publications and appear in column 1.

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current safety review does not include determination of mechanism(s) of action of green tea extracts.

1. Product Description

Tea (*Camellia sinensis* [L.] Kuntze, Family: Theaceae) is considered the second most consumed beverage in the world, next only to water.[6] Compared with black tea, green tea is unfermented, which helps to preserve its antioxidant polyphenolic catechols.[7] In addition to about 30% of its weight consisting of catechols (predominantly epigallocatechin gallate [EGCG] and epicatechin gallate [ECG]), green tea contains alkaloids and other components.[8] Green tea is used in several forms: consumed as dilute infusion or concentrated supplements or applied topically. Commercial preparations use various extraction techniques and manufacturing procedures and are not uniform.[7] Recently, the FDA approved a topical ointment containing green tea extract as a prescription drug for the treatment of genital warts.[9]

2. Literature Search Methodology

The current systematic safety review was conducted in the following ways: freely available English-language information about adverse event reports was collected in June 2006 from FDA's MedWatch program from 2001 (reports before then were considered in the DSI EC original evaluation and did not suggest an association between green tea and hepatotoxicity); USP's MEDMARX® adverse event reporting system (all available reports evaluated); the Australian Therapeutic Goods Administration (TGA, all available reports evaluated); the UK Medicines and Healthcare products Regulatory Agency (MHRA, all available reports evaluated); Health Canada's Canadian Adverse Drug Reaction Monitoring Program (CADRMP, all available reports evaluated) and the French–Spanish reports pertaining to Exolise®[1] and other products.[10] In addition, the Committee searched PubMed (January 1966–June 2007 and EMBASE (January 1988–June 2007) for clinical case reports (search words: 'English language', 'human', 'green tea', 'liver') and animal pharmacological or toxicological information (search words: 'English language', 'animal', 'green tea', 'liver'). Adverse event reports of liver damage were critically analysed using the Naranjo causality algorithm to assess the likelihood that exposure to green tea products caused hepatotoxicity.[11-13] The Naranjo scale analyses adverse event reports according to several criteria: the patient's previous experience with the substance, alternative aetiologies, temporal correlation, correlation with intake, and de-challenge/re-challenge information. The likelihood of causation is estimated on a scale ranging from 0 (doubtful or unlikely), to 1–4 (possible), 5–8 (probable) and 9–13 (definitive or certain).

The Committee debated the merits and limitations of using different causality algorithms, including the Naranjo scale,[11] Jones scale,[14] Kramer scale,[15] WHO causality method[16] and the Roussel Uclaf Causality Assessment Method (RUCAM).[17] Each of these methods analyses adverse event reports on the basis of different strings: the patient's previous experience with the substance, alternative aetiologies, temporal correlation, correlation with dosage and de-challenge/re-challenge information. Each method scores the question strings to assign the likelihood of causation: doubtful/unlikely, possible, probable and definitive/certain. The objective in choosing a causality scale is to provide a reproducible method of identifying and understanding the causality of adverse event reports and to assist in scientific judgment. The algorithms make clear that the more detailed the information available, the more accurate and reliable the assessment of causality. Some studies have compared the causality scales. Michel and Knodel,[13] for example, suggest that the simpler and less time-consuming Naranjo algorithm, which has been adopted by USP's MEDMARX® reporting system, compares favourably with the Kramer algorithm as a method of scoring adverse event reports. These investigators also note that more data are needed to support the use of the Jones algorithm. The WHO causality method utilizes the same set of parameters as the Naranjo scale, but lacks the flexibility to accommodate missing information. RUCAM was developed as an instrument to assess causality in drug-induced liver

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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injury (DILI), but the instrument is marred by seemingly arbitrary selections, the scoring of its components, its relative inflexibility and its inability to deal well with missing data.[18,19] Recognizing the limitations of RUCAM and similar causality assessment instruments, many studies rely upon the consensus opinion of experts. The DILI Network currently utilizes such a process to assess causality in both retrospective and prospective studies.[20] Considering the limitations of dietary supplement adverse event reports, most of which contain incomplete information or confounding variables, DSI EC recognized the need for consistent evaluation using reliable causality scales. Accordingly, the Committee adopted the Naranjo scale as a means of achieving consistency in evaluations and minimizing biases through the use of a validated causality scale. The facility of the Naranjo scale to accommodate the limitations of missing data was considered a further bonus.

In the present study, each of the case reports considered was ranked according to the Naranjo criteria (table III). Case reports that contained accurate information about product quality, dosage, duration of treatment, patient history and/or confounding variables helped ensure reliable causality assessment. When such information was missing from case reports that alleged links to hepatotoxicity, review and analysis obviously were difficult.

