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Interaction of Green Tea Catechins with Breast Cancer Endocrine Treatment: A Systematic Review

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Key Words

Green tea catechins · Breast cancer · EGCG · Tamoxifen · Raloxifene · Synergistic interaction

Abstract

Recent data have shown strong chemopreventive and possibly cancer chemotherapeutic effects of green tea polyphenols and EGCG against breast cancer. This systematic review aims to synthesize data on the possible interaction of green tea catechins with breast cancer endocrine treatment. Electronic databases were searched with the appropriate search terms. Experimental trials suggest a synergistic interaction of green tea catechins with tamoxifen or raloxifene in the treatment of estrogen receptor-positive and estrogen receptor-negative breast cancer through estrogen receptor-dependent and -independent mechanisms. No evidence of an interaction of green tea catechins with aromatase inhibitors or fulvestrant has been reported. As green tea catechins are natural compounds with a rather favorable safety profile, the strategy of co-administrating green tea catechins with tamoxifen seems to be a rational approach in chemoprevention, adjuvant and metastatic breast cancer treatment that needs further investigation.

Introduction

Catechins (flavan-3-oils) are the main flavonoids present in green tea. The 4 major catechins are (–)-epigallocatechin-3-gallate (EGCG), which represents approximately 59% of all catechins; (–)-epigallocatechin (EGC), corresponding to approximately 19%; (–)-epicatechin-3-gallate (ECG), standing for approximately 13.6%, and (–)-epicatechin (EC), which encompasses approximately 6.4% [1]. Recent data have shown strong chemopreventive and possibly cancer chemotherapeutic effects of green tea polyphenols and EGCG against cancers of the skin, lung, breast, colon, liver, stomach, and prostate [2–5]. Most data concern EGCG, the most abundant catechin in green tea. An appealing strategy would be the combination of SERMS (selective estrogen receptor modulators) with green tea catechins. Although tamoxifen is used in the treatment of estrogen receptor (ER)-positive breast cancer, it is known that tamoxifen elicits proapoptotic effects in ER-negative breast cancer through the modulation of cell signaling pathways in an ER-independent manner [6]. However, these effects have been mostly reported with high concentrations of tamoxifen. The combination of tamoxifen with green tea catechins could enhance its action in ER-negative breast cancer. In addition, such a combination could allow a dosage reduction of breast endocrine treatment in ER-positive breast cancer and in breast cancer chemoprophylaxis, leading to an

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amelioration of the safety profile. This systematic review aims to synthesize data on the possible interaction of green tea catechins with breast endocrine treatment.

Methods

PubMed, Scopus, Google Scholar, and Science Citation Index were searched using the search terms 'EGCG', 'green tea', 'catechins', 'tamoxifen', 'raloxifene', 'aromatase inhibitors', 'anastrazole', 'letrozole', and 'SERMS'. The search covered the period from 1966 up to and including February 2013. Epidemiological, experimental or clinical trials, which investigated the interaction of green tea catechins with breast cancer endocrine treatment, were included. Only full publications were considered. There was no language restriction. The reference lists of all identified trials were checked for more relevant articles. Double publications were identified. For articles published in a non-European language, the English version was included; while the most complete report was included for articles published in European languages.

Results

Initially, 29 potentially relevant trials were identified, and after reviewing their titles and abstracts, 8 experimental trials were included.

In vitro Studies

Chisholm et al. [7] investigated if low concentrations of catechins with and without 4-hydroxytamoxifen (4-OHT) would cause significant cytotoxicity in human breast cancer cells. MCF-7 (a breast carcinoma cell line showing a high level of ER-alpha expression), T47D, MDA-MB-231 and HS578T cells were incubated with EGCG, EGC or ECG (5–25 μM) individually and in combination with 4-OHT for 7 days. None of the catechins were cytotoxic to T47D cells. Only EGCG (20 μM) elicited cytotoxicity in MCF-7 cells. This combination treatment had no benefit for T47D and MCF-7 cells. All three catechins were significantly cytotoxic to HS578T cells at concentrations of 10 μM, while in this cell line, the combination with 4-OHT did not increase cytotoxicity. In MDA-MB-231 cells, EGCG (25 μM) produced a greater cytotoxic effect than 4-OHT (1 μM), and the combination of the two resulted in synergistic cytotoxicity [7].

