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Effects of Different Tea Products on the Growth of Cancer Cells

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Abstract

Tea preparations are popular for its anti-oxidant and anti-cancer effects. We want to understand how different tea products could differently affect the growth of cancer cells with heterogeneity. Here we evaluated 4 popular tea products on the growth of multiple cancer cells with different genetic makeovers, including 3 green teas and a black tea, namely Bigelow Tea - Green Tea with Mint (Bigelow), Kusmi Tea - Chinese Green Tea (Kusmi), Onko Tea - Base Tea Blend (Onko), and Lipton Tea - Lipton Black Tea (Lipton). Panels of breast cancer cells, melanoma cells, liver cancer cells, and bladder cancer cells were tested. The results showed that 1) the effects of tea on cell proliferation was concentration dependent. At lower concentrations (< 100 μg/mL), all the 4 tea extracts increased cell viability at 24h treatment. The increase of cell viability diminished, and inhibitory effects was observed as the treatment duration was longer. At a higher concentration range (200 - 800 μg/mL), all 4 tea products inhibited the cancer cells, typically with Onko tea showing the best inhibitory effect and Lipton tea the least. 2) The inhibitory effect was cell line dependent. The melanoma cells A375 cells showed the best sensitivity to the Onko Tea treatment, which harbors homologous BRAF mutation. The bladder cancer cell line 5637 showed good sensitivity to the tea products, whereas the liver cancer cell line HepG2 was the most resistant of all the tested cells. The results showed that complicated reasons contribute to the inhibitory effects of tea products towards cancer cells, which depend on the product itself, treatment duration and concentration, as well as the genetic characteristics of the cancers cells. These complicated reasons may partially explain the conflicting results from cancer clinical trials utilizing tea products.

Keywords: *Tea Products; Cancer*

Introduction

Made from the dried leaves of the plant *Camellia sinensis,* tea is the 2nd most consumed beverage in the world only next to water. Originating in China and South East Asia, tea plants are now cultivated in more than 30 countries with an annual production of ~3.8 million tons of teas [1]. Consuming of tea beverages is a cultural tradition in many countries, and tea is the major source of dietary polyphenols for many populations [1].

Different teas have different compositions of bio-active polyphenols. Factors influence the tea components include types and ages of tea leaves, climate, horticultural practices, and production methods. The characteristic tea polyphenols are known as catechins, which include (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin [2,3]. The major types of tea consumed are black tea (78% of world tea consumption) and green tea (20% of world tea consumption) [1]. The pro-

duction methods of green tea preserve the catechins, with EGCG being the most abundant catechin, and presenting in smaller amount are catechin gallate, gallocatechin, gallocatechin gallate, epigallocatechin digallates, epicatechin digallate, methylepicatechin and methyl EGC, and flavonols such as quercetin, kaempferol, myricetin and their glycosides [1]. In the production processes of black tea, the fermentation process causes enzyme-catalysed oxidation and polymerization of tea catechins, and resulted in the formation of oligomers and polymers such as theaflavins and thearubigins [1].

Tea polyphenols have been extensively studied for their health benefit, including anti-cancer effects. Both green tea and black tea have been tested for their cancer-preventing activity in various animal models of tumorigenesis [4], including skin, breast, lung, oral cavity, esophagus, stomach, liver, pancreas, bladder, small intestine, colon, and prostate [5-7]. Many of these studies showed that administration of tea preparations in drinking water inhibited incidence of tumors in mice after carcinogen treatment [4]. In most studies, inhibition in the number of tumors per mouse was also observed [4]. In an NNK-induced lung tumorigenesis model, black tea preparation significantly inhibited tumor cell proliferation and suppressed the progression of adenoma to carcinoma [8]. Oral treatment of green tea or EGCG inhibited tumor invasion and metastasis in transplanted and spontaneous metastasis models [9,10]. Green or black tea was also shown to significantly inhibit the spontaneous development of lung adenoma and rhabdomyosarcoma in A/J mice [11]. The tea-treated mice were found leaner than the control group, i.e. they had lower body weight and body fat [11]. At the same time, numerous mechanisms of action have been proposed, including actions due to their anti-oxidant and pro-oxidant activities, induction of apoptosis and inhibition of proliferation, and epithelial-to-mesenchymal transition (EMT) in cancer cells, due to decreased levels or activities of many key kinases, growth factors, receptors, proteinases and other enzymes including AP-1, NF-κB, PI3K, p-Akt, p-Jun, p-Erk, Mcl1 and Bcl-X, β-catenin, Myc, cyclin-D1, COX-2 along with many other proteins involved in cell proliferation and apoptosis [1,4,12-24]. Reduction in the angiogenic factor VEFG, and the metastatic factors MMP2 and MMP9 (metalloproteinases) were also found [19,20].