3. Safety Review

DSI EC encountered numerous clinical studies detailing the efficacy of green tea. The committee reviewed six clinical studies that were conducted with various green tea preparations and found that no adverse reactions were reported in these trials.[7] The present report does not evaluate reports of efficacy but focuses on the case reports concerning the safety of green tea, with specific reference to potential hepatotoxicity. In this section, reports from the following sources are analysed:

- French-Spanish reports
- Published adverse event case reports
- FDA MedWatch reports
- USP MEDMARX® reports
- Australian TGA reports
- UK MHRA reports
- Health Canada CADRMP reports
- Clinical pharmacokinetic studies
- Animal and *in vitro* toxicological reports.

As mentioned in section 2, table III summarizes all cases analysed according to the Naranjo algorithm, including detailed information on the assignation of scores.

3.1 French-Spanish Reports

In April 2003, French and Spanish authorities suspended market authorization of Exolise®, a weight-loss product containing a hydroalcoholic extract of green tea (standardized to 25% catechins) because the product was suspected of causing elevated liver enzymes in 13 subjects (nine cases reported in France and four cases in Spain).[21] The estimated frequency of this adverse effect was 1 case per 100 000 boxes of Exolise® sold from 1999 to 2003. Liver toxicity appeared on average following 50 days of use. In 12 of the 13 patients, the problem was resolved following discontinuation of Exolise®. However, in the remaining patient (with reported co-administration of other drugs and regular alcohol intake), the problem did not resolve and progressed to liver failure. In suspending the marketing of Exolise®, French regulators clarified that their decision "does not call in question the traditional use of green tea in food or phytotherapy." The details of the cases leading to the recall of Exolise® are listed in table IV.

Reports of liver toxicity with use of Exolise® were mostly cases of mixed hepatitis with good outcome after cessation of product use.[29] The time of onset of liver damage ranged from 9 days to 5 months with usage of 2–5 doses/day. Exolise® was the only therapy in four cases. Patients were admitted to hospital in six cases. When the Naranjo algorithm was applied to these 13 reports involving Exolise®, two case reports (G293-1 [1999] and H364-1 [2000]) scored probable causality because no alternative causal factors were reported. However, information was incomplete in these two reports, with patient medical histories not being available. Accordingly, the causality score for these two reports may change if additional information becomes available. One case (CN0100091),[21] in

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Table III. Naranjo scores for green tea adverse event (AE) reports concerning liver damage[a]

Case ID (year)	Did AE appear after suspected drug administered?	Did AE improve when drug discontinued? (de-challenge)	Did AE appear when drug readministered? (re-challenge)	Any other causes that on their own could have caused the AE?	Was AE confirmed by objective evidence?	Naranjo score
BS0100614[10]	2	1	0	0	1	4 (possible)
BS0100401[10]	2	1	0	−1	1	3 (possible)
CN0100091[21]	2	0	0	−1	1	2 (possible)
LL0000241[22]	2	1	0	−1	1	3 (possible)
LY0000143[23]	2	1	0	−1	1	3 (possible)
G293-1[10] (1999)	2	1	0	2	1	6 (probable)
H364-1[10] (2000)	2	1	0	2	1	6 (probable)
H320-1[10] (2000)	2	1	0	0	1	4 (possible)
K329-1[10] (2002)	2	1	0	0	1	4 (possible)
321530440[24]	2	1	0	0	1	4 (possible)
Case 4[10] (2001)	2	0	0	0	1	3 (possible)
Case 5[10] (2001)	2	0	0	0	1	3 (possible)
Case 6[24] (2002)	2	0	0	0	1	3 (possible)
GR0000822[10]	2	1	0	−1	0	2 (possible)
PA9607529[10]	2	1	0	−1	1	3 (possible)
98.9155[10]	2	1	0	0	0	3 (possible)
J085-2 (2000)[10]	2	1	2	0	0	5 (probable)
Camiline Arkocaps tea leaf powder[10]	2	1	2	0	1	6 (probable)
Jimenez-Saenz and Martinez-Sanchez[25] (2006)	2	1	2	−1	1	5 (probable)
Stevens et al.[26] (2005) [case 1]	2	1	0	0	1	4 (possible)
Stevens et al.[26] (2005) [case 2]	2	1	0	0	1	4 (possible)
Porcel[27] (2005)	2	1	0	0	1	4 (possible)
Javaid and Bonkovsky[28] (2006)	2	0	0	0	1	3 (possible)
Molinari et al.[29] (2006)	2	0	0	2	1	5 (probable)
Bonkovsky[30] (2006)	2	1	2	0	1	6 (probable)
MedWatch 15606	2	0	0	0	0	2 (possible)
MedWatch 15737	2	0	0	0	1	3 (possible)
MedWatch 62758	2	0	0	0	1	3 (possible)
MedWatch 80859	2	1	0	0	1	4 (possible)
MedWatch 85756	2	0	0	−1	1	2 (possible)
TGA 180741	2	0	0	0	1	3 (possible)
TGA 191840	2	0	0	0	1	3 (possible)
TGA 210566	2	1	0	0	1	4 (possible)
CADRMP 30069	2	0	0	−1	1	2 (possible)

a Information that would allow answers to the following questions on the Naranjo scale was not available in the AE reports: are there previous conclusive reports regarding this reaction? Did the reaction reappear when a placebo was administered? Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? Was the reaction more severe when the dose was increased or less severe when the dose was decreased? Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Accordingly, these questions are not listed in this table.