Stuart et al. [8] investigated the role of apoptosis in the synergistic cytotoxicity elicited by 4-OHT (1 μM) and EGCG (25 μM) in MDA-MB-231 cells. They concluded that the combination of EGCG and 4-OHT results in an earlier and enhanced apoptotic response [8].

Sartippour et al. [9] observed that green tea increased the inhibitory effect of tamoxifen on the proliferation of the ER-positive MCF-7, ZR75 and T47D human breast cancer cells in vitro. In addition, this combination regimen was also more potent than either agent alone at increasing cell apoptosis [9].

Stuart et al. [10] demonstrated that a 7-day treatment with EGCG (25 μM) and raloxifene (1–5 μM) produced enhanced cytotoxicity toward MDA-MB-231 breast cancer cells compared to either drug alone. The earlier and enhanced induction of apoptosis was proposed as a potential mechanism for the synergistic effect, probably due to a reduced phosphorylation of the EGFR- and AKT-signaling proteins [10]. In another trial, the authors demonstrated that the combination of raloxifene with green tea catechins decreased the phosphorylation of 3 key signaling proteins (mTOR, Akt and EGFR) as well as induced the phosphorylation of SAPKs, JNK1/2 and P38. The above changes in protein phosphorylation were associated with a reduced nuclear localization of p63. Thus, the authors concluded that the mechanisms of synergistic interaction of green tea catechins with raloxifene were ER independent [11].

Sakata et al. [12] demonstrated that EGCG and tamoxifen exhibited dose-dependent antiproliferative effects on MCF-7 cells. The combination of EGCG with tamoxifen was more effective than either agent given alone [12].

Huang et al. [13] showed that a co-treatment with 5 μM EGCG and 200 nM tamoxifen had a synergistic effect in the inhibition of MCF-7 and AU565 cell growth, through the downregulation of the Skp2 protein, an S-phase kinase protein 2 (Skp2), component of the Skp1-cullin 1-F-box protein (SCF) ubiquitin ligase complex, which modulates the p27 proteolysis, a key regulator of G1-to-S phase progression [13].

In vivo Studies

Scandlyn et al. [14] investigated the interaction of EGCG with tamoxifen in a xenograft model of ER-negative breast cancer. Athymic nude female mice were implanted with MDA-MB-231 cells and treated with tamoxifen, EGCG, EGCG plus tamoxifen or vehicle (controls) for 10 weeks. The tumor volume in EGCG (25 mg/kg) plus tamoxifen (75 μg/kg) -treated mice decreased by 71% as compared with that of vehicle mice ($p < 0.05$), whereas the tumor weight decreased by 80% compared with controls ($p < 0.01$). Tamoxifen alone was not effective at suppressing ER-negative tumor growth, whereas EGCG had a modest effect on tumor growth. The authors suggested that the dominant mechanism for tumor suppression by the combination of green tea catechins with tamoxifen was the concomitant decrease in tumor protein expressions of mTOR and EGFR [14].

In animal experiments, Sartippour et al. [9] demonstrated that mice treated with both green tea and tamoxifen had the smallest MCF-7 xenograft tumor size and the highest levels of apoptosis in tumor tissue, as compared with either agent administered alone [9].

Sakata et al. [12] investigated the growth-inhibitory effect of EGCG and tamoxifen alone or in combination on preneoplastic lesions in C3H/OuJ mice. Animals were treated with green tea extract in drinking water (1%, 0.1%), a tamoxifen pellet (10 mg/animal, subcutaneously inoculated) or both agents in combination (1% green tea extract plus 10 mg tamoxifen). The tumor incidences were decreased in the treated groups. Even more importantly, in the group treated with green tea extract and tamoxifen, no tumors developed [12].