Although most of the cell and animal studies showed positive results [4], some animal studies failed to demonstrate inhibition of tumorigenesis by tea preparations [4]. For example, Witschi., *et al*. reported that green tea did not reduce lung tumor multiplicity in NNK-induced or cigarette smoke-induced lung tumorigenesis model [25]. In a high-fat diet rat model, tea and caffeine in drinking water significantly increased colon tumor incidence after carcinogen treatment [26]. Moreover, epidemiologic studies in humans have inconsistent results and are not conclusive for the anti-cancer activity of tea products [1,4,27,28]. Pilot intervention studies in humans have shown promising results, usually with large doses of green tea polyphenol preparations [29-32], but they are also not conclusive. Various confounding factors are proposed to influence the epidemiologic studies, including quality and quantity of the tea consumed, varied cancer aetiology in different populations, and heterogeneity in populations [1]. In the interventional studies, bioavailability is thought an issue (< 10% as represented by EGCG) [1,33]. Plasma EGCG concentrations detected after oral administrations were often below 0.5 μg/mL [33,34]. The poor bioavailability influences the concentration and time the targeted tissues are exposed to the tea preparations. Neumours efforts have been made to improve the bioavailability. Recently developed combination oral doses brought EGCG plasma concentrations higher than 1.0 μg/mL [33,35]. It was reported in a rat model that EGCG nanoparticles raised EGCG levels over 20 μg/mL without toxicity [36]. Tissues concentrations can be higher than the plasma levels [36,37]. In this study, we aimed to examine different tea products on the growth of cancer cells with heterogeneity, to provide information in help with better understanding of the factors contributing to the activities of tea preparations.

Materials and Methods

Tea preparations

Four tea products were used including 3 green teas and a black tea. The green tea Onko Tea - Base Tea Blend (Onko) was provided by Natural Source Inc. (New York, NY). The Bigelow Tea - Green Tea with Mint (Bigelow), Kusmi Tea - Chinese Green Tea (Kusmi), and the black tea Lipton Tea - Lipton Black Tea (Lipton) were purchased from general grocery stores. One gram of each tea product was steeped

in 40 mL of 80°C water for 3 minutes, and then filtered with regular coffee filter paper. The filtered solution was put in 50 mL tube for lyophilization (Lanconobo FreeZone 2.5, Kansas City, MO) for 8 - 10 days to freeze dry.

Cell culture

The estrogen receptor positive (ER+) breast cancer cell lines MCF-7 was donated by Dr. Nikki Cheng at the University of Kansas Medical Center. The triple-negative breast cancer (TNBC, ER-PR- and no excess HER) cell line MDA-MB-231 was donated by Dr. Fariba Behbod at the University of Kansas Medical Center. Melanoma cell lines A-375 (homozygous mutant B-Raf, CDKN2A homozygous), UACC-257 (heterozygous BRAF, wildtype p53, CDKN2A deletion), SK-MEL-2 (wildtype B-Raf and homozygous mutant N-Ras, heterozygous p53) and SK-MEL-5 (heterozygous mutant B-Raf and wildtype N-Ras and p53, CDKN2A deletion) were obtained from American Type Culture Collection (ATCC). The liver cancer cell line HepG2 was donated by Dr. Lisa Zhang at the University of Kansas Medical Center, and the bladder cancer cell line 5637 was donated by Ben Woolbright at the University of Kansas Medical Center. All cell lines were sub-cultured and maintain in our lab. Cells were cultured in media recommended by ATCC (the American Type Culture Collection, Manassas, VA), supplemented with 10% fetal bovine serum (FBS) (Sigma-Aldrich, St. Louis, MO), 100 units/ml penicillin/streptomycin (Corning, Manassas, VA) at 37°C in a humidified 5% CO_2 atmosphere. Ten µg human insulin (Sigma-Aldrich, St. Louis, MO) was added to MCF-7 culture media.

Cell viability assay - MTT assay

Detection of cell viability used the MTT assay. Cells were plated into 96 well plates at a starting density of 5000 cells/well. After 14 - 16 hours incubation, the culture medium was removed and replaced with 100 uL of fresh culture medium containing different concentrations of tea extractions. Cells were incubated for up to 72 hours. At 24, 48 and 72h, 20 µl of 5 mg/ml MTT (EMD Millipore Corp, USA) in PBS was added into each well and then the plates were incubated for 3.5 - 4 hours. After careful removing of the supernatant, 150 uL/well DMSO was added to dissolve the formazan crystals. The purple color absorbance was measured at 570 nm on a micro-plate reader (BioTek Synergy 2, Winooski, VT). Cell viability was calculated as % Cell viability = OD(treated)/OD(untreated) x 100%.

Statistical analysis

Comparison between multiple groups used one-way ANOVA analysis with a post-hoc Turkey's test with a familywise error rate of 0.05. Adjusted $p < 0.05$ was considered statistically significant. Comparison between two groups used T-tests.