CADRMP = Canadian Adverse Drug Reaction Monitoring Program; **ID** = identification; **TGA** = (Australian) Therapeutic Goods Administration.

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Table IV. Details of cases of liver damage leading to the recall of Exolise® in France and Spain in 2003

Case ID (year)	Patient (sex/age)	Exolise® intake (caps/day); duration	Type of liver damage/disturbance	Outcome	Remarks
BS0100614[10]	F/47	5 caps/day; 5 months	Cytolytic + cholestatic	Recovered in 15 days	Patient had Hashimoto thyroiditis
BS0100401[10]	F/39	Not available	Cytolytic + cholestatic	Recovered in 2 months	Patient had hepatic adenoma
CN0100091[21]	F/49	4 caps/day; 6 weeks	Cytolytic + cholestatic	Liver transplant	Patient taking several medications; reported alcohol use
LL0000241[22]	F/50	4 caps/day; 41 days	Cytolytic + cholestatic	Recovered in 2 months	Patient's hepatitis considered Exolise®-induced; concurrent use of omeprazole
LY0000143[23]	F/46	4 caps/day; 81 days	Cytolytic + cholestatic	Recovered in 15 days	Patient taking several medications; re-challenge positive for concomitantly administered chromocarb diethylamine (Campel)
G293-1[10] (1999)	F/27	4 caps/day; 31 days	Cytolytic	Recovered in 28 days	No alternative causality reported
H364-1[10] (2000)	F/46	3 caps/day; 1 month; then later 18 days	Cytolytic	Recovered in 2 months	No alternative causality reported
H320-1[10] (2000)	F/50	Unknown intake; 1 month	Cytolytic + cholestatic	Recovered in 2 months	Patient taking several medications
K329-1[10] (2002)	F/42	4 caps/day; 3 months	Cytolytic + cholestatic	Recovered in 3 months	Patient taking several medications, including paracetamol (acetaminophen)
321530440[24]	F/35	2 caps/day; 35 days	Cytolytic + cholestatic	Recovered in 2 months	No information about other medications
Case 4[10] (2001)	M/32	Unknown intake; 3 months	Jaundice	No information	No further information available
Case 5[10] (2001)	F/69	2 caps/day; 23 days	Hepatitis	No information	No further information available
Case 6[24] (2002)	F/29	4 caps/day; 1.5 months	Cytolytic + cholestatic	No information	No further information

F = female; **ID** = identification; **M** = male.

which the reported outcome was liver transplantation, had confounding issues such as concurrent medication use and regular alcohol intake. Positive re-challenge was reported with Exolise® in one case (LY0000143).[23] However, in this case, Exolise® was given with another drug (Campel® [chromocarb diethylamine], Chiesi, France) for 10 days. Symptoms appeared after 8 days of chromocarb diethylamine therapy and resolved when chromocarb diethylamine was discontinued. Thus, this case (LY0000143) scored possible causality.

Because Exolise® contains a hydroalcoholic extract of green tea, it is possible that a hepatotoxic substance may have been extracted from the green tea leaves by alcoholic extraction. It is important to note, however, that cases have also been reported involving Tealine®, a product that contains an aqueous extract of green tea. Accordingly, attributing hepatotoxicity to the alcoholic extracts of green tea is to date an unresolved hypothesis.

In addition to the 13 cases that led to the recall of Exolise®, a report from the Besançon Regional Drug Surveillance Center, France, detailed four cases that involved Tealine®, a product containing an aqueous extract of green tea, white tea and red tea (*Aspalathus linearis*) with 40–50% catechins.[10] The details of the case reports involving Tealine® are listed in table V. One case (J085-2 [2000]) reported positive re-challenge (probable causality on the Naranjo scale); the other three cases involved use of multiple medications (possible causality). No objective data confirming hepatotoxicity were available in these reports involving Tealine®, and the causality assignation may change if new information arises.

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The report from Besançon states that the number of hepatic adverse effects reported via the European Community for other products containing green tea is very limited. One case of cytolytic hepatitis with positive re-challenge was reported for the most widely sold green tea leaf powder, Camiline Arkocaps. In this case, a 19-year old female reportedly consumed 1800 mg of the product for 1 month and developed cytolytic hepatitis. No further information about co-administration of other medications or patient history is available. Given the limitations in the available information, analysis according to the Naranjo algorithm results in a score of 6 (probable causality).

3.2 Published Adverse Event Case Reports

A literature search revealed a total of 79 publications within the limits of the keywords. Most of the publications reported exploratory research on diverse pharmacological activities of green tea or EGCG. Over the past 3 years, seven articles reporting eight cases of liver damage associated with green tea products have been published.[21,25-30] Details of these seven publications are included in table VI.

