

Nonclinical and Clinical Safety Studies on Green Tea Extracts

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Abstract

Green tea, one of the most popular beverages in the world, has been reported to show beneficial effects in prevention and treatment of diseases. Although green tea extract (GTE) is believed to have pharmacological effects on the reduction of body lipid and blood cholesterol levels, regulatory agencies in France and Spain suspended market authorization of a weight-loss product containing GTE due to hepatotoxicity concerns. Although the pathogenesis of the liver damage caused by GTE is said to be unknown, epigallocatechin-3-gallate (EGCG) has been identified as the main component in the GTE probable responsible for hepatotoxicity. The present review is aimed to provide a comprehensive overview of safety from nonclinical and clinical studies on GTE as dietary supplements. Peer-reviewed articles on nonclinical and clinical safety of GTE from 2005 to 2017 were acquired from Pub Med, Scopus, Science Direct, and SCI Finder. Based on repeated dose toxicity tests, the no-observed-adverse-effect levels (NOAEL) of GTE, EGCG and catechin fraction were estimated to be more than 500, 67.8, and 500 mg/kg/day, respectively. Several clinical trials showed the hepatotoxicity risk associated with GTE is limited. For the safety management of dietary supplements containing GTE, it is needed to set up the specification on the upper limit of EGCG content. Furthermore, the warning label on the GTE supplement should be mandatory to inform the consumers of using the product with food intake and paying closer attention to ingestion of the GTE preparations in patients with high susceptibility to liver damage or liver transplantation.

Keywords: Hepatotoxicity; Green Tea Extract; Catechin; Epigallocatechin-3-Gallate

Abbreviations: GTE: Green Tea Extract; NOAEL: No-Observed-Adverse-Effect Levels; EGCG: Epigallocatechin-3-Gallate.

Introduction

Green tea (*Camellia sinensis*), traditionally popular in China, Korea and Japan, is a widely used consumed

beverage worldwide. Green tea has been believed to be associated with various health benefits including the prevention and treatment of cancers such as upper gastrointestinal tract, breast and prostate cancers and oral leukoplakia [1-3], and improved cardiac function, decreased atherosclerosis, cholesterol-lowering activity, and obesity prevention [4-7]. The beneficial health effects of green tea are primarily attributed to polyphenolic

catechins such as epicatechin (EC), epicatechingallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG) [8,9]. Among polyphenolic catechins, EGCG is the most abundant and pharmacologically active [10,11]. Other polyphenols include flavonols and their glycosides such as chlorogenic acid, coumarylquinic acid and theogallin [12]. Caffeine is present at an average level of 3% along with very small amounts of theobromine and theophylline. The amino acid theanine is also unique to green tea [13]. Although normal consumption of green tea seems safe, the consumption of concentrated green tea extract (GTE) has been associated with clinical cases of hepatotoxicity and hepatocellular damage in rodents [14-17]. Concern has been raised as to the safety of the intake of high doses of GTE and led to the recent publication of a systematic review of the safety of GTE by the US Pharmacopeia (USP) [18]. The USP concluded that significant safety issues are minimal if GTEs are formulated correctly and used as directed, and suggested a warning to be placed on any GTE marketed as a dietary supplement. This review is aimed to provide a comprehensive overview of safety of GTE through the systematic analysis of peer-reviewed articles on nonclinical and clinical safety of GTE. Specific emphasis was given to hepatotoxicity, which has been reported in animal models and clinical trials, and linked to adverse events (AEs). A literature search was conducted in Pub Med, Scopus, Science Direct, and SCI Finder for laboratory toxicology tests and human intervention studies published in English from 2005 to 2017.

Signal Analysis of Adverse Events Associated with GTE

One of the most important objectives of post-marketing monitoring of dietary supplements is the early detection of unknown and unexpected adverse events (AEs). The process to analyze signals from AEs consists of the following 4 steps: 1) the collection of AEs (voluntary reporting from consumers and experts as well as mandatory reporting from manufacturing & importing companies); 2) the construction of an integrated database for AE analysis (merged with AE monitoring DB, product information DB and safety information DB); 3) the signal detection (data mining to draw significant signals out from an integrated database using several statistical parameters such as PRR, ROR, and IC); 4) the data evaluation (algorithm analyses to find the feasible signals in relation to dietary supplement intake) [19]. Depending on the seriousness of the problem, some signals require urgent attention to protect the public. Automatic classification of all AE reports into serious or non-serious

events may improve the timeliness of detection of serious adverse events (SAEs) [20].

In April 2003, French and Spanish authorities suspended market authorization of a phytotherapeutic drug which was suspected of having caused liver disorders in 13 subjects (9 cases reported in France and 4 cases in Spain) [21]. One capsule of the phytotherapeutic drug contained 375 mg of a patented hydroalcoholic green tea extract, which was obtained using 80% ethanol as the extraction agent and which was standardised to 25% EGCG. Furthermore, the extract contained 5-10 % caffeine. At a recommended dose of two capsules twice a day (daily dose corresponds to 375 mg EGCG), the phytotherapeutic drug was said to facilitate weight-loss as part of a calorie-controlled diet. The estimated frequency of the hepatotoxic effects was 1 case per 100 000 boxes of the drug sold from 1999 to 2003. Liver toxicity appeared on average following 50 days of use. The time of onset of liver damage ranged from 9 days to 5 months with usage of 2-5 capsules/day (187.5 – 468.75 mg EGCG/ day), mostly 4 capsules /day (375 mg EGCG/ day). Regarding the US FDA Med Watch reports on liver damage associated with green tea products during the period from January 2001 to July 2006, 5 cases are listed, all associated with intake of polyherbal formulations and categorized as “possible causality” according to the Naranjo scale [18]. In the Australian Therapeutic Goods Administration Report and the Canadian Adverse Drug Reaction Monitoring Program Reports, 4 cases of abnormal liver function were associated with green tea products all of them being polyherbal formulations and resulting in “possible causality” ratings according to the Naranjo scale [18]. There have also been 6 reports on serious adverse events concerning the intake of green tea supplement during the period from Nov 2012 to Apr 2015 in Korea [22].