Results

Enhancing of cell viability by tea preparations at low concentrations

Because the bioavailability of oral tea polyphenols (evaluation based on EGCG) are considered poor [33], we first exposed the cells to a low range of concentrations of the 4 tea preparations. A bladder cancer cell line 5637, a hepatocellular carcinoma cell line HepG2, an ER+ human breast cancer cell line MCF-7 and a triple-negative breast cancer (TNBC) cell line MDA-MB-231 were treated with the 4 tea preparations at the concentration range of 3.125 to 100 µg/mL. At this concentration range, most of the treatments did not inhibited the cancer cells up to 72 hours. No inhibition in cell viability was seen with all the 4 tea preparations with concentrations lower than 50 µg/mL (Figure 1). The only inhibitory effect was in 5637 cells with the green teas Kusmi and Onko at 100 µg/mL and with treatment duration longer than 48 hours (Figure 1).

In contrast, under most of these conditions, increase in cell viability was observed (Figure 1). For MCF-7 cells, increase in cell viability was detected at 24h with the green teas Bigelow and Kusmi, and the effects lasted for 48 hours. The black tea Lipton increased cell viability only after 48 hours. Onko tea did not show either inhibitory or enhancing effects. For the TNBC cells MDA-MB-231, there was an increase in cell viability with all 4 tea preparations at 24 hours, and the effect of Bigelow tea lasted up to 72 hours. For HepG2 cells, all 4 tea preparations increased cell viability at 24 hours, and the effects diminish as treatment prolonged, but no inhibitory effect was detected

up to 72 hours. For 5637 cells, increased cell viability was also observed with Bigelow tea and Onko tea. Overall, Lipton tea showed less activity in enhancing cell growth, and Onko tea showed the best potential in inhibiting these cancer cells growth.