Analysis of these case reports identified four possible and three probable cases of liver damage induced by products that contained green tea (not including Gloro et al.,[21] which is a repeat of the French–Spanish case, CN0100091, discussed in section 3.1). The reports of probable causality involved diverse products: an unknown marketed green tea infusion,[25] a product named The Right Approach (TRA®) Complex,[30] and an unknown product that contained green tea extract.[29] The two case reports by Stevens et al.[26] involved Hydroxycut®, a polyherbal formulation consisting of green tea (91mg EGCG) in addition to *Garcinia cambogia, Gymnema sylvestre* leaf extract, guarana extract, calcium, chromium polynicotinate, potassium, glucomannan, α-lipoic acid, willow bark extract, L-carnitine and caffeine. The authors of this case report admitted that the evidence for involvement of Hydroxycut® was not definitive and that it was unclear which ingredients of Hydroxycut® may have been responsible for the reported hepatotoxicity. A comment on these reports[31] stated that chromium polynicotinate,[32] in combination with other herbal extracts in Hydroxycut®, is the ingredient likely to be responsible for the hepatotoxicity.

In 2007, Bonkovsky[30] detailed a case study involving a patient with a positive response to re-challenge with TRA® Complex, a multi-ingredient formulation that contains green tea. This author also reviewed eight case reports (including three published case reports[26,27] and three reports on Exolise® [case identification (ID) 321530440[24], Case 6 (2002),[24] and LY0000143[23]] previously discussed in section 3.1 and table IV) of mixed hepatocellular-cholestatic hepatotoxicity associated with green tea. In addition, the author reviewed two case reports from non-English journals concerning Camilina Akocapsulas and Oolong tea (not included in this analysis). The onset of hepatotoxicity reportedly ranged from 5–120 days and was associated with consumption of 0.7–3 g of extract per day. There were no reports of chronic liver injury in any of the patients, who all recovered after discontinuing the supplements. Because of the multiplicity of the ingredients and co-ingestants, the reviewer ac-

Table V. Details of case reports of liver damage for Tealine® in France[10]

Case ID (year)	Patient (sex/age)	Daily intake/duration	Type of liver damage/ disturbance	Outcome	Remarks
GR0000822	F/76	Intake unknown; 31 days	Hepatitis	Recovered	Patient taking ciprofibrate for 10 years
PA9607529	F/47	Intake unknown; 90 days	Rise in transaminases	Recovered	Patient had cholecystectomy 10 years ago; currently taking several medications, including piroxicam
98.9155	F/49	6 caps/day; 3 weeks	Rise in transaminases	Recovered in 4 months	No other information
J085-2 (2000)	F/38	6 caps/day; 20 days	Cytolytic hepatitis	Recovered	Positive re-challenge reported

F = female; **ID** = identification.

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Table VI. Published case reports of liver damage associated with green tea products

Case ID (year)	Patient (sex/age)	Product intake (amount/day); duration	Type of liver damage/ disturbance	Outcome	Remarks
Gloro et al.[21] (2005) [repeat of French-Spanish case CN0100091]	F/49	Exolise®; 4 caps/day; 6 weeks	Fulminant hepatitis	Liver transplantation	Confounding factors: alcohol consumption, weight-loss programme, use of paracetamol (acetaminophen), other polyherbal formulation
Jimenez-Saenz and Martinez-Sanchez[25] (2006)	M/45	Green tea infusion (brand/ quantity not reported); 6 cups/day; 4 months	Jaundice	Positive de-challenge and positive re-challenge	Case report did not include patient's medical history
Stevens et al.[26] (2005) [case 1]	M/27	Hydroxycut®; 9 tabs/day; 5 weeks	Rise in transaminases	Recovered in 4 weeks	Polyherbal formulation; no other medications reported
Stevens et al.[26] (2005) [case 2]	M/30	Hydroxycut®; 9 tabs/day; 5 days	Cholestatic hepatitis	Recovered in 2 months	Polyherbal formulation; no other medications reported
Porcel[27] (2005)	F/53	Fitofruit grasas acumuladas; 3 caps/day; 2 weeks	Elevated liver enzymes	Positive de-challenge	No other information available
Javaid and Bonkovsky[28] (2006)	F/46	Chinese green tea; 7 months	Severe hepatocellular injury	Not known	No other information about patient history or concurrent medications available
Bonkovsky[30] (2006)	F/37	TRA® Complex; 2 g/day; 4 months	Increased liver enzyme values	Positive re-challenge	Confounding factors: multiplicity of ingredients and co-ingestants
Molinari et al.[29] (2006)	F/44	Green tea extract; 720 mg/ day; 6 months	Acute liver failure	Liver transplantation	Product information (brand, solvent of extraction, total catechins and % EGCG) not provided

EGCG = epigallocatechin gallate; **F** = female; **ID** = identification; **M** = male; **tabs** = tablets; **TRA** = The Right Approach.

knowledged the difficulty of establishing a causal relationship between extracts of green tea and reported cases of hepatotoxicity. Complete information was not available for all parameters, and the causality assignment might change if additional information became available.

