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File: ■ Green Tea (*Camellia sinensis*)
■ Adverse Effects

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RE: Adverse Effects Reported with Concentrated Green Tea Extracts

Schönthal AH. Adverse effects of concentrated green tea extracts. *Mol Nutr Food Res*. 2011;55(6):874-885.

Consumed in Oriental medicine for thousands of years, green tea (*Camellia sinensis*) has become increasingly popular in the Western world. In addition to conventional green tea infusion, concentrated green tea extract (GTE) is consumed by individuals to improve their overall health. Although there is evidence of the health benefits of green tea and GTE, some reports indicate adverse events associated with the consumption of large amounts, especially of the latter. This review article summarizes documented examples of adverse effects of green tea in humans and discusses the risks associated with consumption of large amounts of highly concentrated GTE. Included are 129 cited articles.

The predominant contents of green tea – the four polyphenolic catechins epigallocatechin-3-gallate (EGCG), epicatechin gallate, epigallate catechin, and epicatechin – are presumed to provide most of tea's health benefits.

The authors cite eight major pharmacokinetic and safety studies of GTE, with a total of 250 subjects in all studies. Two studies included cancer patients, while the other six included healthy subjects.

Among those studies is a phase I trial with 49 adult cancer patients conducted to determine the maximally tolerated dose of oral GTE on a once-daily and three-times-daily schedule.[1] Mild-to-moderate toxicities (gastrointestinal, neurological, and cardiovascular effects) were seen at most dose levels and were promptly reversed on discontinuation of GTE. An earlier study[2] of healthy subjects ingesting a decaffeinated beverage formulation containing 1.5, 3.0, and 4.5 g of GTE reported no adverse effects.

The major dose-limiting ingredient in GTE, say the authors, appears to be caffeine. Although this would suggest the preferential use of decaffeinated GTE products, there are indications in the literature[3,4] that caffeine might contribute to at least some of the beneficial effects of green tea.

Regarding the safety studies of GTE, the authors conclude that purified EGCG, GTE, and Polyphenon E® (Poly E; high-grade, highly standardized GTE; Mitsui Norin Co. Ltd.; Japan), equivalent to the EGCG content of 8-16 cups of green tea, were safe and well tolerated. However, say the authors, "A major limitation of all of these clinical trials was their open-label, small-scale design, which does not possess the statistical power to detect any adverse effects other than those that are very common."

On the other hand, an increasing number of case studies report detrimental effects after the ingestion of large amounts of green tea or GTE. Individual cases of hepatotoxicity, ranging from acute hepatitis to acute liver failure, from consuming large amounts of green tea are reported.

In 2008, the United States Pharmacopeial Convention (USP) Dietary Supplements Information Expert Committee (DSI-EC) systematically reviewed the safety information for green tea products.[5] Of the 34 case reports in its review indicating hepatotoxicity from GTE, the DSI-EC categorized 27 as "possible causality" and 7 as "probable causality," assuming the likelihood that exposure to green tea products caused hepatotoxicity.

In another recently published systematic review of interventional and observational studies on green tea consumption and liver disease, the investigators concluded that green tea may reduce the risk of liver disease,[6] in particular, liver cancer[7]; however, several confounding variables, including the caffeine content of green tea, make it difficult to establish the precise contribution of catechins.

Several studies provided examples in which EGCG displayed in vivo anticancer activity only when administered as Poly E, but not when given by itself without other green tea constituents. According to the authors, those studies suggest that complex GTE might be more suitable for cancer prevention than individual green tea components, such as highly concentrated EGCG-only capsules, because other catechins may possibly amplify the beneficial effects of EGCG.

Several studies have identified situations in which green tea or GTE may interfere with the absorption, bioavailability, or activity of prescription drugs and other compounds. The authors note green tea's interference with the absorption of iron supplements, where the tannin content in green tea reduces the bioavailability of iron.

Other reported interactions involving the efficacy of pharmaceuticals include the modulation of the activity of the transmembrane protein P-glycoprotein with green tea catechins (some animal studies have established that oral EGCG is able to alter the pharmacokinetics and efficacy of coadministered prescription drugs such as nicardipine, tamoxifen, doxorubicin, diltiazem, and verapamil); interactions with uridine diphosphate glucuronosyltransferase 1A and with the metabolic enzyme cytochrome P450 3A4; and direct molecular interactions with bortezomib and sunitinib.

In their review of articles about green tea's interaction with other natural supplements, the authors cite a study[8] in mice that demonstrated the ability of genistein to enhance EGCG bioavailability and in vitro growth-inhibitory activity. The combination of the two, however, displayed cancer-promoting effects in vivo. The authors note that this adverse outcome was achieved at herbal dosages possible to attain with dietary supplements in humans.

"There is a possibility that adverse events caused by GTE may be underreported, and thus more vigilance may be appropriate." Large, ongoing human intervention studies should include protocols to assess potential adverse effects, including hepatotoxicity.

—Shari Henson

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The American Botanical Council has chosen not to reprint the original article.