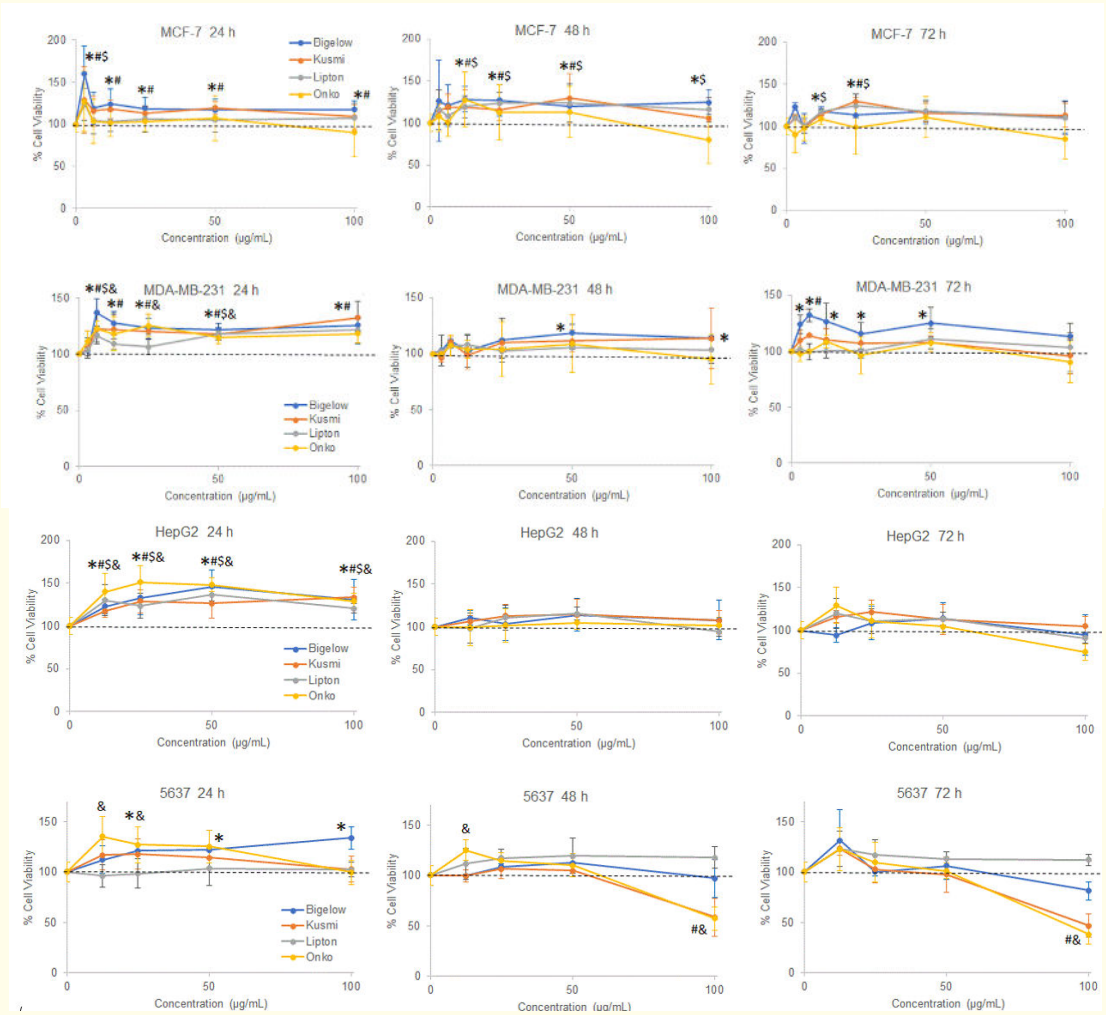

Figure 1: *Viability of multiple cancer cells under treatment with tea preparations at low concentrations. MCF-7, estrogen receptor positive (ER+) human breast cancer cells; MDA-MB-231, highly metastatic triple-negative human breast cancer cells (TNBC); HepG2: Human Hepatocellular Carcinoma Cells; 5637, human bladder cancer cells. Cells were treated with each of the 4 tea preparations at 0 - 100 µg/mL. *p < 0.05 for Bigelow tea, # p < 0.05 for Kusmi tea, $ p < 0.05 for Lipton tea, and & p < 0.05 for Onko tea, compared to untreated controls.*

We further tested Onko tea and Lipton tea with 4 melanoma cells harboring different key mutations (Table 1). The increase in cell growth was again evident in UACC257 cells at concentrations lower than 100 µg/mL with both tea preparations at 24h treatment (Figure 2). The increase in cell viability vanished as treatment duration went longer. The tea preparations at these concentrations showed minimal effects on the other 3 melanoma cell lines. No inhibition in cell growth was detected.

Gene name / Cell name	BRAF	N-RAS	P53	CDKN2A
A-375	Homozygous mutation			Homozygous mutation
UACC-257	Heterozygous		Wildtype	Deletion
SK-MEL-2	Wildtype	Homozygous mutation	Heterozygous mutation	Deletion
SK-MEL-5	Heterozygous mutation	Wildtype	Wildtype	Deletion

Table 1: *Mutation status of melanoma cells tested.*
Information derived from https://web.expasy.org/cellosaurus [47]. Access date: July 20th, 2019.

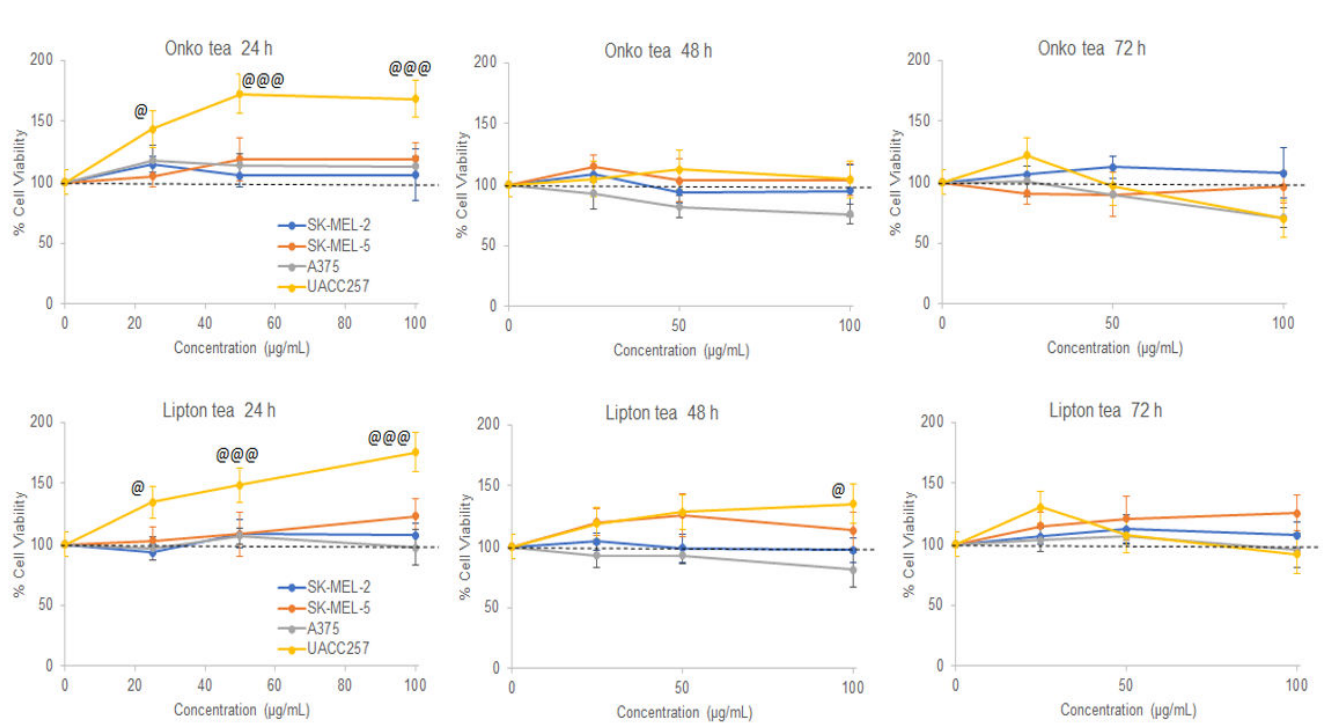

Figure 2: *Viability of melanoma cells under treatment with Onko tea or Lipton tea at low concentrations. The genetic characteristics of the 4 melanoma cell lines are listed in table 1. Cells were treated with Onko tea or Lipton tea preparations at 0 - 100 µg/mL. @, $p < 0.05$ and @@@, $p < 0.001$ for UACC257 cells, compared to untreated controls.*

