

Toxicity of Green Tea Extracts Used for Weight Loss

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ABSTRACT

There have been several green tea products seen in the market recently and such oral supplements have been considered to be safe as they are perceived to be natural. It has been used for anticarcinogenic, antioxidant, cardiovascular protection and as a treatment for diabetes mellitus and obesity. However, there are several case series and reports that incite green tea extracts as the agents of hepatotoxicity. This article attempts to present the proposed mechanisms of action for anticarcinogenesis and antiobesity agent. The adverse effects and toxicology of green tea extracts are also discussed.

Keywords: *Camellia sinensis*, catechin, obesity, weight loss

INTRODUCTION

Green tea is made from leaves of *Camellia sinensis*. Its primary active ingredients are mainly the catechins. There have been several green tea products seen recently and they are marketed as oral health supplements and hence perceived to be natural and “safe”. They have been used for medical and health benefits. However, there are several case reports that incite green tea extracts as agents of hepatotoxicity. This article attempts to present the proposed mechanism of action, adverse effects and toxicology of green tea extracts.

GREEN TEA

Background of Green Tea

Green tea is made from leaves of the plant *Camellia sinensis*. It is chemically characterised by the presence of large amounts of polyphenolic compounds known as catechins¹. The most abundant catechin in green tea is epigallocatechin-3-gallate (EGCG)¹. Other major green tea catechins include epigallocatechin (EGC), epicatechin (EC) and epicatechin-3-gallate (ECG)². These catechins account for 30–40% of the dry weight of green tea³.

The chemical structure of green tea contains simple hydroxybenzoic acids such as gallic acid and propyl gallate².

Green Tea Products and Contents

There have been several brands of green tea products seen over the past year. Examples include brands such as Zoeta, Stamina Rx, Natural Fat Burner, Trim Spa, Slimming Formula, Hydroxycut and Herbalife.

Although most commercially available supplements have not been rigorously tested for safety and efficacy, they have found an enlarging market because of the obesity pandemic⁴. These oral supplements containing green tea extract have been marketed as effective for weight loss and to prevent and cure some solid tumours. Although they are oral supplements, they may contain many other additional contents that may or may not be included in the nutritional labels, such as caffeine, yohimbine, L-arginine, lotus leaf, glucosamine, cocoa, “vitamin supplements”, *Ephedra Sp.* amongst the few.

PHARMACOKINETICS

Absorption

Peak plasma concentration is reached at 1.3–1.6 hours⁵ with a half life hours. Repeated exposure had little effect on plasma levels or elimination time⁶.

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Bioavailability

Tea polyphenols have low bioavailability⁷. EGCG is preferentially excreted through the bile in the colon⁵.

Elimination

The major route of elimination is via the faeces¹. EGCG is also eliminated in the bile while EGC and EC are mainly eliminated via the urine⁵.

USES

The uses of green tea include anticarcinogenic, antioxidant, antiviral, cardiovascular protection and as a treatment or prevention of diabetes mellitus and obesity. Many beneficial effects of tea have been attributed to the antioxidant effects of polyphenols. However the exact mechanisms of such activity have not been firmly proven in any animals or humans^{8,9}.

Anticarcinogenesis

Green tea has shown cancer chemopreventive activity¹⁰⁻¹² but there are also conflicting epidemiological studies that have reported either no association or reduced risk between tea consumption and the risk of cancer¹³⁻¹⁶.

EGCG have been shown to inhibit and suppress the growth and induce cell cycle arrest and apoptosis in different cancer cell lines¹⁰. It inhibits lipid peroxidation in vitro¹⁷, causes antiangiogenesis¹⁸ and impairs tumor invasion and nourishment^{19,20}.

Most studies use high concentrations of tea compounds that often far exceed those found in animal tissues or plasma following tea consumption¹. Anticarcinogenesis is the reason why people believe that green tea is beneficial to health. However the mechanism that prevents cancer may be the same reason that causes hepatotoxicity affecting highly active hepatic cells as well.

Weight Loss and Antiobesity

EGCG has been shown to be involved in regulation of a variety of metabolic processes, and has been used as an anti-obesity reagent in animal models and in humans²¹⁻²⁴. Although its effectiveness in the treatment of human diabetes has not been established, EGCG has been shown in rodents to be effective in preventing the development of Type I diabetes and treatment of Type II diabetes^{25,26}. EGCG causes many of the same cellular effects as insulin, including repression of glucose production and gene

suppression of the rate controlling gluconeogenic enzymes (phosphoenolpyruvate carboxykinase and glucose-6-phosphatase).

