Mini-review

**The interactions of anticancer agents with tea catechins: current evidence from preclinical studies**

Weihu Shang¹, Jinping Qiao¹,*, Weidong Lu², Mei Han¹,*

¹Key Laboratory of Radiopharmaceuticals, Ministry of Education, College of Chemistry, Beijing Normal University, Beijing 100875, China
²Leonard P. Zakim Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA

*Correspondence:
Mei Han Ph.D. PI
Professor of Medicinal Chemistry, Key Lab of Radiopharmaceutical Chemistry, Ministry of Education, College of Chemistry, Beijing Normal University
No.19 XinJieKouWai Avenue, HaiDian District, Beijing 100875, P.R.China
Tel: +86-10-62207786
Fax: +86-10-62206031
Email:hanmei@bnu.edu.cn

Running title: Interactions of anticancer agents with tea catechins
Abstract

Tea catechins exhibit a broad range of pharmacological activities that impart beneficial effects on human health. Epigallocatechin-3-gallate (EGCG), a primary component of tea catechins, has been widely associated with cancer prevention and treatment. In addition, tea catechins in combination with anticancer drugs are being evaluated as a new cancer treatment strategy. However, the interactions of anticancer drugs with tea catechins are largely unknown. Accumulated data indicate significant interactions between anticancer drugs and tea catechins, such as synergistic tumor inhibition or antagonist activity. Therefore, it is critical to understand comprehensively the effects of tea catechins on anticancer drugs. Focusing on evidence from preclinical studies, this paper will review the interactions between anticancer drugs and tea catechins, including pharmacodynamics and pharmacokinetics effects. We hope that by detailing the interactions between anticancer drugs and tea catechins, more attention will be directed to this important therapeutic combination in the future.

Keywords:
Drug interaction, Tea catechins, EGCG, Pharmacodynamics, Pharmacokinetics
Introduction

Tea is an aromatic beverage made from the leaves of the plant *Camellia sinesis* Theaceae. Tea has been used for thousands of years in Asia, and it has transitioned from a medicinal herb to a consumed beverage. Now, tea is popular throughout the world [1], as it is the most widely consumed beverage, being second only to water. During the last 30 years, tea production increased by 148% from 1838 thousand tons in 1981 to 4563 thousand tons in 2011 (Fig. 1). The majority of the tea-producing countries are located in Asia and Africa. China, India, Sri Lanka, Kenya and Indonesia are the major producers, account for 77% of the world’s production and 80% of global exports. Depending on the manufacturing process, teas can be categorized into three major groups, green tea (non-fermented), black tea (fermented), and oolong tea (semi-fermented) [1, 2].

Green tea constitutes approximately 20% of the world’s tea production. In addition to being a popular beverage, the pharmacological effects of green tea have been studied extensively, resulting in a significant increase in the number of scientific publications in the last 30 years (Fig. 2). For example, numerous studies have shown that green tea possesses anti-cancer [3], anti-oxidative [4], anti-viral [5], anti-bacterial [6], cancer prevention [7, 8], hypolipidemic [9], anti-inflammatory [10] and hypotensive activities [11]. These remarkable health benefits are inseparable from a large number of bioactive compounds found in tea production. When green tea is brewed in hot or boiling water, it is comprised of 1/3 water-extractable materials, including polyphenols, caffeine, theobromine, theophylline and phenolic acids [1, 2, 12]. As shown in Fig. 2, more papers have been published on tea catechins than tea caffeine. Polyphenols (generally known as catechins) are the major constituents of green tea, accounting for approximately 1/3 of the compounds found in green tea [1, 2]. The major catechins in green tea are (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG) and (-)-epigallocatechin (EGC). (Fig. 3)

A total of 146 clinical trials involving green tea are listed in ClinicalTrials.gov
As shown in Fig. 4, most of these studies are in cancer (31% of therapeutics analyzed). The cancer prevention and treatment activities resulting from tea consumption have been widely studied and discussed in several review articles [7, 13-16]. In 1993, Yang et al. reported the first comprehensive review of the cancer-preventive activities of tea [17]. In recent decades, numerous laboratory studies in different animal models suggest that tea (mainly green tea) and tea constituents inhibit carcinogenesis [18]. Research in cell lines has also demonstrated that tea catechins can affect a range of signaling and metabolic pathways, subsequently resulting in cancer cell growth inhibition and apoptosis as well as inhibition of invasion, angiogenesis and metastasis [19]. In addition, epidemiological studies suggest that increased intake of green tea offers protective effects against the development of cancer at several human organ sites, particularly the upper gastrointestinal tract, lung and hepatocellular cancers [7, 14].