Inhibition of cell viability by tea preparations at high concentrations

Since a potential of inhibition began to be observed at the 100 µg/mL, a higher range of concentrations (100 to 800 µg/mL) was evaluated. At this range, all 4 tea extracts showed inhibitory activity against the cancer cells lines tested (Figure 3). The IC_{50} values were listed in table 2 and plotted in figure 4. The bladder cancer cells 5637 was the most sensitive with IC_{50} values ranging from 85 - 200 µg/mL for 24 to 72 hours treatment, and the liver cancer cells HepG2 was the most resistant to the tea treatments. There seems to be no difference in sensitivity between the ER+ breast cancer cells MCF-7 and the TNBC cells MDA-MB-231. Among the tea preparations, Onko tea showed

the best inhibitory effects, whereas the black tea Lipton was the least active. The inhibitory effect was time dependent up to 72 hours for Bigelow and Kusmi teas across the treated cell lines. For Onko tea and Lipton tea the time dependency was observed in HepG2 and 5637 cells up to 72 hours, but in the breast cancer cell lines the best inhibitory effects were achieved at 48 hours.

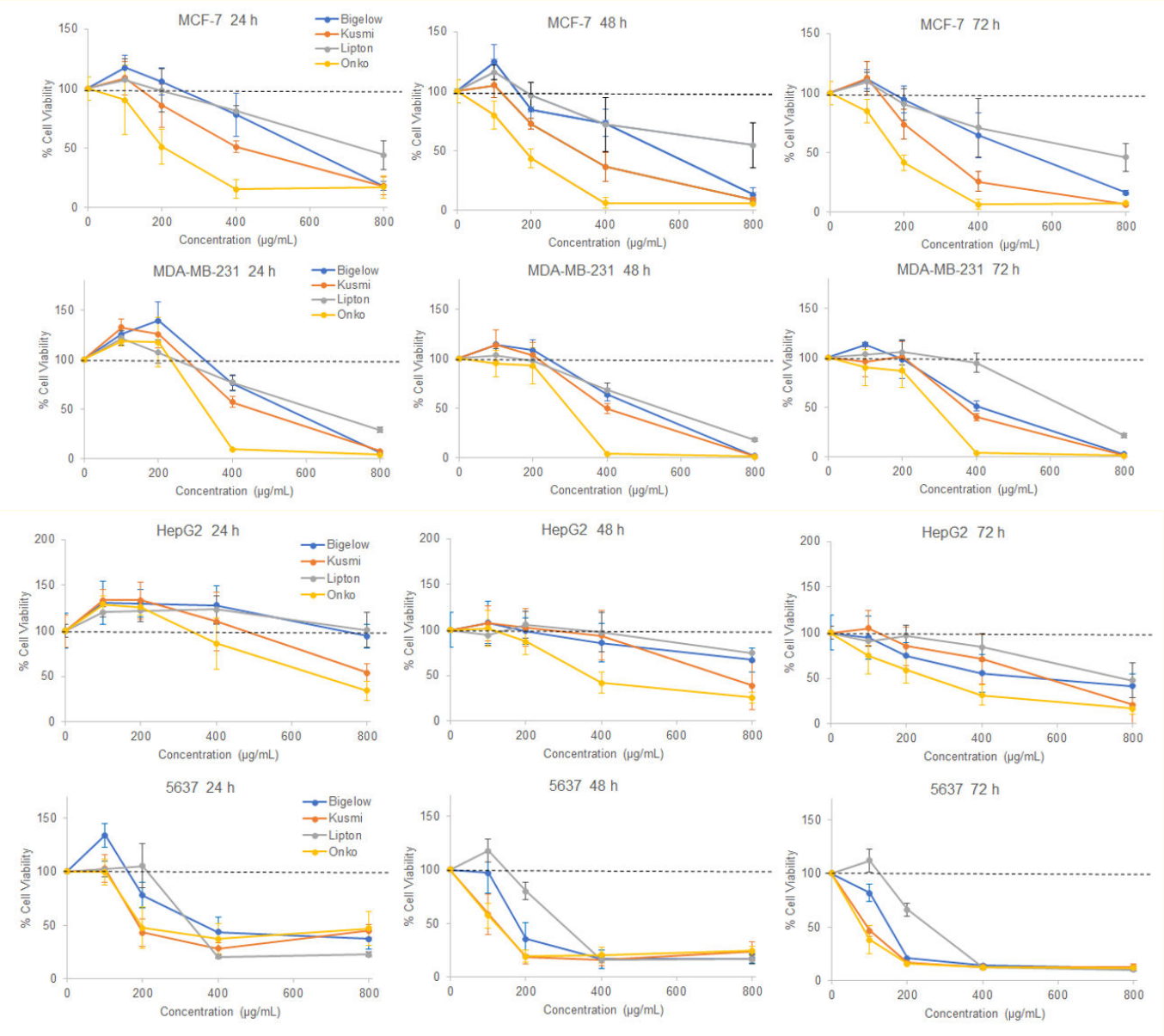

Figure 3: *Viability of multiple cancer cells under treatment with tea preparations at high concentrations. Cells were treated with each of the 4 tea preparations at 100 - 800 µg/mL.*

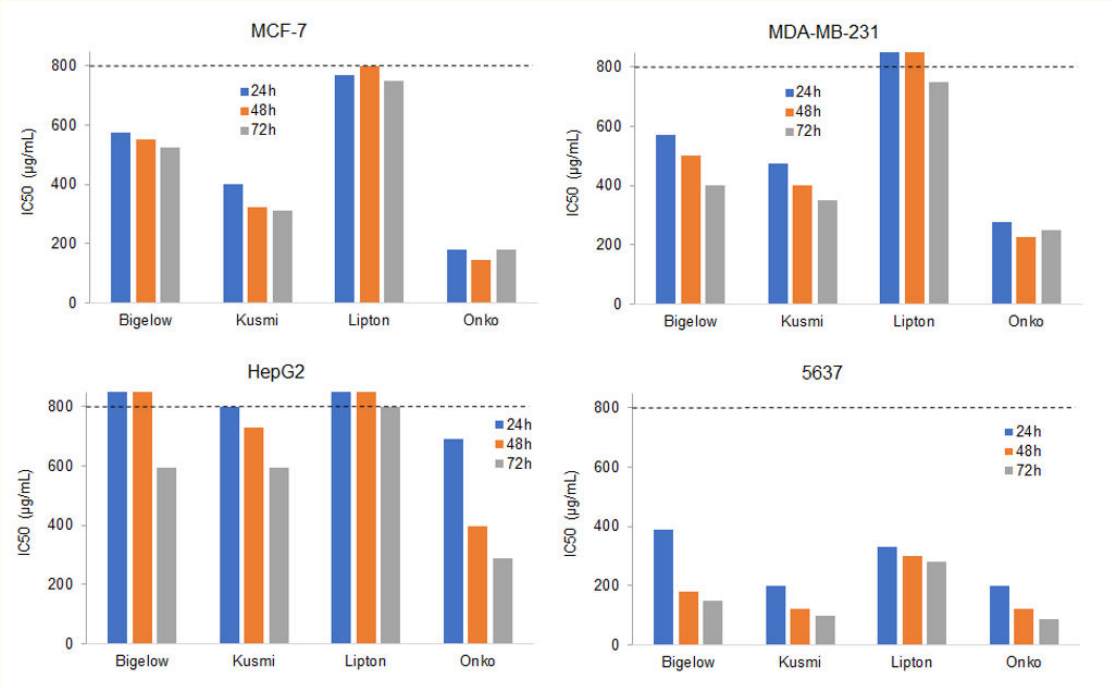

Figure 4: *IC_{50} values of the tea preparations against multiple cancer cells. The IC50 values (μg/mL) were derived from the growth curve as shown in Fig. 3, defined as the concentration required to inhibit 50% of the cell viability.*