Discussion

Green tea has been found to block certain steps in carcinogenesis. Green tea inhibits the formation of PhIP (2-amino-1-methyl-6-phenylimidazo pyridine)-induced DNA adduct formation, which leads to a reduced tumorigenicity in animal chemoprevention studies. EGCG induces apoptosis of cancer cells through different pathways involving both the pro-oxidant and epigenetic modulation of apoptosis-related genes such as human telomerase reverse transcriptase [15]. Furthermore, green tea catechins have also been shown to reduce cell proliferation through the modulation of cell cycle progression [13, 16].

In addition, green tea catechins modulate multiple signaling pathways including the inhibition of nuclear factor-κB signaling pathway; the inhibition of MAPKs and activator protein 1; the inhibition of nitric oxide synthesis; the inhibition of epidermal growth factor-mediated signal transduction pathways via the suppression of binding of EGF (epidermal growth factor) to its receptor; the inhibition of IGF-1 (insulin-like growth factor-1)-mediated signaling pathways; the inhibition of cyclo-oxygenase-2 overexpression, and the inhibition of proteasome activity [17]. The upregulation of tumor suppressor genes by EGCG has been reported. Green tea may also inhibit HER-2/neu signaling in breast cancer cells. In addition, green tea catechins have been reported to modulate cell signaling pathways associated with angiogenesis, metastasis and invasion including the inhibition of vascular endothelial growth factor as well as the inhibition of matrix metalloproteinases [17]. However, the reported actions of green tea catechins are observed in high concentrations, which are difficult to be achieved in the clinical setting. This drawback could be overcome by designing green tea catechins with better bioavailability and/or by co-treatment combining breast cancer endocrine treatment with green tea catechins.

Indeed, the present review suggests that green tea catechins exhibit a synergistic interaction with SERMS in the treatment of ER-positive and ER-negative breast cancer cases. The co-administration of tamoxifen with green tea catechins would be an appealing strategy especially in the case of ER-negative breast cancer, where green tea catechins have been reported to re-activate ER. Indeed, in a very recently published study, Meeran et al. [18] have observed that the treatment of ER-alpha-negative breast cancer cells with green tea polyphenols led to the reactivation of ER-alpha expression [18].

The co-administration of green tea catechins with tamoxifen could also be useful in tamoxifen-resistant breast cancer cases, where green tea catechins have been reported to reverse the tamoxifen-resistant phenotype [19–21]. Furthermore, it has been shown that green tea polyphenols may inhibit the multidrug resistance P-glycoprotein activity, which is responsible for much of the resistance to chemotherapeutic drugs. Since orally administered tamoxifen is a substrate for the CYP3A-mediated metabolism and P-glycoprotein-mediated efflux in the intestine and liver, the presence of EGCG might inhibit this metabolic pathway [22].

The synergistic interaction between EGCG and tamoxifen has also been observed in the lung cancer cell line PC-9. Yet, EGCG has also been reported to interact synergistically with sulindac in the prevention of colon carcinogenesis in rats [23]. Most experimental data suggest a pharmacodynamic synergistic interaction between green tea catechins and SERMS via ER-dependent and -independent mechanisms [24]. However, a pharmacokinetic interaction between green tea catechins and tamoxifen has also been reported. Sakata et al. [12] have proposed a pharmacokinetic interaction between green tea catechins and 4-OHT. The authors suggest that, since 4-OHT and EGCG are both extensively glucuronidated, 4-OHT might inhibit the conjugation of EGCG and thus increase its cytotoxicity [12]. Supporting this hypothesis, in a pharmacokinetic analysis, Shin and Choi [25] reported that EGCG significantly increased the $AUC_{0-\infty}$ and C_{max} of oral tamoxifen in rats.

No evidence of an interaction between green tea catechins and aromatase inhibitors has been reported. Experimental data indicate that green tea catechins exert no aromatase-inhibitory activity [26]. However, Way et al. [27] have reported that black tea theaflavins inhibit aromatase activity and attenuate tamoxifen resistance in HER2/neu-transfected human breast cancer cells through tyrosine kinase suppression. In addition, modest aromatase inhibition by green tea has been reported [27].

In conclusion, experimental data indicate a synergistic interaction between green tea catechins and SERMS in the treatment of ER-positive and -negative breast cancer cases. As green tea catechins are natural compounds with a rather favorable safety profile, 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.

Disclosure Statement

The author declares no conflicts of interest.

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