Currently, an increasing number of cancer patients consume tea concomitantly with chemotherapeutics agents. However, tea may affect the pharmacokinetics and pharmacodynamics of chemotherapeutic agents, causing tea-drug interactions. Unfortunately, clinicians and consumers do not always have information regarding the interactions between tea constituents and chemotherapeutics agents. This article highlights data on the interactions of tea with chemotherapeutics agents by focusing on pharmacodynamics and pharmacokinetics. An additional goal is to make recommendations to encourage additional clinical trials investigating tea and anticancer agents.

**The synergistic effects of green tea with anticancer drugs in xenograft mouse models**

Numerous laboratory studies have demonstrated that green tea or catechins display synergistic tumor growth inhibition with chemotherapeutics agents [20-24]. For example, in various animal tumor models, tea catechins (especially EGCG) inhibit tumor formation in mice and enhance the growth inhibition of xenografted tumors.
The animal tumor models involve metastasis to different organ sites, including the lung, breast, prostate, liver and stomach [22]. In addition, previous cellular studies indicate that tea catechins, especially the most abundant and biologically active EGCG, enhance cancer cell growth suppression and inhibit angiogenesis [25]. Furthermore, the synergistic effects observed in the animal models and cancer cell lines involved multiple molecular mechanisms, such as the induction of growth arrest, DNA damage and the inhibition of receptor-dependent signaling pathways [23]. Numerous anticancer drugs were analyzed in studies of synergy with tea catechins. The following is a review of studies utilizing some of the anticancer drugs.

**Paclitaxel**

Paclitaxel is a microtubule-targeted drug commonly used for cancer treatment. However, resistance to paclitaxel is frequently encountered in the clinic [26]. Using a murine model of breast carcinoma, Luo et al. reported that the combination of paclitaxel and the green tea polyphenol EGCG significantly inhibits tumor growth, whereas the single agent of paclitaxel or EGCG was minimal [27]. They established a transplantation model by inoculating Balb/c mice with the mouse mammary gland cancer cell line 4T1. The tumor-bearing mice were treated with or without EGCG (30 mg/kg) by intraperitoneal injection (i.p.) daily and paclitaxel (10 mg/kg, i.p.) every other day. The tumor growth was monitored for 24 days. The results indicate significantly reduced tumor volumes in the mice treated with the combination compared with the control group. In addition, the mice treated with EGCG and paclitaxel displayed no significant changes in weight, suggesting no overt systemic toxicity. Moreover, systematic examination of the major organs, including liver, spleen, heart and kidneys, revealed no histological changes indicative of drug toxicity [27].

The mechanism of synergistic inhibition of tumor growth by EGCE and paclitaxel involves modulation of chemo-resistance related proteins. It has been reported that EGCG binds to glucose-regulated protein 78 (GRP78), which is over-expressed in chemo-resistant cancer cells [28]. After co-treatment with EGCG and paclitaxel, the
expression of GRP78 in tumor tissues were reduced compared with the paclitaxel-treated tumors, indicating that EGCG can overcome paclitaxel-induced GRP78 expression [27, 29]. Thus, EGCG could be used as a sensitizer of paclitaxel cytotoxicity.

Stearns and Wang examined the efficacy of EGCG in combination with taxane (paclitaxel and docetaxel) in a xenograft mouse model of human prostate cancer [30]. Single-cell suspensions of the human prostate cancer cell line PC-3ML (1 × 10^6 cells) from less than 10 passages were i.p. injected in 5- to 6-week-old CB17 SCID mice. After approximately 1 week, the drug in a volume of 0.50 ml/mouse was i.p. injected weekly using a 28-gauge needle for 9 weeks. Compared with the control group, the tumor volumes significantly decreased in EGCG and/or paclitaxel treated groups after 1–9 weeks. EGCG (200 μM, 228 mg/kg) plus paclitaxel (20 mg/kg) synergistically inhibited human prostate PC-3ML tumor cell growth. Similarly, no synergistic or additive toxicity characterized by increased body weight was observed. More importantly, the combination therapy inhibited bone metastases after intravenous injection of the PC-3ML cells through the tail vein [30].