	MCF-7			MDA-MB-231			HepG2			5637		
	24h	**48h**	**72h**	**24h**	**48h**	**72h**	**24h**	**48h**	**72h**	**24h**	**48h**	**72h**
Bigelow	575	550	525	570	500	400	> 800	> 800	595	390	180	150
Kusmi	400	325	310	475	400	350	800	730	595	200	120	100
Lipton	770	800	750	> 800	> 800	750	> 800	> 800	800	330	300	280
Onko	180	145	180	275	225	250	690	395	290	200	120	85

Table 2: *IC_{50} values (μg/mL) of the tea preparations against multiple cancer cells.*

Onko tea and Lipton tea were further tested in the melanoma cells. Overall, the Onko tea preparation reduced cell viability of all 4 tested melanoma cell lines (Figure 5) with IC_{50}s ranging from 150 to 370 μg/mL for 24 to 72 hours treatment (Table 3 and Figure 6). The inhibition increased as the treatment time increased from 24 up to 72 hours (Figure 5). Lipton tea preparation had much less activity in inhibiting cell viability under the same conditions. Among the melanoma cell lines, A375 cells which harbor homozygous BRAF mutation showed the best sensitivity to both the Onko tea and Lipton tea treatment, and the inhibitory effect was achieved as early as 24 hours (Figure 5 and 6). UACC-257 which harbors heterozygous BRAF mutation required at least 48 hours of treatment to exhibit inhibitory effects, and once treatment was longer than 48 hours UACC-275 cells exhibited similar sensitivity as A375 cells. SK-MEL-5 cells also have heterozygous BRAF mutation but have wildtype N-RAS and p53. These cells had higher IC_{50} values than UACC-275 cells for both teas at 48 and 72 hours treatment (Figure 6 and Table 3). SK-MEL-2 cells, which have wildtype BRAF, were the most resistant to Lipton tea treatment (Figure 5 and 6).