3.3 US FDA MedWatch Reports

A total of 131 relevant reports were recorded in FDA's MedWatch reports during the period January 2001 to July 2006. In 37 of these reports, the implicated products contained ephedra in addition to green tea. In view of earlier adverse event reports associated with ephedra,[33] these 37 reports were excluded from the analysis. Five reports were concerned with the effect of green tea-containing products on the liver (table VII). Rash or allergy was cited in 18 reports, vomiting, diarrhoea or gastric upset in 18, microbial contamination in nine and packaging issues in five. Common adverse reports involved dehydration, heart palpitation, fever, headache, tremors, elevated blood pressure, dizziness, chest tightness, and hot flushes. However, complete information about dosage, duration of use, patient history, and product quality was missing in all case reports. Several products were multicomponent formulations, which made ascribing causality to a single ingredient difficult. Only one report to MedWatch concerned Exolise® (Case 15689; report date: 2 May 2002) and cited severe abdominal pain.

Table VII shows that all the green tea-containing products associated with liver damage were polyherbal preparations, and that all reports included confounding variables. In one case report

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Table VII. US FDA MedWatch reports on liver damage associated with green tea products

Case ID	Report date	Type of liver damage/disturbance	Comments
15606	3 April 2002	Reported as "acute and possible drug-induced hepatitis"	Polyherbal formulation; no further information reported
15737	11 June 2002	Fulminant liver failure	Polyherbal formulation
62758	8 September 2003	Elevated liver function test values	Polyherbal formulation
80859	12 September 2005	Reportedly "developed jaundice"	Patient took more than double recommended dose of polyherbal formulation; recovered after 2 months
85756	22 May 2006	Patient reportedly "developed jaundice"	Patient reportedly increased alcohol consumption to 5 times/week (5–6 drinks each time); polyherbal formulation included *Cascara sagrada* and skullcap

ID = identification.

(85756), the patient reportedly consumed alcohol regularly and took a polyherbal formulation that contained *Cascara sagrada* and skullcap in addition to green tea. Liver injury has been reported with use of *C. sagrada*.[34] When the available information was applied to the Naranjo scale, it resulted in possible causality ratings for all five case reports.

3.4 US Pharmacopeia MEDMARX® Report

The USP MEDMARX® database primarily collects adverse event reports associated with medication errors in the hospital setting. The MEDMARX® database has an adverse drug reaction module that uses the Naranjo scale to assess the probability of causality for individual suspected medications. Because dietary supplements are nonprescription agents, their use is likely to be prone to errors, especially in the context of herb–drug interactions. For this reason, the authors searched the USP MEDMARX® database for reports concerning green tea and found one report concerning a green tea product. A 41-year-old female patient used a herbal product containing green tea and guarana (*Paullinia cupana*) for 1 day and reported headache and blurry vision. The reporter's responses to the Naranjo scale questions returned a possible causality rating for this report.

3.5 Australian Therapeutic Goods Administration Report

The Australian TGA recorded 45 adverse event reports involving *C. sinensis*. All the products in these reports were polyherbal formulations. Thus, ascribing an adverse event report to a single ingredient is difficult in these cases. Furthermore, several reports indicated co-administration of several medications. The most commonly reported reactions were rash, nausea, vomiting, headache, and gastrointestinal discomfort. Three cases of abnormal liver function were reported. A summary of the TGA cases that reported liver damage is provided in table VIII. As was the case with other reports, the green tea products were not characterized, which made ascribing the causality of hepatotoxic reactions to green tea difficult. When the available information (table VIII) was applied to the Naranjo scale, it resulted in possible causality ratings for the three reports.

Table VIII. Australian Therapeutic Goods Administration reports on liver damage associated with green tea products

Case ID	Report date	Type of liver damage/disturbance	Comments
180741	18 December 2002	Abnormal hepatic function	Used polyherbal formulation (Jump Start for Women) for 7 days; recent acute renal failure; concurrent medications
191840	Unknown	Abnormal liver function tests	Used polyherbal formulation (Women's Ultivite®, containing 20 ingredients); reportedly needed visit to doctor's office
210566	10 August 2005	Abnormal liver function tests; hepatitis	Used polyherbal formulation (4321 Slim and Detox™ containing 10 ingredients) for 4 days; positive de-challenge

ID = identification.

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3.6 UK Medicines and Healthcare Products Regulatory Agency Reports

A total of five adverse reports were filed between 1963 and August 2006 regarding C. sinensis. These adverse event reports included no fatal outcome. Reactions included sinus tachycardia, cholestatic hepatitis, hepatic failure, hepatitis, abnormal liver function test, increased blood pressure, myalgia, panic attack, increased tendency to bruise and flushing. Further information is not presented in the current review because of a confidentiality agreement with MHRA.