Mechanistically, it was hypothesized that EGCG synergizes with paclitaxel by increasing the expression of apoptotic genes to induce tumor cell apoptosis. In this study, freshly established PC-3ML tumors (i.e., 2 weeks after i.p. inoculation of mice) typically express minimal or no p53, p73, and p21 protein. However, after mice were treated with daily i.p. injections of EGCG or paclitaxel, the expression of p53 and p73 increased more than one- and three-fold, respectively. In comparison, EGCG plus paclitaxel treatment for 2 and 4 days caused the levels of p53, p73, and p21 to increase by more than 5- to 10-fold, respectively. These data suggest that the combination therapy significantly increased the expression of apoptotic genes [30]. In sum, EGCG used in combination with paclitaxel could offer a curative therapeutic approach for the eradication of primary tumors and metastatic prostate cancer. The mechanism(s) governing the synergistic activities of EGCG and paclitaxel require further investigation.
**Docetaxel**

Docetaxel is a well-established anti-mitotic chemotherapy drug that induces a mitotic block. It displays a broad range of anticancer effects in a variety of cancers, including breast, ovarian, colorectal, prostate, lung, liver, renal, gastric, head and neck, and melanoma [31, 32]. Wu and co-workers reported that docetaxel in combination with EGCG inhibits angiogenesis and tumor growth in nude mice with gastric cancer xenografts [33]. To establish the xenograft model, the human gastric cancer cell line BGC-823 (2 × 10^6) were suspended in 0.2 mL of PBS and injected into the right flank of BALB/c nude mice. After each tumor achieved an average size of 100 mm^3, the mice were divided into five groups: control (0.2 mL physiological saline daily, i.p.); maximum tolerated dose (MTD; 15 mg/kg docetaxel once every 2 weeks, i.p.); low-dose metronomic (LDM; 0.5 mg/kg docetaxel thrice weekly, i.p.); EGCG (1.5 mg/day EGCG, i.p.) and the combined therapy (LDM docetaxel and 1.5 mg/day EGCG, i.p.). The tumor volumes of the MTD and LDM groups were 1234 ± 125 and 775 ± 98 mm^3, respectively, 42 days post implantation. In contrast, the tumors of more than half of the mice in the control group were greater than 2000 mm^3 in volume. The volume of the tumors in the combination group was significantly reduced compared with the other groups, suggesting that the combination therapy of LDM docetaxel and EGCG remarkably delays the tumor growth [33]. However, the exact mechanisms governing the interaction between LDM docetaxel and EGCG remain unclear and require further study.

**Erlotinib**

Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has demonstrated strong antitumor and chemopreventive effects through blockade EGFR-related signal transduction pathways in a variety of cancer types [34]. Zhang and co-workers reported the synergistic inhibition of head and neck tumor growth by green tea EGCG and EGFR-TKI [35]. In this study, the nude mice (athymic nu/nu) were randomly divided into 4 treatment groups: vehicle control (1% Tween 80), EGCG, erlotinib or the combination of EGCG (125 mg/kg) and erlotinib
(50 mg/kg). Each group received treatment by oral gavage for 7 days prior to the inoculation of $2 \times 10^6$ Tu212 cells by s.c. injection into the right flank. The animals were continuously administered the agents 5 days a week after tumor cell injection. Single agent EGCG or erlotinib moderately inhibited tumor growth, but the results were not statistically significant compared with the control (p=0.14 and p=0.07, respectively). In contrast, the combination of erlotinib and EGCG suppressed tumor growth compared with the control (p=0.006), single agent EGCG (p=0.02) and single agent erlotinib treatment groups (p=0.01). In addition, the combination group did not achieve a tumor size of 500 mm$^3$, whereas the control, erlotinib alone, and EGCG alone groups achieved this size at 19.5, 27, and 25 days, respectively. Furthermore, the combined treatment yielded significantly reduced mean pEGFR levels compared with the control group based on analysis of the proteins extracted from the xenograft tumor tissues. These results suggest that EGCG combined with erlotinib exhibit synergistic antitumor activity with no significant side effects [35].