EGCG has been shown to reduce food intake, plasma levels of glucose, and body weight^{27,28}. EGCG inhibits proliferation and adipose differentiation, and induces apoptosis in adipocytes^{29,30}. These modulate the adipocyte marker proteins, down-regulates lipogenic enzymes as well as other potential targets, making the fat from food less available to the body by inhibiting their ability to break down fat into digestible particles. Pure EGCG and green tea extracts have both been shown in humans to stimulate brown fat thermogenesis^{31,32}. This is a specialised kind of fat that creates heat by burning calories at a very high rate. EGCG can modulate insulin secretion and insulin sensitivity^{33,34}. EGCG has also been shown in skeletal muscle to promote fatty acid oxidation³⁵. Furthermore, EGCG has been suggested to reduce blood pressure through enhancing vascular endothelial function and insulin sensitivity³⁶.

EGCG has also been shown to inhibit hepatic gluconeogenesis by mimicking insulin function³⁷.

The net effect is that of a lowered body production of fatty acids, blood fat and cholesterol.

Many of these studies have interesting findings with few reports of adverse effects, and the actual mechanism of EGCG regulation of metabolism and anticarcinogenesis has not been established.

ADVERSE EFFECTS

Adverse effects are usually minimal in its liquid tea form.

Extract Form

A study on healthy volunteers found dose-limiting side effects of gastrointestinal complaints (abdominal pain and bloating, dyspepsia, flatulence, diarrhoea, nausea, and vomiting) and central nervous system stimulation (agitation, dizziness, insomnia, tremors, headaches, dyspnoea, fever, tachycardia, tachypnea and hypotension and restlessness). This dose level is roughly equivalent to drinking 7-8 Japanese-style cups (one cup = 120 ml) of green tea three times daily (a total of 21-24 cups of tea/day)⁶. All these adverse events were considered to be mild.

The adverse events were attributed to caffeine component although the decaffeinated version

also had reported adverse events such as headache, stomachache, heartburn, excess gas, dizziness, nausea and muscle pain. However, caffeine has been implicated as an important component of the beneficial effects of tea, such as chemoprevention^{38,39}.

Several studies on healthy patients and patients with tumours have demonstrated only mild to moderate dose-limiting adverse effects with no changes in their chemistries of liver function tests. Doses were tolerated at up to 3 g/m² for between 4 weeks to 6 months duration^{40,41}.

There were no significant changes in blood counts and blood chemistry profiles after 4 weeks of green tea polyphenol treatment⁶.

Since not all herbal supplements are standardised, one must be wary that there may be additional products, which may have unforeseen adverse effects.

TOXICITY

EGCG, the most abundant tea phenolic found in green tea, was found to be the most cytotoxic of the catechins. This is followed by ECG (also a food additive), EGC, and EC. Their cytotoxicity is likely to be due to their lipophilicity⁴². EGCG and ECG were best at inducing reactive oxygen species (ROS) formation and mitochondrial damage in rat hepatocytes and prostate cancer cells². The onset of cytotoxicity caused by green tea constituents depends on its intracellular energy status and its mitochondrial dysfunction. Mitochondrial depolarisation and ROS formation were suggested to be the early processes that led to the final stages of apoptosis⁴³.

All phenolics depleted hepatocyte glutathione (GSH) and GSH-depleted hepatocytes were more susceptible to gallic acid or EGCG cytotoxicity and ROS formation². EGCG, ECG, EGC, and propyl gallate readily collapsed the hepatocyte mitochondrial membrane potential with EGCG being the most effective mitochondrial toxin. *In vivo* evidence shows possible cytoprotective role of catalase, ascorbic acid, iron (Fe) and pyruvate. Heavy metals like iron incubated with gallic acid form free-radical scavengers, while copper increases toxicity².

In another study showing that EGCG was not toxic at relatively low concentrations ($\leq 1 \mu\text{M}$) that inhibited glucose production via gluconeogenesis and expression of key gluconeogenic genes, it demonstrated significant cytotoxicity at 10 μM and higher concentrations²⁷.

CASE REVIEWS AND REPORTS OF GREEN TEA ASSOCIATED HEPATOTOXICITY

Molinari *et al*⁶ reported a case of a previously healthy 44-year-old female who presented with Grade 1 encephalopathy and severe hepatotoxicity. She had taken diet pills (containing green tea extract 720 mg/day) for the past 6 months. There was no other contributory history to the cause of her jaundice (eg. social, alcohol, drug, family or travel). Extensive workups were all negative for infective, autoimmune, toxicology or genetic causes of jaundice. She developed coagulopathy and required ventilatory and intensive care support. The patient underwent cadaveric liver transplant and the explanted liver showed multiple patterns of hepatic necrosis with some areas of relatively preserved liver parenchyma demonstrating centronuclear necrosis and bridging necrosis. A toxicological analysis obtained from a single pill of oral supplement consumed by the patient showed that the only active ingredient was 120 mg of green tea extract (GTE) and the rest of the excipients and composition of the capsule were benign substances⁴.