Toxicological studies on GTE

Hsu, et al. reported that oral administration of GTE at doses of 0, 625, 1250, 2500 mg/kg body weight/day for 28 days did not cause adverse effects on body weight, organ weights, hematology, serum biochemistry, urinalysis, or histopathology in ICR mice [23]. From the study, the no-observed-adverse-effect level (NOAEL) of GTE was estimated to be 2500 mg/kg/day. The National Toxicology Program (NTP) 14-week toxicity study suggested the contradictory results with the above ones. Due to liver necrosis, GTE treatment-related mortality occurred in male and female mice in the 1000 mg/kg dose groups [24]. The NOAEL for the liver in mice was 500

mg/kg/day. Interestingly, it is apparent that there was an approximately 10- fold difference in maximum tolerated dose between fasted and non fasted states [25]. According to the studies reported above, the NOAEL systemic exposures were actually lower in faster than non fasted state, leading to the speculation that fasting had rendered the target organ systems potentially more vulnerable to the effects of green tea extract.

The toxicity of EGCG was studied as a component of GTE or purified preparations. Based on pure EGCG-induced hepatotoxicity, 14-day tolerable dose of EGCG was established as 21.1 mg/kg/day for i.p and 67.8

mg/kg/day for p.o [26]. However, in another sub acute toxicity testing, the dietary administration of EGCG preparation to rat for 13 weeks was not toxic at doses up to 500 mg/kg/day [27]. As to green tea catechin preparations, the NOAEL was 1200 mg/kg/day for male, the highest dose tested, and 400 mg/kg/day for female due to reduced body weight gains [28]. Increase in plasma alanine transaminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST) levels was reported in rats administered with green tea catechin preparations at dose of 3525 mg/kg/day [29]. Taken together, the NOAEL of GTE, EGCG and catechin fraction were estimated to be more than 500, 67.8, and 500 mg/kg/day, respectively.

Material tested	Animal model	Administration route	Dose (mpk)	Duration	Toxicological Effect	NOAEL (mpk)	Ref No.
GTE	ICR mouse	oral	625, 1,250, 2,500	28 d	none	2,500	[23]
GTE	B6C3F1 mouse	oral	62.5, 125, 250, 1000	14 wk	hepatotoxicity	500	[24]
GTE	beagle dog	oral	50, 150, 300, 500	13 wk	death	50 (fasted) 500 (non-fasted)	[25]
EGCG	swiss albino mouse	oral, i.p	6.6, 21.1, 67.8, 108, 217	14 d	hepatotoxicity	67.8 (p.o.) 21.1 (i.p.)	[26]
EGCG	Wistar rat	diet	0.3%, 1.25%, 5%	90 d	none	500	[27]
Catechin fraction	SD rat	oral	120, 400, 1200	182 d	none reduced body weight gain	1200 (male) 400 (female)	[28]
Catechin fraction	F344 rat	diet	0.3%, 1.25%, 5%	90 d	hepatotoxicity	764 (male) 820 (female)	[29]

Table 1: Repeated dose toxicity studies on green tea extract, purified EGCG or catechin fraction.

Clinical safety studies on GTE

Several clinical trials showed the hepatotoxicity risk associated with GTE is limited [30-34]. Daily ingestions of GTE or EGCG for up to 1 year have generally shown no

adverse reactions except for temporal increase of serum ALT level and significant adverse reactions in gastrointestinal track [32,34].

Material tested	Subjects	Administration route	Dose (mg/d)	Duration	Toxicological Effect	Ref No.
GTE	Patients with Chronic Stable Angina (n=79)	oral	1,500	6wk	no adverse reaction	[30]
GTE	healthy men (n=35)	oral	2,304	3 wk	no adverse reaction	[31]
EGCG	Patients with multiple sclerosis (n=12)	oral	800	1yr	significant adverse reactions in GI track	[32]
EGCG	Patients with prostatic intra-epithelial neoplasia(n=97)	oral	400	1yr	no adverse reaction	[33]
EGCG	postmenopausal women at risk for breast cancer (n=1075)	oral	843	1yr	no adverse reaction except for temporal increase of ALT level	[34]

Table 2: Clinical trials for the safety evaluation of GTE or EGCG.

Conclusion

Taken together, GTE can be considered to be safe in animal toxicity testing's and clinical trials. The hepatotoxicity is probably due to EGCG or its metabolites, which under particular conditions related to the patients' metabolism, can induce oxidative stress in the liver. Therefore, for the safety management of dietary supplements containing GTE, it is needed to set up the specification on the upper limit of EGCG content in the product.

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Conflict of Interests

The author has no conflicts of interest to declare.

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