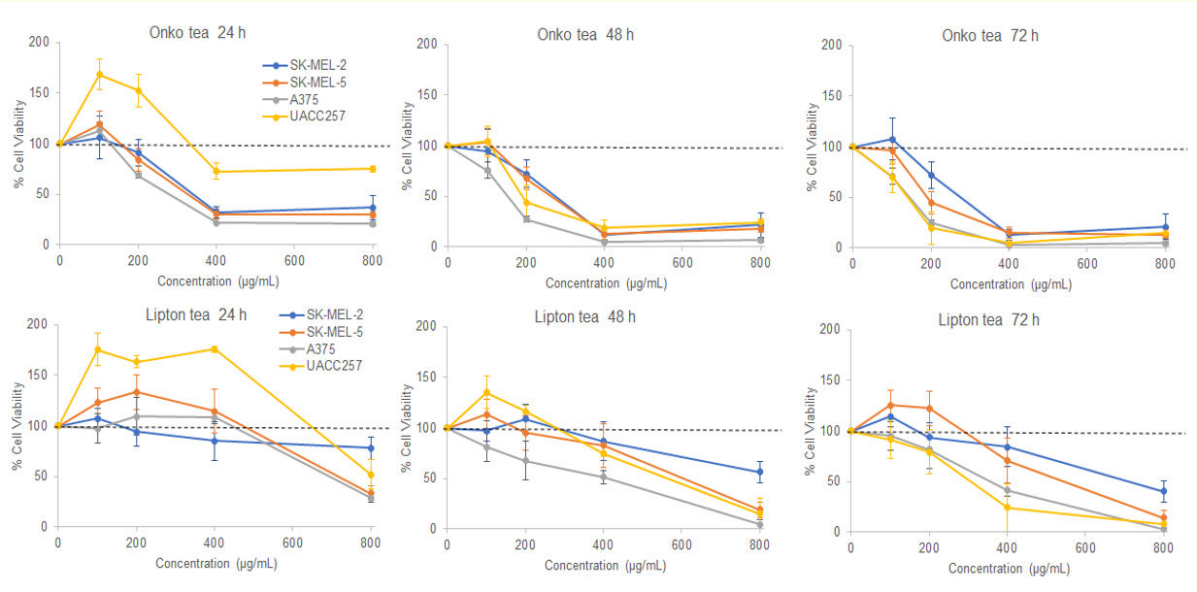

Figure 5: *Viability of melanoma cells under treatment with Onko tea or Lipton tea at high concentrations. The genetic characteristics of the 4 melanoma cell lines are listed in table 1. Cells were treated with Onko tea or Lipton tea preparations at 100 - 800 µg/mL.*

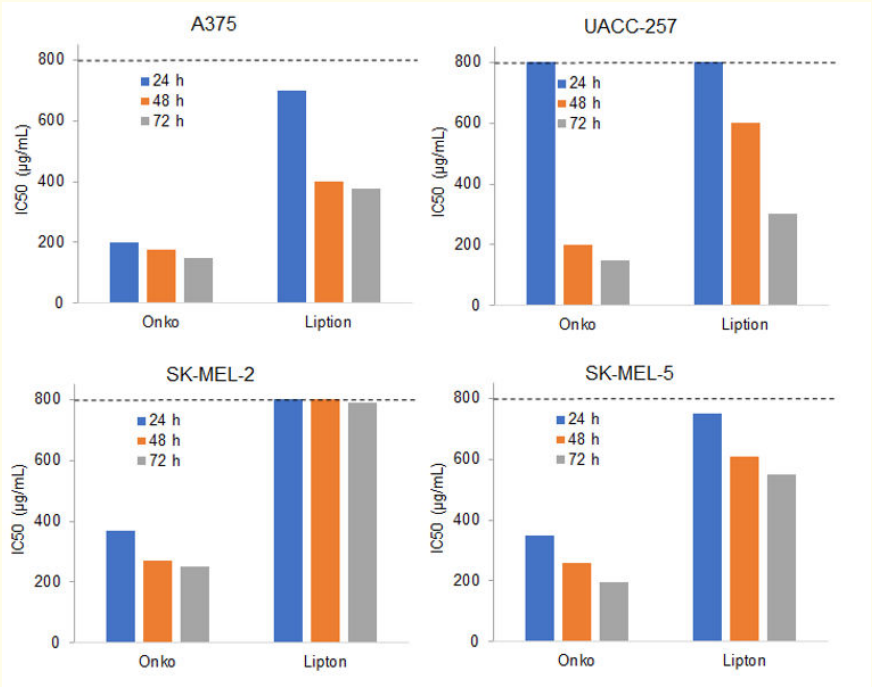

Figure 6: *IC_{50} values of the Onko tea and Lipton tea preparations against melanoma cells. The IC50 values (µg/mL) were derived from the growth curve as shown in figure 5, defined as the concentration required to inhibit 50% of the cell viability.*