Bonkovsky⁵⁴ reported a 37-year-old woman who took "The Right Approach" diet pill (containing GTE 383 mg/day) for 4 months. She presented similarly to the prior case and had no other causes of hepatitis identified. She recovered with normalised liver function tests after a month. However, 1 year post-incident, the patient re-challenged herself with "The Right Approach" for 1 month and presented with liver failure again⁴⁴.

Exolise is an 80% ethanolic dry extract of green tea (*Camellia sinensis*) standardised at 25% catechins expressed as epigallocatechin gallate, containing 5–10% caffeine. It was available in Europe since 1999 but removed from the market following reports of hepatotoxicity^{45,46}. It was used for weight loss. Although most cases of toxicity were self limited and resolved after discontinuation of the supplement, there was a case of fulminant hepatitis during self-medication with Exolise, requiring liver transplantation⁴⁷.

A series of 12 patients with acute idiopathic liver injury in association with consumption of Herbalife products were investigated⁴⁸. One patient developed sub-fulminant and 2 had fulminant episodes of hepatic failure. Although 11 patients recovered, one patient succumbed to complications following liver transplantation. Three patients

resumed consumption of Herbalife products following normalisation of liver enzymes, resulting in a second bout of hepatitis.

Another series of 12 cases of toxic hepatitis implicating Herbalife preparations (1998–2004) were retrieved⁴⁹. One patient with fulminant liver failure was successfully transplanted and the explant showed giant cell hepatitis. Liver biopsies in 7 patients showed hepatic necrosis, marked lymphocytic and eosinophilic infiltration and cholestasis in 5 patients. The causality assessment of adverse drug reaction was classified as certain in 2, probable in 7 and possible in 1 case(s), respectively.

Other case reports have implicated Hydroxycut⁵⁰, Fitofruit graasa acumuladas⁵¹, Camilina Akocapsulas⁵², Oolong tea fine tonic⁵³ and Herbalife⁵⁴ amongst others.

DISCUSSION

The pathogenesis remains unknown and given the relative rarity of the reaction, it seems that host genetic factors are important in modulating susceptibility⁵⁵. However, there are other possibilities as well. They may include the presence of unidentified toxins, microbacteria such as *bacillus cereus* or even contamination with chemicals during growth of leaves or during the production of the supplement itself, such as softeners, preservatives, flavour enhancers, pesticides or heavy metals (intentional or in manufacturing process or in unrefined raw products).

Allergic reaction to the green tea or extracts of its components is also possible although unlikely as there were no biopsy findings consistent with allergy.

Drinking up to 20 cups of green tea per day is common in certain populations, and yet, there have been no reports of clinical toxicity⁵⁶. Although there are controlled human intervention trials to evaluate the biological activity of green tea or green tea components in oral supplements, the safety data based on human consumption cannot be extrapolated to the consumption of large amounts of an isolated component or an enriched extract at regimens that would gain better compliance in intervention trials⁶. Also, most commercially available supplements have not been rigorously tested for safety and efficacy, and their safety data may be dubious or even lacking. Many herbal products may also suffer from mislabelling and have poor scientific records⁵⁷.

The mechanism of hepatotoxicity deserves further investigation and its widespread consumption requires increased recognition and attention by the treating physicians and the relevant authorities. It is difficult to establish a definitive causal relationship between green tea extract and reported cases of hepatotoxicity because of the multiplicity of ingredients and presence of coingestants in many cases. The temporal sequence of the abnormal liver enzymes and the green tea extract administration with positive rechallenge and exclusion of other possible causes strongly suggests that the supplements were the inciting agent for the severe liver illnesses. Doctors could have warned the patients against taking the products or informed the authorities to remove the product from the market in those cases. However, most products bought over the internet will not be screened by regulators. Also, since many “herbal” or “natural” products are not considered medicinal, they do not pass through regulations or testing, and are not obliged to list their ingredients. Doctors should advise their patients that the use of such products are at their own risks.

CONCLUSION

Although rare, green tea extract may cause hepatotoxicity as seen in several case reports.

Toxicity may be due to ROS formation via assault on mitochondrial membrane, but its exact mechanism is not fully known. Hepatotoxicity is often self-resolving, but may require liver transplant in severe cases. Green tea extract should be suspected as a differential cause of hepatitis in patients with history of ingestion of such supplements.

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