3.7 Canadian Adverse Drug Reaction Monitoring Program Reports

The only case of liver damage associated with a green tea-containing product (CADRMP Case Report 30069; 24 October 2005) involved a 42-year-old female patient who presented with stomach discomfort. The patient reportedly was taking Green Lite™ Polyphenon® 100-mg capsules (recommended dose, 6/day) for 6 months prior to admission. Green Lite™ Polyphenon® is a product that contains hot water extract of green tea (100-mg green tea catechins/capsule, 65% EGCG). The patient's liver function enzymes were elevated, her ammonia levels were increased and she was negative for hepatitis B and C serology. She was reported to be taking concomitant medication (medroxyprogesterone injections, 150 mg every 3 months) over the previous few years. One of the known serious adverse effects of parenteral medroxyprogesterone is abnormal liver function.[35] The patient subsequently underwent liver transplantation and reportedly recovered. When the available information was applied to the Naranjo scale, it resulted in a possible causality rating for the report.

Seven other reports filed with CADRMP involved green tea but none of these included any reports of abnormal liver function.

4. Clinical Pharmacokinetic or Safety Studies

Several clinical studies provide significant information about the pharmacokinetics of green tea constituents.

An 8-week clinical trial (in 49 cancer patients) demonstrated that the maximum tolerated dose of green tea extract was 4.2 g/m^2 once daily or 1.0 g/m^2 three times daily (equivalent to 7–8 Japanese cups [120 mL each] of green tea three times daily).[36] The observed toxicities were dose dependently mild to severe (National Cancer Institute grade 1 to grade 3) and included gastrointestinal (abdominal bloating, flatulence and nausea), neurological (insomnia, headache, pain, paraesthesias, tremor and restlessness) and cardiovascular (palpitations) complaints. The time to maximum concentration (t_{max}) for EGCG was 1–3 hours and the plasma maximum concentration (C_{max}) of EGCG was 100–225 ng/mL following 4.2 g/m^2 once daily administration. Although the number of data sets per dose level was small, these observations of t_{max} and C_{max} were comparable with the clinical pharmacokinetics results reported in another study.[37]

Another clinical study (five subjects per group) demonstrated that EGCG and Polyphenon® E (a decaffeinated extract of green tea containing 60% EGCG) produced similar plasma EGCG concentrations at the dose levels tested (200–800 mg as EGCG).[38] In this single-dose study, the authors reported that the systemic availability of EGCG increased with increasing doses, possibly as a result of saturable presystemic elimination. The only adverse effects observed by the investigators were mild headache and fatigue.

A randomized, placebo-controlled study in healthy volunteers (eight subjects per group) showed that EGCG or Polyphenon® E administered at 800 mg/day for 4 weeks was safe and well tolerated.[39] Both catechin formulations exhibited similar EGCG pharmacokinetics (EGCG C_{max} 390.3 ± 231.4 ng/mL; t_{max} 210 ± 73.5 minutes; half-life 158.9 ± 78.7 minutes).

Studies in healthy volunteers (ten subjects per group) also showed that Polyphenon® E, 800 mg administered as a single dose, was well tolerated when taken with food.[40,41] Notably, the plasma C_{max} of free EGCG in the fasting condition was more than five times that obtained after administration of the same dose with food.

A randomized, double-blind, placebo-controlled study[42] investigated the pharmacokinetic profile of single doses of EGCG (50 mg, 100 mg, 200 mg,

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400 mg, 800 mg, 1600 mg) or placebo in 50 healthy subjects.[42] The study reported that EGCG 1600 mg administered under fasting conditions produced a peak plasma concentration of 7.4 μmol/L (3300 ng/mL) after 1.3–2.2 hours. In a repeated administration study,[43] consumption of EGCG 800 mg doses after an overnight fast resulted in an average C_{max} of total EGCG of 1682 ng/mL on day 1 and 2431 ng/mL on day 10, with an average t_{max} ranging between 1.39 and 2.00 hours. According to the investigators, an increase in elimination half-life and in the accumulation factor in the 800-mg dosage group indicated dose-dependent saturation of capacity-limited excretion routes or an increase in hepatoduodenal re-circulation.

From the foregoing literature review, it appears that plasma concentrations of EGCG are significantly increased when concentrated green tea extracts are consumed under fasting conditions. Although these studies provided information about the pharmacokinetics of EGCG, a major limitation was the design of these clinical trials (open-label, small scale), which do not possess the statistical power to detect any adverse effects other than those that are very common.

