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Short Review

Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements

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ABSTRACT

The safety of green tea infusions and green tea extract (GTE)-based products is reviewed regarding catechins. Epigallocatechin 3-gallate (EGCG), the major catechin present in green tea, is suspected of being responsible for liver toxicity reported in humans consuming food supplements. Intake of EGCG with green tea infusions and GTE-based beverages is up to about 450 mg EGCG/person/day in Europe and higher in Asia. Consumption of green tea is not associated with liver damage in humans, and green tea infusion and GTE-based beverages are considered safe in the range of historical uses. In animal studies, EGCG's potency for liver effects is highly dependent on conditions of administration. Use of NOAELs from bolus administration to derive a tolerable upper intake level applying the margin of safety concept results in acceptable EGCG-doses lower than those from one cup of green tea. NOAELs from toxicity studies applying EGCG with diet/split of the daily dose are a better point of departure for risk characterization. In clinical intervention studies, liver effects were not observed after intakes below 600 mg EGCG/person/day. Thus, a tolerable upper intake level of 300 mg EGCG/person/day is proposed for food supplements; this gives a twofold safety margin to clinical studies that did not report liver effects and a margin of safety of 100 to the NOAELs in animal studies with dietary administration of green tea catechins.

1. Introduction

Green tea infusions are widely used as beverages and a number of chemical components present in green tea such as epigallocatechin 3-gallate (EGCG, see Fig. 1) are claimed to have chemopreventive actions on a variety of health-related endpoints in humans (Wickremasinghe, 1978; Singh et al., 2011). Therefore, green tea-based products are marketed as "nutraceuticals". The marketed nutraceuticals are dried green tea extract (GTE)-based beverages to be consumed as ready-to-drink (RTD) and dried GTEs intended as food supplements in the form of capsules.

GTE-based food supplements have been associated with cases of liver toxicity in humans. Therefore, the Norwegian Food Safety Authority asked the Norwegian Institute of Public Health (NIPH) (NIPH et al., 2015) to develop a safety assessment on the levels of EGCG in GTEs used in food supplements. The NIPH concluded that margins of safety between doses of GTEs or their major components causing adverse effects in animals and estimated human consumption are less than 10 and thus "higher than what is recommended by the MOS approach".

This manuscript provides a short overview on exposure of humans to green tea infusion, green tea extract-based beverages, and dried green tea extracts used as food supplements and includes separate considerations on health aspects and safety assessment of these products and specifically EGCG, since green tea extracts (GTEs) have been implicated in some cases of liver damage in humans. The safety assessment considers both animal toxicology and human clinical studies on GTEs to conclude on a tolerable upper intake level for GTEs used as nutraceutical supplements and for medicinal uses.

2. Safety of green tea infusions

Traditional green tea infusions use young leaves and leave buds from *Camellia sinensis* (L.) Kuntze to produce traditional "green tea" as the basis for traditional aqueous green tea infusions. Green tea is manufactured without fermentation and contains a number of catechins (for structures, see Fig. 1) (Nishitani and Sagesaka, 2004; EFSA, 2009).

The contents of catechins and other constituents in green tea show considerable variation due to growing conditions of the plant, age of leaves harvested, and processing. The contents of catechins in green tea infusions also vary with the ways to brew (Negishi, 2013; Bhagwat and

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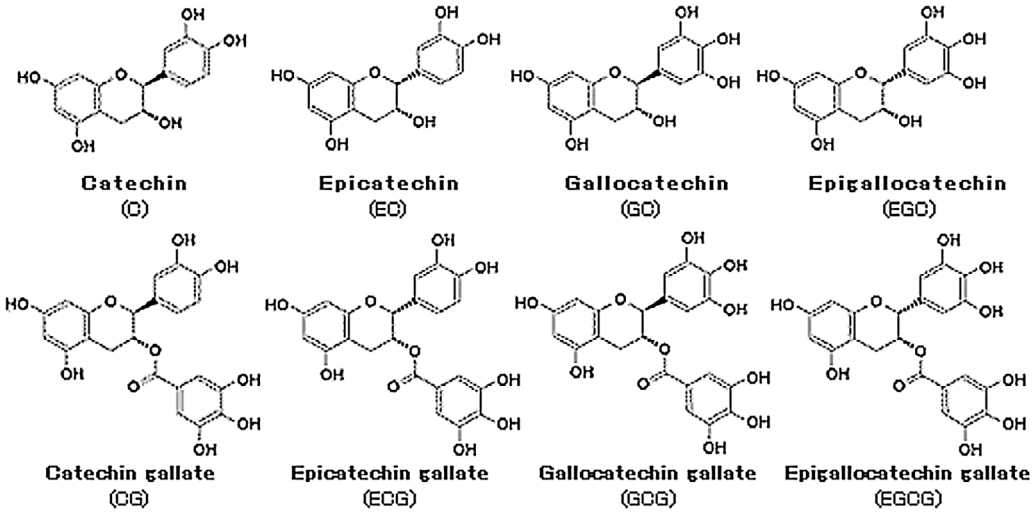

Fig. 1. Structures of green tea catechins and EGCG.

