

# The Safety of Epigallocatechin-3-Gallate (EGCG) as a Potential Chemopreventative and Chemotherapeutic Agent in Hepatocarcinogenesis

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Green tea, made from the unfermented leaves of *Camellia sinensis*, is one of the most widely consumed beverages in the world. It is comprised of several polyphenolic compounds (catechins) and can be concentrated into a Green Tea Extract (GTE), which, in turn, is a common ingredient in many dietary supplements. Epigallocatechin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE, comprising typically ~40% of the total polyphenol content [1]. EGCG has antioxidant, antiviral, anticarcinogenic, antimutagenic and anti-inflammatory properties, shown in several preclinical and epidemiologic studies [2-6]. Preclinical data in cell culture and animal models suggest green tea may have a role as a chemopreventative agent for many types of cancer, including Hepatocellular Carcinoma [7-11]. Currently, there is a need for more effective treatments for hepatocellular carcinoma which occurs primarily in patients with viral hepatitis and cirrhosis. Given these easily identifiable risk factors, hepatocellular carcinoma is an ideal disease for the development of effective chemopreventative agents.

It is estimated that approximately 2% of the US population is infected with HCV; cirrhosis develops in 20% of those infected and HCC develops in 25% of cirrhotics [12]. The majority of patients who present with symptoms associated with HCC do not survive one year [13]. Recent data has demonstrated that successful eradication of HCV in patients with cirrhosis was associated with a reduction in the rate of hepatic decompensation, liver transplant, and liver-related death [14-17]. Although, patients with cirrhosis stand to benefit from HCV therapy the rates of Sustained Virological Response (SVR) are substantially lower in patients with cirrhosis compared with those without cirrhosis [17].

EGCG has been found to be a potent inhibitor of HCV entry in hepatoma cell lines as well as primary human hepatocytes. The effect was independent of the HCV genotype, and both infection of cells by extracellular viruses and cell-to-cell spread was blocked [18,19]. Beyond its antiviral effect on HCV, recent data indicate that the receptor tyrosine kinases are one of the critical targets of EGCG to inhibit cancer cell growth. EGCG has also been shown to modulate the expression of target genes which are associated with induction of apoptosis and cell cycle arrest in cancer cells [20]. EGCG's chemopreventative effect has been demonstrated in human subjects with chronic hepatitis B and a very high risk of hepatocellular carcinoma. In a randomized, double-blinded, placebo-controlled trial of 124 individuals with sero-positive HBsAg and aflatoxin-albumin adducts showed a significant decrease of 8-hydroxydeoxyguanosine, a biomarker of oxidative DNA damage, after three months of green tea polyphenol intake [11].

Clinical investigations on the potential benefits of EGCG's anti-inflammatory and anti-tumor properties in patients with cirrhosis are warranted. Although the safety and pharmacokinetics of EGCG in patients with cirrhosis has been partially described, there are concerns regarding a risk for hepatotoxicity with EGCG [21]. This is especially where such risk may be unpredictable due to differences in EGCG's disposition in this patient population as a result of the underlying liver disease. Reports of adverse effects, mainly hepatitis, associated with

the consumption of green tea preparations have been published [22-24]. The mechanism of the potential hepatotoxicity of GTE is unclear [24]. However the impact of a hepatotoxic event may be magnified in patients with preexisting liver disease as a result of alterations in pathways involved in EGCG's hepatic metabolism or excretion. Differences in the disposition of silymarin, another herbal product used by patients for the self-treatment of liver disease, has been seen in volunteers with liver disease [25,26]. Alterations in the expression of hepatobiliary transporters induced by liver disease, which may lead to differences in drug disposition, have been reported [27,28].

GTE is a common ingredient in several dietary supplements, some of which have been withdrawn from the market due to safety concerns. An example of this is when the manufacture of *Exolise* (Arkopharma, France), a weight loss supplement containing high EGCG levels was withdrawn from the market in April 2003 due to 13 cases of liver damage possibly due to its consumption [29]. Case series and a systematic review by the United States Pharmacopeia (USP) further illustrated evidence for the potential for green tea extract to cause hepatotoxicity [24]. Since 1966, 216 case reports of toxicity with green tea extracts were identified by the USP, of which 34 were concerning for liver toxicity. The majority of cases present with an acute hepatocellular injury pattern and most recover with cessation of use [22-24]. It was unclear in most case reports whether the toxicity was due to the green tea extract or possibly by the extraction process, concomitant medications, or from the other herbs in the supplements. Taking into account that most of the reported liver injuries involve women, a gender susceptibility to green tea hepatotoxicity may be hypothesized. An idiosyncratic or an immune-allergic mechanism appears to be the likely mechanism of injury [23]. Recent animal studies with high doses of GTE and EGCG have described dose dependent hepatotoxicity resulting in severe morbidity and mortality. However, chronic moderate to high dose daily GTE and EGCG use in healthy human volunteers was not shown to cause severe adverse effects or impair liver function [30].

In summary, EGCG has anti-angiogenic, anti-oxidant and anti-fibrotic properties that may have therapeutic potential in Hepatitis C Virus (HCV) induced cirrhosis. Given its potential role as adjunct to HCV therapy and as a chemopreventative agent in the HCV cirrhotic

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population, further study is needed in the safety and efficacy of EGCG in cirrhotic patients.

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