



Safety assessment of heat-sterilized green tea catechin preparation: A 6-month repeat-dose study in rats [☆]

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ABSTRACT

Evidence suggests that the purported health benefits associated with green tea consumption are related to tea catechins. In the present study, potential adverse effects of a standardized heat-sterilized green tea catechin (GTC-H) preparation was investigated following gavage administration to rats at doses of 0, 120, 400, 1200 mg/kg/day for 6 months. A decaffeinated high-dose group (1200 mg/kg/day) (GTC-HDC), was included for comparison. A possibly test article-related clinical finding of intermittent increased activity was noted in the 400 and 1200 mg/kg/day GTC-H groups, but was not considered to be adverse. Lower body weight gains without any decrease in food consumption were noted in the high-dose (1200 mg/kg/day)-treated GTC-H and GTC-HDC females. In the high-dose male GTC-H group, a lower total motor activity count for the 60-min session was noted prior to dosing at the study week 25 evaluations compared to the control group. Similar changes were not observed in the GTC-HDC group. Based on the results of this study, the no-observed-adverse-effect level (NOAEL) for GTC-H was 1200 mg/kg/day for males, the highest dose tested, and 400 mg/kg/day for females based on reduced body weight gains. The NOAEL for GTC-HDC was 1200 mg/kg/day for males and could not be determined in females.

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1. Introduction

Tea prepared from the leaves of *Camellia sinensis* is one of the most widely consumed beverages in the world. Green tea has been associated with many cultures in Asia, particularly in China and Japan. The primary constituents believed to be responsible for the purported health benefits of green tea have been identified as catechins. Catechins have been reported to possess various physiological and pharmacological properties such as antioxidative activity (Yoshino et al., 1994), antiallergic potentials by inhibiting hyaluronidase activation (Kakegawa et al., 1985), antiviral action (Nakayama et al., 1993), the inhibition of plaque formation (Hattori et al., 1990),

hypotensive action (Henry and Stephen-Larson, 1984), the prevention of certain types of cancer (Katiyar and Mukhtar, 1996), radioprotector activity (Uchida et al., 1992), and blood glucose-lowering effects (Matsumoto et al., 1993). Additionally, results of multiple preclinical and clinical studies suggest beneficial effects of tea catechins on lipid metabolism, including a reduction in triglycerides and total cholesterol (Chan et al., 1999), inhibition of liver and body fat accumulation (Chaudhari and Hatwalne, 1977; Ishigaki et al., 1991; Nagao et al., 2001, 2005, 2007), stimulation of lipid catabolism in the liver (Murase et al., 2002) and enhanced energy consumption (Dulloo et al., 2000; Osaki et al., 2001). As a result of these observations, catechin-rich beverages have been marketed as “Food for Specified Health Use” in Japan.

Green tea catechins (GTC) are low-molecular-weight polyphenols consisting primarily of flavanol (flavan-3-ol) monomers. Catechins found in green tea include catechin, epicatechin, gallo-catechin, epigallocatechin, catechin gallate, epicatechin gallate, gallo-catechin gallate, and epigallocatechin gallate (EGCG) (Fig. 1). Because of the bitter taste of these polyphenols, conventional green tea drinks with high levels of tea catechins are not readily accepted by consumers. Pasteurization-induced changes in the flavor of green tea liquor are a technical barrier in ready-to-drink tea commercial production (Kim et al., 2007). Additionally, the qualitative and quantitative composition of catechin isomers in beverages can vary according to the heat-sterilization conditions as

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechin-*o*-methyltransferase; EDTA, ethylenediaminetetraacetic acid; EGCG, epigallocatechin gallate; FDA, Food and Drug Administration; FOB, functional observational battery; GTC, green tea catechins; GTC-H, heat-sterilized green tea catechins; GTC-HDC, decaffeinated GTC-H; ICH, International Conference on Harmonization; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MHLW, Ministry of Health, Labor and Welfare; NOAEL, no-observed-adverse-effect level; OECD, Organization for Economic Co-operation and Development.