5. Animal Pharmacological and *in vitro* Toxicological Reports

The pharmacokinetics of radiolabelled EGCG (intravenous, single dose, 25 mg/kg; oral, single dose, 250 mg/kg) have been investigated in beagle dogs.[44] This study found that approximately 20% of orally administered EGCG is absorbed systemically in beagle dogs compared with 1.6%[45] to 14%[46,47] in rats. The volume of distribution for oral EGCG was calculated to be 0.3–0.7 L/kg (the same order of magnitude as total body water) and the major route of elimination was faeces (25.1% ± 6.12%). The biodistribution data under conditions intended to simulate chronic administration revealed significant uptake of EGCG by the liver (17.47% ± 4.65%, approximately 150 μg equivalents EGCG/g tissue in liver) and gastrointestinal tract. Accumulation of EGCG took place predominantly in the liver rather than in other organs, as has also been observed in rat and mice models,[48,49] but the extent of accumulation was not striking.[45,48,49] DSI EC noted that tissue distribution studies of EGCG in human clinical research are lacking. A significant observation in the mouse model was the increase in the concentration of EGCG in all tissues (predominantly in the liver) when a second dose of EGCG was administered orally to mice 6 hours after the first dose.[48] This observation may have safety implications in terms of accumulation of EGCG in the human liver following consumption of concentrated green tea extracts over short intervals.

A study[44] of beagle dogs administered a single dose of oral radiolabelled EGCG 250 mg/kg resulted in a C_{max} of EGCG equivalents of 88.1 ± 23.88 μg/mL under fasting conditions. This study highlighted the effect of food on green tea bioavailability. Although *in vivo* and *in vitro* data cannot be compared with certainty, the observed C_{max} concentrations under fasting conditions are close to the 50% lethal dose (LD_{50}) for EGCG (91.6 μg/mL or 200 μmol/L) in isolated rat hepatocytes *in vitro*.[50] The LD_{50} for other polyphenols, such as gallic acid, epicatechin, epigallocatechin and ECG, was >2000 μmol/L.

The effect of food on green tea bioavailability and related safety implications have also been observed in other studies.[51] No adverse effects were noted when a spray-dried green tea preparation (500 mg [80% EGCG]/kg/day) was administered to pre-fed dogs in divided doses. However, this dose caused morbidity when administered to fasted dogs as a single bolus.[51] Accordingly, the no observed adverse effect level (NOAEL) was determined to be 500 mg preparation/kg bodyweight (kg-bw)/day for fed dogs and 40 mg/kg-bw/day for fasted dogs. In addition, maximum plasma levels of free EGCG were approximately ten times greater in fasted than pre-fed dogs (C_{max} = 55.6 μg/mL in fasted male dogs after 81 days of administration at 500 mg/kg-bw/day vs 5.75 μg/mL in prefed dogs under similar administration conditions).[51]

In analysing the safety data for green tea, DSI EC also reviewed animal studies that have reported a hepatoprotective effect of green tea preparations[52-56] or hepatotoxic effects (at higher concentrations)[50,57] in *in vivo* or *in vitro* models.

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6. Discussion

Green tea has been consumed for centuries by different cultures around the world. In addition to its use as a beverage, green tea consumption has increased because of putative health benefits. Recently, several concentrated extracts of green tea have appeared on the market as weight loss and sports supplements. These extracts are formulated to contain higher concentrations of EGCG or caffeine. To put this into perspective, a cup of green tea can provide 80–106 mg of polyphenols. Although 1–3 cups per day may be a common consumption level in the US, ingestion of as many as 9 cups per day of tea is not uncommon in Japan, according to epidemiological studies.[58] Green tea extracts are often standardized to polyphenol levels that vary from 25% to 97%. For example, the suggested dose of an extract standardized to 25% catechins (Exolise®, one capsule three times daily) provides 375 mg catechins per day, of which 270 mg is EGCG. This is roughly the equivalent of three cups of tea. Another product (Tegreen 97®) is standardized to 97% polyphenols with a recommended serving that provides nearly 600 mg polyphenols per day.

The foregoing analysis provides a total of 216 adverse event reports (not organ-specific) on products containing green tea extracts, including duplicate reports. The sources of these reports are: FDA MedWatch (131 reports), Australian TGA (45 reports), Exolise® recall (13 reports), CADRMP (eight reports), MHRA (five reports), Tealine (four reports), USP MEDMARX® (one report), Camiline Arkocaps tea leaf powder (one report) and the following publications: Stevens et al.[26] (two reports) and one report each from Gloro et al.,[21] Jimenez-Saenz and Martinez-Sanchez,[25] Porcel,[27] Bonkovsky,[30] Javaid and Bonkovsky[28] and Molinari et al.[29] This total number of 216 reports includes 34 nonduplicate adverse event reports (listed in table III) that concerned reports of liver damage. The implicated products in these cases were: Exolise® in 13 cases; Tealine in four cases; Hydroxycut® in two cases; TRA® Complex in one case; Camiline Arkocaps tea leaf powder in one case; and Green Lite™ Polyphenon® in one case. Of these reports, probable causality for liver damage associated with green tea-containing products was found in seven case reports, and possible causality was assigned in the rest of the cases. Probable causality was assigned in two reports for Exolise®, one report for TeaLine, one report for Camiline Arkocaps tea leaf powder, one report for an unidentified infusion, one report for TRA® Complex and one report for an unknown product. There is notable diversity in these reports with respect to product composition, solvent of extraction, dose and duration of use. Product composition was analysed in only one report.[29]

During the safety review, the Committee also noted the limitations of the dietary supplement adverse event reporting systems. As observed in an FDA-commissioned study, the agency receives <1% of all adverse event reports associated with dietary supplements.[59] Because DSHEA does not mandate large-scale, randomized, controlled safety studies for dietary supplements, a strong adverse event reports monitoring programme is required to protect public health. Although the scope and intentions of the present study prevented DSI EC from collecting and evaluating information about the large range of green tea formulations and potential adverse event reports in Asian and other nations, a thorough review of these data would certainly be a positive contribution to public health.