Haytowitz, 2015). EFSA has derived intake estimates for green tea and EGCG intakes with means of 95.2 and 147.7 mg EGCG/day with a high intake of 288.5 and 447.6 mg EGCG/day for European consumers (EFSA, 2009). Based on a number of epidemiology studies and the concentration of EGCG in green tea sold in Japan, we have estimated mean EGCG consumption from green tea in Japan as 314 mg/day with a maximum of 734 mg/day (see Appendix A in Supplementary material and Khokhar et al., 1997). Intake of EGCG may be even higher depending on the brewing conditions. While green tea infusion has sometimes been associated with liver damage in predisposed humans (EMA, 2013a,b), such events have not been observed in controlled studies and may be due to the presence of confounders (EMA, 2013a,b). Green tea infusions have a history of safe use in Asia and no alerts regarding liver toxicity are established for green tea infusions in Japan despite high consumption. Adverse effects of green tea consumption have not been reported in Japan despite high intakes (Appendix A in Supplementary material). Therefore, it can be concluded that EGCG intake in the form of green tea infusions should be safe up to the maximum consumption of 734 mg EGCG/person/day.

3. Safety issues with GTE-based beverages

Green tea extract (GTE)-based beverages (for example, “Healthya green tea” and “Healthya water”) marketed in Japan include 540 mg of total green tea catechins (140–209 mg EGCG) in one serving which is the recommended daily consumption. The total intake of green tea catechins from one serving of such a beverage is equivalent for 4–6 cups of green tea and intake of green tea catechins and EGCG from this source at the recommended consumption are thus well within the historical daily consumption of green tea catechins in Asia. The GTE-based beverages marketed in Japan have been approved by the Japanese Consumer Affairs Agency (CAA) as “Foods for Specified Health Uses (FOSHU)” and the efficacy and safety of Kao Corporation’s GTE-based beverages “Healthya” have been assessed by the Japanese Ministry of Health Labor and Welfare in 2003 resulting in approval for marketing (now the authority of the FOSHU has been transferred to CAA), based on historical safe uses of green tea as food, absence of genotoxicity, several repeat-dose toxicity studies in rodents with GTE used by Kao Corporation (Chengelis et al., 2008; Ogura et al., 2008; Morita et al., 2009a, 2009b) and clinical trials conducted by Kao Corporation (see Nagao et al., in Appendix B in Supplementary material). In addition, a number of clinical studies with beverages fortified with GTEs have been published with durations of up to one year (median duration of 12 weeks) and the highest intake of 498.6 mg EGCG/person/day without concerns for hepatotoxicity (for details of study design and outcome, see Appendix B in Supplementary material). Liver function was assessed in 17 of the 20 publications without adverse effects of the GTE-based beverages on this endpoint. Treatment-related adverse effects on other endpoints were also not reported in these 20 publications. Therefore, GTE-based beverage can be considered as safe up to EGCG doses that are identical to those delivered by traditional green tea infusions based on the history of safe use of green tea and the absence of adverse effects induced by GTE-based beverages in clinical studies.

4. Safety issues with dried green tea extracts used as food supplements

As mentioned above, consumption of food supplements containing green tea extracts (GTEs) has been associated with adverse liver effects in humans in a number of case reports (NIPH et al., 2015), but the causative agent responsible for the liver injury due to the consumption of these GTEs is unknown (Navarro et al., 2017). In addition, observations made in the available toxicity studies on GTEs in experimental animals have raised concerns regarding safety of GTEs (Lambert et al., 2010). These have been extended to include green tea catechins in general.

The human daily doses of GTEs from food supplements may vary widely due to different methods to obtain GTEs, different recommendations regarding intake by manufacturers, and consumer attitude. The Norwegian Institute of Public Health, based on data from food authorities in the Nordic countries, conclude that exposures of up to 1944 mg/day for GTEs and up to 980 mg/day of EGCG (NIPH et al., 2015) are possible. However, some consumers may have higher intakes of GTEs due to the easy palatability of capsule formulations.

An assessment of the safety of dried GTEs needs to consider both the results of liver function testing in the many available clinical studies on GTEs and the results of animal toxicity studies with dried GTEs. Well-designed human clinical studies are more relevant for a safety assessment than animal toxicity studies.

A large number of human studies have assessed possible health-protective effects of dietary supplementation with dried GTEs and many of these studies have also monitored “liver enzymes” in blood or determined other parameters indicative of liver function impairment in the dried GTE-exposed subjects (for details of study design and outcome, see Appendix B in Supplementary material). Doses of EGCG applied ranged from 100 to 4000 mg EGCG/human subject/day with durations between one day and two years, median duration of the dried GTE-application was 90 days. Increased “liver enzymes” were only seen in studies that administered daily doses of EGCG > 800 mg/human subject/day. A systematic review of the literature published up to 2013 (Isomura et al., 2016) concluded, based on an analysis of the reports from 34 randomized clinical trials, that liver-related adverse events