Erlotinib, a specific EGFR antagonist, has shown clinical efficacy in the clinic, but tumors often develop resistance [36]. Milligan et al. investigated the efficacy of EGCG and erlotinib in xenograft model using SCID mice implanted with the human non-small cell lung carcinoma (NSCLC) cell line H460, which has acquired resistance to erlotinib [37]. Male SCID/bg mice were s.c. injected with $2 \times 10^6$ H460 cells in 100 μL PBS. The mice were treated with 2% Tween-80 (control), erlotinib (10 mg/kg), EGCG (15 mg/kg), or erlotinib and EGCG via gavage 3 days after implantation. Next, the mice were placed on a 5-days-on, 2-days-off dosing schedule. The tumors were surgically removed and weighed 22 day after implantation. Treatment with erlotinib or EGCG alone did not show any statistically significant effects compared with the control group. However, the combination of EGCG and erlotinib significantly reduced tumor size (P=0.03) and weight (P=0.011). The promising combinatorial results suggest that this strategy may be clinically effective for controlling lung cancer progression. The authors are conducting a clinical trial to investigate the effects of erlotinib in combination with polyphenon E (Polyphenon Pharma), which contains EGCG and the three additional green tea catechins, in NSCLC patients [37].
**Celecoxib**

Celecoxib is a selective inhibitor of cyclooxygenase-2 (COX-2), which has been implicated in the pathogenesis of many cancer types [38]. Huang and co-workers discovered a new treatment strategy for urothelial carcinoma [39]. They found that celecoxib induces cell cycle G1 arrest, endoplasmic reticulum stress, and subsequent apoptosis in human UC cells. Co-treatment with celecoxib and EGCG reduces the expression of GRP78 and enhances celecoxib-induced apoptosis [39].

Adhami et al. found that celecoxib suppresses prostate carcinogenesis in transgenic mouse model of prostate adenocarcinoma [40]. They also investigated the combined inhibitory effects of green tea polyphenols and celecoxib on the growth of a human prostate tumor in a xenograft mouse model. To establish human tumor xenografts, the right and left flanks of mice were s.c. implanted with $1 \times 10^6$ CWR22Rv1 androgen-sensitive prostate carcinoma cells. Mice received one of the following treatments: a combination of 0.1% green tea polyphenol (w/v, ad libitum) in the drinking water and celecoxib (5 mg/kg, daily i.p. injections, 5 days per week), 0.1% green tea polyphenol alone, celecoxib alone, or drinking water as a control. The combination group achieved a tumor volume of 1300 mm$^3$ at 48 days. In contrast, the control, green tea polyphenol alone, and celecoxib alone treatment groups achieved this size at 28, 36, and 40 days, respectively. These results suggest an increased efficacy of celecoxib in combination with tea polyphenols in the growth inhibition of human prostate cancer cells *in vivo*. Compared with the results of the single-agent treatment, the synergistic and/or mechanisms may involve reduced expression of the prostate-specific antigen and insulin-like growth factor-1 as well as reduced circulating serum levels of the insulin-like growth factor binding protein-3 [40, 41]. Rationally designed human clinical trials are also needed to confirm the synergistic effects.

**Doxorubicin**

Doxorubicin (DOX), an anthracycline antibiotic, is a drug used for cancer treatment
based on its ability to intercalate DNA [42]. It is commonly used in the treatment of a wide range of cancers, including hematological malignancies, carcinomas, and soft tissue sarcomas. Liang et al. reported that green tea catechins could augment the antitumor activity of DOX in a mouse model of chemoresistant liver cancer [43]. The nude mice (BALB/c nu/nu) were subcutaneously injected on the right axilla with 0.2 ml suspension of $5 \times 10^7$ BEL-7404/DOX human hepatocellular carcinoma (HCC) cells, which are resistant to DOX. After tumor establishment, the mice were treated with PBS only (control), DOX alone (2 mg/kg, q4d, i.p.; DOX), EGCG alone (80 mg/kg, qd, ig; EGCG), DOX combined with low-dose EGCG (40 mg/kg, qd, ig; DE low group), DOX combined with medium-dose EGCG (80 mg/kg, qd, ig; DE mid group), or DOX combined with high-dose EGCG (160 mg/kg, qd, ig; DE high group). The average tumor volumes on day 33 were $5.0 \pm 1.4$, $4.0 \pm 0.9$, and $3.7 \pm 0.9 \text{ cm}^3$ for the DE Low, DE Mid, and DE High groups, respectively. In contrast, the tumor volumes in the control, DOX alone, and EGCG alone groups were $9.4 \pm 1.2$, $7.0 \pm 1.0$, and $9.8 \pm 1.3$, respectively. The rate of tumor inhibition calculated from the tumor weights of the three combination groups (DE Low, DE Mid, and DE High) were 56.7%, 62.2%, and 65.1%, respectively. These rates were significantly increased compared with the DOX alone group (P<0.01). Thus, the administration of DOX with EGCG significantly inhibits hepatocellular carcinoma growth in a xenograft mouse model compared with either agent alone at the same dose [43].

