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**File: ■ Green Tea (*Camellia sinensis*, Theaceae) Catechins**
**■ Breast Cancer**
**■ Endocrine Treatment**
**■ Systematic Review**

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## RE: Systematic Review Shows Green Tea Catechins Work Synergistically with Endocrine Treatment for Breast Cancer

Yiannakopoulou EC. Interaction of green tea catechins with breast cancer endocrine treatment: a systematic review. *Pharmacology*. 2014;94(5-6):245-248.

The main flavonoids in green tea (*Camellia sinensis*, Theaceae) leaf are its catechins. Among the catechins, (–)-epigallocatechin-3-gallate (EGCG) represents about 59%, (–)-epigallocatechin (EGC) about 19%, (–)-epicatechin-3-gallate (ECG) about 13.6%, and (–)-epicatechin (EC) about 6.4%. Studies have suggested strong chemopreventive and possible chemotherapeutic effects of green tea polyphenols and EGCG against several cancers, including breast cancer. The author conducted a systematic review to synthesize the data on the possible interaction of green tea catechins with breast cancer endocrine treatment. Endocrine, or hormonal, therapies target estrogen receptor (ER)-positive and ER-negative breast cancer.

The author searched PubMed, Scopus, Google Scholar, and Science Citation Index (1966 through February 2013) for epidemiological, experimental, and clinical trials that investigated the interaction of green tea catechins with breast cancer endocrine treatment. After identifying 29 potentially relevant trials, the author selected eight trials for this review.

Investigating whether low concentrations of catechins with and without 4-hydroxytamoxifen (4-OHT) would result in significant cytotoxicity in ER-positive and ER-negative human breast cancer cells, Chisholm et al.[1] reported that only EGCG elicited cytotoxicity in MCF-7 cells (a breast cancer cell line with a high level of ER-alpha expression). In HS578T cells, EGCG, EGC, and ECG caused significant cytotoxicity; combining the catechins with 4-OHT did not increase cytotoxicity. In MDA-MB-231 cells, EGCG produced a greater cytotoxic effect than did 4-OHT and, when combined, EGCG and 4-OHT exhibited synergistic cytotoxicity.

Stuart et al.[2] concluded that combining EGCG and 4-OHT resulted in an earlier and enhanced apoptotic response (programmed cell death) in breast cancer cells.

Sartippour et al.[3] observed that green tea increased the inhibitory effect of tamoxifen on the proliferation of ER-positive human breast cancer cells and that the combination of green tea and tamoxifen was more potent than either treatment alone at increasing cell apoptosis. Sartippour et al. also demonstrated that mice treated with both green tea and tamoxifen had smaller xenograft tumor size and higher levels of apoptosis in tumor tissue, compared with either agent given alone.

Stuart et al.[4] demonstrated that a combined treatment of EGCG and raloxifene for seven days produced greater cytotoxicity against breast cancer cells than did either therapy alone. In another trial,[5] investigators demonstrated that combining raloxifene with green tea catechins decreased the phosphorylation of three key signaling proteins (mTOR, Akt, and EGFR) and induced the phosphorylation of stress-activated protein kinases, which led investigators to conclude that the mechanisms of synergistic interaction of green tea catechins with raloxifene were ER independent. They state that further trials are needed to investigate the combination of EGCG and raloxifene as a potential treatment for ER-negative breast cancer.

Sakata et al.[6] demonstrated that EGCG and tamoxifen exhibited dose-dependent antiproliferative effects on breast cancer cells and that the combination of EGCG and tamoxifen was more effective than either agent alone. Also investigating the growth-inhibitory effect of EGCG and tamoxifen alone and in combination on preneoplastic lesions in mice, Sakata et al. found the incidence of tumors decreased in the treated groups and that no tumors developed in the group treated with green tea water extract and tamoxifen.

Huang et al.[7] concluded that the combined treatment of EGCG and tamoxifen had a synergistic effect in inhibiting the growth of human breast cancer cells.

After studying the interaction of EGCG with tamoxifen in a xenograft model of ER-negative breast cancer for ten weeks, Scandlyn et al.[8] reported that tamoxifen alone was not effective at suppressing ER-negative tumor growth and that EGCG alone had a modest effect on tumor growth. However, when combined with EGCG, tamoxifen appears to suppress the growth of ER-negative breast cancer. Tumor volume decreased by 71% and tumor weight decreased by 80% in the group treated with tamoxifen (75 µg/kg) and EGCG (25 mg/kg).

This review suggests that green tea catechins interact synergistically with selective ER modulators (namely, tamoxifen and raloxifene) in the treatment of ER-positive and ER-negative breast cancers. The author points out that combining tamoxifen with green tea catechins would be appealing especially in ER-negative breast cancer cases, in which green tea catechins have been reported to reactivate ER-alpha expression, and in tamoxifen-resistant breast cancer cases, where green tea catechins have been reported to reverse the tamoxifen-resistant phenotype.

The author concludes that "the strategy of co-administration of green tea catechins with tamoxifen seems to be a rational approach in the chemoprevention, adjuvant and metastatic breast cancer treatment that needs further investigation."

*—Shari Henson*

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