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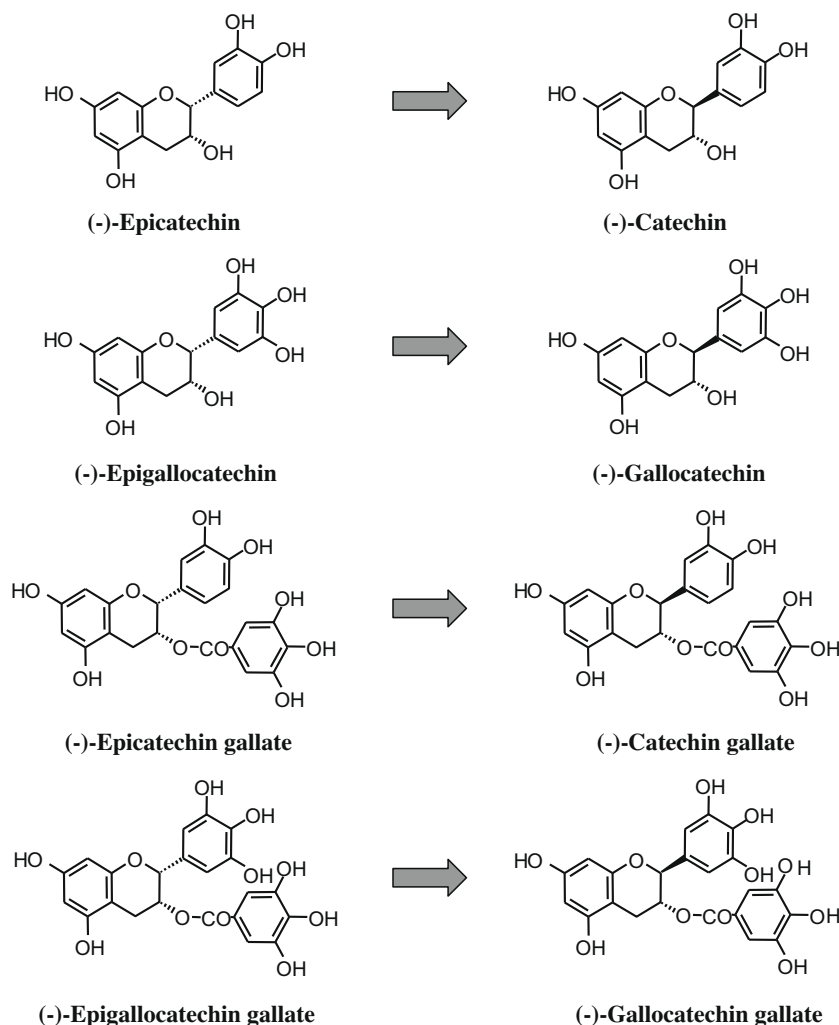


Fig. 1. Chemical structures of catechins and their corresponding epimers.

epimerization of tea catechins occurs during heating (Seto et al., 1997). To increase consumer acceptability, several investigators have developed processes to prepare green tea beverages with high levels of catechins. During heat sterilization, approximately half of the tea catechins in green tea beverages are epimerized to catechin, gallocatechin, catechin gallate, and gallocatechin gallate (Chen et al., 2001; Seto et al., 1997; Kim et al., 2007; Ikeda, 2008). Heat sterilization conditions are dependent on features of the beverage, including pH and packaging, such that significant epimerization of catechins occurs in certain types of green tea beverages and not in others (i.e., sports drinks; because of their acidic pH, these types of beverages do not require excessive sterilization).

Products containing green tea extracts, particularly with high levels of catechins produced using heat sterilization, are commonly marketed for health benefits. In the published literature, very few studies have explored the toxicity potential of green tea preparations that contain high levels of catechins or their epimers. Daily oral administration of standardized and defined green tea polyphenols (containing 800 mg EGCG) to humans for 28 days was found to be safe (Chow et al., 2003). Similarly, oral administration of standardized heat-sterilized green tea catechins (GTC-H) preparations to rats at dose levels of up to 2000 mg/kg/day for 28 days was safe (Chengelis et al., 2008). In another dose-response study (Takami et al., 2008), dietary exposure of F344 rats to GTC at levels up to 5% in diet for 90 days resulted in reduced body weights in males, increased alanine aminotransferase (ALT) and alkaline phosphatase

(ALP) in males and females, and increased aspartate aminotransferase (AST) in females. While suggestive of weak hepatotoxicity, the liver enzyme changes were not associated with any clinically significant histopathological correlates in these animals. The no-observed-adverse-effect level (NOAEL) of GTC was determined as 1.25% (~800 mg/kg body weight/day). The objective of the present study was to systematically investigate the potential dose-related adverse effects over the longer term (i.e., 6-month) of repeat-dose exposure via oral gavage of GTC preparations that have undergone heat sterilization for inclusion in green tea beverages. Additionally, effects of decaffeinated GTC-H (GTC-HDC) at the highest dosage level also were investigated to distinguish potential effects resulting from the presence of caffeine in the preparation.

2. Materials and methods

2.1. Experimental overview

Green tea catechin preparations GTC-H or GTC-HDC in the vehicle (deionized water) were administered orally (via gavage) once daily to rats (10/sex/group) for a minimum of 182 consecutive days. The dose levels used for the animals in groups treated with GTC-H were 120, 400, and 1200 mg/kg/day, while animals in the GTC-HDC group received only the highest dose level (1200 mg/kg/day). The vehicle-treated animals served as the control group (0 mg/kg/day). The initiation of dose administration was set as study week 0. All animals were observed twice daily for mortality and morbidity. Clinical examinations were performed daily at the time of dosing and 1–2 h post-dosing for signs of toxicity. Detailed physical examinations were conducted weekly, and body weights, and feed consumption were recorded

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