The mice were sacrificed 33 days after drug administration, and the tumors were resected to measure the intracellular accumulation of DOX, assess P-gp levels, and detect MDR1 mRNA expression [43]. The results showed that administration of DOX in combination with EGCG markedly enhanced intracellular DOX accumulation. Moreover, EGCG increased topo II expression and significantly reduced the MDR1 and HIF-1·mRNA expression in the tumor xenografts [43]. The study further demonstrated that the mechanism of action for the combination of DOX and EGCG might occur directly or indirectly through the reversal of multidrug resistance and the enhancement of intracellular DOX accumulation. This action could involve the suppression of MDR1 expression or inhibition of P-gp function.
The combination of EGCG and DOX not only inhibited tumor growth in a xenograft mouse model but also suppressed metastatic tumor growth. Stearns and co-workers found that EGCG (228 mg/kg) in combination with low levels of DOX (0.14 mg/kg) blocked the tumor growth of PC-3ML cells injected intraperitoneally (i.e., in CB17 severe combined immunodeficient mice) and significantly increased mouse survival rates [44]. In addition, EGCG (57 mg/kg) combined with DOX (0.07 mg/kg) eradicated established tumors (i.e., in nonobese diabetic–severe combined immunodeficient mice) derived from CD44hi tumor-initiating cells isolated from PCa-20a cells. The results suggest that localized delivery of high EGCG doses combined with low levels of DOX might have significant clinical application in the treatment of metastatic prostate and/or the eradication of primary tumors derived from tumor initiating cells [44].

Cardiac injury is the most serious adverse complication of the oxidative stress-generating DOX [45]. On the other hand, EGCG has been reported to possess a cardioprotective role in diseases associated with oxidative stress [46]. Therefore, Li et al. investigated whether EGCG protected against DOX-induced toxicity in cardiomyocytes [47]. The results suggested that EGCG protected cardiomyocytes from DOX-induced oxidative stress by attenuating reactive oxygen species (ROS) production and apoptosis as well as increasing the activity and expression of endogenous antioxidant enzymes (such as manganese superoxide dismutase, catalase, and glutathione peroxidase) [47].

**Cisplatin**

Cisplatin, the first member of a class of platinum-containing anticancer drugs, can bind to and crosslink DNA, triggering tumor cell apoptosis. It is used to treat a variety of cancers, including sarcomas, carcinomas such as small cell lung cancer and ovarian cancer, lymphomas, and germ cell tumors [48]. Lee and co-workers recently demonstrated that EGCG inhibits the self-renewal capacity of head and neck cancer stem cell by decreasing the transcriptional level of Notch, resulting in the inhibition of Notch signaling [49]. Furthermore, they investigated the combination EGCG and
cisplatin in a xenograft model. Head and neck squamous carcinoma (HNSC) cancer stem cells (CSCs) were treated \textit{in vitro} with either cisplatin (10 μM) alone, cisplatin plus EGCG (5 μM) or control DMSO. After 48 hours, $5 \times 10^3$ cells were subcutaneously injected into the flank of 8-week-old female BALB/c nude mice. After three months, the combination treatment only generated minimally visible tumors in the nude mice compared with the large tumors observed upon treatment with cisplatin alone. TUNEL staining revealed an increase in the number of apoptotic cells in the combination group, suggesting that EGCG combined with cisplatin inhibits tumor formation and induces apoptosis in tumor cells [49].

These data from pharmacodynamics studies demonstrate tea catechins have a synergistic effect when co-administration with anticancer drugs in xenograft animal models. Oral consumption of green tea in combination with anticancer drug treatment might enhance the antitumor activity without toxic side effects. This promising new therapeutic combination may improve the quality of life in patients receiving cancer chemotherapy and warrants further clinical exploration. In addition, other studies demonstrate the induction of synergistic/additive effects when tea catechins are administered in combination with anticancer drugs, such as gemcitabine [50], vorinostat [51, 52], SU-5416 [53], tamoxifen [54], daunorubicin [55], ATO [56], and etoposide [28]. However, whether these drugs have synergistic effects with tea catechins in animal models has yet to be determined.