	SK-MEL-2			SK-MEL-5			A375			UACC257		
	24h	48h	72h	24h	48h	72h	24h	48h	72h	24h	48h	72h
Onko	370	270	250	350	260	195	200	175	150	800	200	150
Lipton	800	800	790	750	610	550	700	400	375	800	600	300

***Table 3**: IC_{50} values (μg/mL) of Onko tea and Lipton tea against melanoma cells.*

Discussion

Tea products and tea polyphenols have been extensively studies for their health benefits, and one of the highlights is the anti-cancer activities [1]. The anti-cancer effects are well documented in numerous cellular and animal studies. However, neither human epidemiologic nor interventional studies have exhibited consistent positive results. The underlying reasons are complicated, and may include the type and quality of the tea, amount of consumption/administration, bioavailability of active components, as well as the types and genetic background of the cancer cells [1,4,27]. Our data here showed that indeed the effects on cancer cells are dependent on the tea preparation. Overall, of the teas tested, the 3 green teas had better inhibitory effects against the cancer cells while the activities varied, and the tested black tea (Lipton) seemed to be less active under the same conditions.

The effects of tea products on cancer cells were concentration dependent. Different concentrations can have opposite effects on cell growth. At lower concentrations of < 100 μg/mL, all the 4 tea preparations increased cell viability at 24h treatment, with green teas Bigelow and Onko showed greater effects than the black tea Lipton. The increase in cell viability diminished as the treatment duration was longer. At 72h, inhibition in cell viability was detected with the green tea Onko. At a higher concentration range of 200 to 800 μg/mL, all 4 tea products showed inhibitory effects on the cancer cell lines, typically with one of the green tea Onko tea showing the best inhibitory effect and the black tea Lipton the least. Of note, it has been reported that most oral ingestion of tea would not increase plasma concentrations of EGCG (the major active compound) more than 0.5 μg/mL, with some exception when tea or tea polyphenols was consumed with other food components [33,35,38-40]. Although tissue exposure could be higher, these low concentrations may contribute to the inconsistency of anti-cancer effects in animal and human anti-cancer studies. As in a study with rats, ingestion of tea in drinking water significantly increased colon tumor incidence after carcinogen treatment [26]. In the studies with negative results, as well as many animal studies with positive anti-cancer results, the concentrations at the targeted tissue sites were not know. Low concentrations of tea or its active components may even stimulate cancer cell growth, especially at a shorter exposure time.

Our data also showed that all tested teas had activities inhibiting cancer cell viability at the concentration range of several hundred microgram per milliliter. Whether these concentrations can be clinically relevant is not known. At least it is possible to reach high concentrations locally. For example, recently developed nanoparticle techniques can greatly improve the bioavailability of tea polyphenols [36] and can target cancer cells with cell specificity [41,42]. Local administration can also achieve high levels locally, such as topical administration for skin cancers [43-45], or accumulation in urines [34] which could possibly result in exposure of cells in the urinary tract including bladder. Intravenous administrations of EGCG have also been investigated in cancer treatment studies [46]. These methods could bring the concentrations high enough for anti-cancer activities.

Genetic makeups of cancer cells can also influence its responsiveness to tea treatment. A study aimed to detect gene signature that can predict efficacy of green tea in lung cancer tumorigenesis reported a 17-gene expression profile specific to green tea exposure [14]. Our data here showed no difference in ER+ and triple-negative breast cancer cells in responding to tea treatment. However, melanoma cells harboring BRAF mutations were more sensitive to the tea treatment. BRAF mutation is one of the most common mutations in malignant melanoma. Whether the BRAF mutations contribute to the cells' responses to tea treatment is worth further investigation.

Conclusion

Taken together, complicated reasons contribute to the inhibitory effects of tea products towards cancer cells. The active components of tea preparations may vary due to the material of the tea, as well as the processing methods. Besides that, the influence of the teas on cancer cells was dependent on concentrations and duration of exposure. It is important to understand the relevant clinical concentrations and time durations that are needed to exhibit an anti-cancer effect. On the other hand, genetic makeups of the cells also influence their sensitivity to tea products. The general idea of using tea products for anti-cancer effects should be examined in detail, but not simplified.

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Conflict of Interest

The authors declare no conflict of interest in this study.

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