Certain challenges in analysing adverse event reports concerning green tea extracts are comparable with those involving other dietary supplements, including multiple ingredients; unknown products; incomplete case reports; weak or missing information about patients' prior medical history, use of alcohol and other concurrent medications; pre-existing risk factors; and other confounding variables. Unique opportunities for analysing the case reports involving the use of green tea extracts include the availability of standardized green tea extracts, tools to analyse components (such as EGCG), and significant bioavailability and toxicological information in humans and animal models. Safety information for green tea extracts may be outlined as follows:

1. Adverse event reports from several monitoring sources provide a signal concerning products containing green tea and their effects on the liver. The authors analysed 34 nonduplicate reports.
2. The predominant green tea catechin (EGCG) was identified as ten times more cytotoxic to isolated rat

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hepatocytes *in vitro* than other minor catechins (LD_{50} 91.6 μg/mL for EGCG).[50]

3. Studies in beagle dogs indicate the potential for toxic EGCG plasma C_{max} concentrations (comparable to lethal concentrations *in vitro*) at high levels of green tea consumption under fasting conditions.[44]

4. Biodistribution data reveal significant uptake of EGCG by the liver in diverse animal models.[44,48,49]

5. A significant observation in the mouse model was the increase in the concentration of EGCG in all tissues (predominantly in the liver) when a second dose of EGCG was administered orally 6 hours after the first dose.[48]

6. Studies in healthy volunteers[40,41] showed that the plasma C_{max} of free EGCG in the fasting condition was more than five times that obtained after administration of the same dose with food.

7. In keeping with other reports about the effect of food on green tea bioavailability, researchers noted no adverse effects when 500 mg of a spray-dried green tea preparation (80% EGCG)/kg/day was administered to pre-fed dogs in divided doses. This dose caused morbidity when administered to fasted dogs as a single bolus.[51]

Although extrapolation of animal toxicology data to typical human consumption under fed conditions suggests a protective effect of food, adverse event reports concerning liver damage in humans following consumption of green tea extracts remain a matter of concern. It appears from the information reviewed above that ingestion of concentrated green tea extracts with food minimizes the possible risk of liver damage.

7. Deliberations of the Dietary Supplement Information Expert Committee and Conclusions

DSI EC concluded that the safety information for green tea arising from diverse sources provides a signal for the possibility of liver damage caused by products that contain concentrated green tea extracts. When analysing these reports, DSI EC discussed the wide usage of green tea as a beverage and the low incidence of a causal relationship to hepatotoxicity. While reviewing the information in order to make a safety class assignment, DSI EC unanimously ruled that class 3 was not the appropriate option for green tea (table I). The Committee members also unanimously rejected a class 1 safety assignment because of the adverse event reports identified by several sources. Thus, DSI EC discussions centred on assigning green tea as safety class 1a or class 2. Members of DSI EC discussed the weaknesses of the adverse event reports as presented above. While recognizing the limitations of the data, DSI EC members noted that multiple aspects of available information point to the possibility of liver damage associated with concentrated green tea extracts, especially when taken under fasting conditions. Clearly, liver failure is a serious problem.

The DSI EC recognized that the individual case reports were not strong, but the preponderance of the reports and significant pharmacokinetic and toxicological data prompted the Committee to propose a label statement for green tea extracts. The label statement is intended to alert consumers and healthcare professionals of the need to pay close attention and be vigilant when using concentrated green tea extract so as to minimize potential risks.

Considering the information reviewed, the DSI EC unanimously decided to assign a Class 2 safety to green tea extract. DSI EC deliberated on the appropriate label statement and suggested that USP green tea extract monographs carry the following labelling statement:

"Take with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice."

In proposing the above labelling statement, the Committee reviewed several comments from interested investigators and organizations. The Committee is deliberating on the conditions of use under which the labelling should be applied. It should be noted that the Committee proposal does not pertain to traditional green tea infusions or other beverage preparations. Because DSI EC constantly monitors current reports concerning the safety of dietary supplements for which USP-NF monographs are developed, the safety classification may be reviewed as new information becomes available. In accordance with USP's open revision policy,[60] the DSI EC also reviews public comments in periodic safety revisions.

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Correspondence: Dr *Dandapantula N. Sarma*, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, USA.
E-mail: dns@usp.org

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