**Pharmacokinetic interactions**

Based on two characteristics of anticancer drugs, their inherent toxicity and narrow therapeutic index, administration of these agents with green tea may cause minor changes in the drug’s pharmacokinetics, potentially significantly altering the drug’s efficacy or toxicity [57]. The catechins found in green tea may affect the expression or activities of drug-metabolizing enzymes and drug transporters [1]. During a chemotherapeutic regimen, the pharmacokinetics and bioavailability of a chemotherapy may be altered in cancer patients who drink tea. Therefore, studies on
the pharmacokinetic interactions of tea catechins with anticancer drugs cannot be ignored.

**5-Fluorouracil (5-FU)**

5-Fu is an antimetabolite drug that is extensively used for the treatment of cancers, including aerodigestive tract, breast and head and neck cancers. The cytotoxicity of 5-FU is exerted through its inhibition of thymidylate synthase and the incorporation of its metabolites into RNA and DNA, resulting in lethal DNA damage [58]. In our previous study, we reported that green tea extracts increase the bioavailability of 5-FU in rats [59]. After orally receiving 50 mg/kg green tea extract daily for 28 days, the rats were injected 5-FU (48 mg/kg, i.p.). The plasma concentrations of 5-FU were determined by HPLC. The maximum concentration ($C_{\text{max}}$) and AUC of 5-FU increased by approximately 151% and 425%, respectively in the pre-treated green tea extract group administered the moderate dose level (equivalent to <6 cups daily in human) compared with control group. Mechanistically, it was inferred that green tea catechins decrease the activity of dihydropyrimidine dehydrogenase (DPD), which is the initial and rate-limiting enzyme in the catabolism of 5-FU. The modulation of DPD could result in decreased 5-FU catabolism, leading to increased plasma concentrations [59].

**Irinotecan**

Irinotecan (CPT-11), a derivative of camptothecin, is an anticancer drug. Irinotecan binds to the topoisomerase I-DNA complex and prevents the re-ligation of the breaks, thereby resulting in the formation of irreversible double strand breaks and ultimately cell death [60]. Lin et al. reported an herb–drug interaction study that examined the role of EGCG in the modulation of P-gp for the disposition of CPT-11. These studies investigated whether EGCG alters the pharmacokinetics of CPT-11 in biliary elimination [61]. Rats in the control group were given the same amount of CPT-11 (10 mg/kg, i.v.) via the femoral vein. The rats in the EGCG treated group were administered EGCG (20 mg/kg) via the femoral vein, followed by CPT-11 (10 mg/kg,
i.v.) after 10 min. The plasma and bile concentrations of CPT-11 were determined by HPLC. The plasma AUC of CPT-11 increased 57.7%, while the bile AUC for CPT-11 decreased 15.8% in EGCG co-administered group compared with control group. These results suggest that the bile efflux transport system of CPT-11 may be markedly reduced upon treatment with EGCG, a P-gp inhibitor. Moreover, the half-life of CPT-11 could be significantly reduced in hepatobiliary excretion and thereby substantially prolonged in the plasma. Therefore, warnings regarding the pharmacokinetic interaction of CPT-11 and EGCG should be provided to patients, especially those who consume green tea [61].

Tamoxifen

Tamoxifen and its active metabolite hydroxytamoxifen are antagonists of the estrogen receptor in breast tissue. It is the standard of care endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre-menopausal women [62]. Shin and Choi investigated the effects of EGCG on the oral bioavailability and pharmacokinetics of tamoxifen and 4-hydroxytamoxifen in rats [63]. The presence of EGCG significantly altered the pharmacokinetics of orally administered tamoxifen. A single dose of tamoxifen (2 mg/kg, i.p. and 10 mg/kg, o.p.) was administered with or without EGCG (0.5, 3 and 10 mg/kg) to rats. Co-administration of EGCG and tamoxifen increased the AUC and Cmax of tamoxifen 48.4–77.0% and 57.1–89.7%, (P<0.05 for 3 mg/kg of EGCG, P<0.01 for 10 mg/kg of EGCG), respectively, compared with the control group (only administered tamoxifen). In addition, the absolute bioavailability of tamoxifen in the presence of EGCG (3 and 10 mg/kg) was 48.9–78.1%, which is increased compared with 23.7% bioavailability in the control group (P<0.05 for 3 mg/kg of EGCG, P<0.01 for 10 mg/kg of EGCG). On the other hand, EGCG (10 mg/kg) significantly increased the AUC of 4-hydroxytamoxifen, the main tamoxifen metabolite. These results were associated with EGCG-mediated inhibition of P-gp and CYP3A, which decreased the first-pass metabolism in the intestine and liver. The increase in the oral bioavailability of tamoxifen in the presence of EGCG could be applied to the treatment of tamoxifen-resistant breast
carcinoma to down-regulate P-gp and breast cancer resistant protein (BCRP) [63].

**Bortezomib**

On the other hand, tea catechins may have the potential to negate the therapeutic efficacy of a chemotherapy. Bortezomib (BZM) is a proteasome inhibitor clinically used for multiple myeloma [64, 65]. Golden *et al.* investigated whether the combination of these compounds would enhance antitumor efficacy in multiple myeloma and glioblastoma cell lines *in vivo* [66]. Unexpectedly, they discovered that various green tea constituents, in particular EGCG and other polyphenols with 1,2-benzenediol moieties, effectively weakened the tumor cell death induced by BZM in cell lines and an animal model. Interestingly, the antagonistic function of EGCG was evident only with boronic acid–based proteasome inhibitors (such as BZM, MG-262, PS-IX), but not with several non–boronic acid proteasome inhibitors (such as MG-132, PS-I, nelfinavir) [66]. This finding can be attributed to the fact that EGCG directly binds with boronic acid–based proteasome inhibitors and blocks their proteasome inhibitory function. As a consequence, this class of proteasome inhibitors could not induce endoplasmic reticulum stress, caspase-7 activation, or tumor cell death. Therefore, green tea polyphenols might have the potential to negate the therapeutic efficacy of BZM. The consumption of green tea products might be contraindicated during BZM cancer therapy [66].

**Sunitinib**

Another example of a chemotherapy that negatively interacts with EGCG is sunitinib, a novel, oral multi-targeted tyrosine kinase inhibitor for patients with metastatic renal cell carcinoma (mRCC) and advanced gastrointestinal stromal tumor [67]. Ge *et al.* initially found that drinking tea could interfere with symptom control in an mRCC patient receiving sunitinib [68]. Therefore, they hypothesized that green tea or its components might be antagonistic to sunitinib. Subsequently, a study on the interactions of EGCG and sunitinib was performed *in vitro* and *in vivo*. The EGCG and the sunitinib solutions were both clear. However, the solutions became turbid
immediately upon mixing and formed an orange precipitate. In addition, the AUC and C\text{max} of plasma sunitinib were markedly reduced after co-administration of EGCG and sunitinib to rats, implying that EGCG reduced the bioavailability of sunitinib. A precipitate formed, and sticky, semisolid contents were found in the stomachs of the mice [68].

**Conclusions**

Natural compounds have been combined with anticancer drugs to enhance the efficacy of cancer therapies and prevent the acquisition of resistance to the therapies [24, 57, 69]. In this article, we outline the pharmacodynamic and pharmacokinetic interactions between tea catechins and anticancer drugs. Examples are provided to demonstrate the broad range of effects that tea catechins have on anticancer drugs via a variety of mechanisms, such as modulations in the levels of drug-metabolizing enzymes, alterations in the activities of drug transporters and direct binding to drugs. However, clinical studies in this area are still limited, and future clinical observations on the interaction between tea catechins and anticancer drugs are needed.

**Conflict of interest**

The authors declare that they have no competing interests.

**Acknowledgements**

This study is supported by the National Key Technology R&D Program (2008BAI49B04), the China National Science Foundation (81173139) and the Major Research Plan of NSFC (21233003).

**References**


Lancet, 2006, 368(9544), 1329-1338.


Figures:

Figure 1. Trends of tea production all over the world (1981-2011).

Figure 2. Trends in the number of papers published with topic: green tea, tea catechin or tea caffeine (ISI web of knowledge).
Figure 3. The chemical structures of (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), paclitaxel, docetaxel, erlotinib, celecoxib, doxorubicin, cisplatin, 5-fluorouracil, irinotecan, tamoxifen, bortezomib, sunitinib.
Figure 4. Indications of green tea studied in clinical trials.