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Evaluation of the Anti-Proliferative Effects of a Green Tea and *Capsicum* Powder Extract in Cancer Cell Lines

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Abstract

In recent years the use of natural supplements in order to prevent, treat or delay recurrence of cancer or reduce chemotherapy toxicity has attracted much attention. One such supplement is Capsol-T which consists of de-caffeinated green tea and chili pepper extracts. The aim of the study was the evaluation of Capsol-T effect on the proliferation of various cancer cell lines representing different cancer types. Cell lines that were used in the study were: DU145, LNCap, MCF7, HCT116 and MOR. The effect of various concentrations and incubation times of Capsol-T on cell viability was determined using the MTT method. The results do not show a common anti-proliferative pattern in all cancer cells. In some cell lines and certain concentrations cell growth was significantly decreased at 24 hr which became more evident at 48 hr. The role of *Capsicum* powder in cancer is unclear since both cancer cell proliferation and growth arrest have been demonstrated. Green tea on the other hand was found to decrease certain drugs' bioavailability. Our results suggest that an anti-proliferative effect in certain types of cancer should not be generalized to other types as well. Different concentrations also affect the net result often having opposite effects. Overall, caution should be taken when using natural supplements for their anti-cancer effects.

Keywords

Proliferation, Cancer, Green Tea, *Capsicum* Powder

1. Introduction

During the past years, a new tendency is on the rise for the use of natural supplements against various diseases. Very often it has been the case that natural

products were used for the prevention and treatment of cancer or the alleviation of the detrimental effects of chemotherapy. One such natural supplement is a green tea concentrate and *Capsicum* powder extract known as Capsol-T.

Capsol-T is a dietary supplement consisting of de-caffeinated green tea and chili pepper (*Capsicum anuum*) extracts. One capsule of Capsol-T is thought to be the equivalent of 16 cups of tea without the liquid or the caffeine [1]. The same study demonstrated that Capsol-T can decrease human cervical carcinoma and mouse mammary cancer cell proliferation.

Extracts from *Capsicum* genus consist mainly of capsaicin although there are at least ten other capsaicinoid variants present [2]. Capsaicin is a neuropeptide releasing agent selective for primary sensory peripheral neurons. It belongs to the vanilloid family and is an agonist of TRPV1 (vanilloid receptor subtype 1) receptor [3]. TRPV1 is a trans-membrane receptor-ion channel complex that when activated it initiates depolarization due to the influx of calcium and sodium ions resulting in action potentials which send impulses to the brain and spinal cord. These impulses result in capsaicin effects of burning sensation. As it is also known to inhibit substance P, the neurotransmitter of pain, from the sensory nerve terminals, is used for the treatment/management of various peripheral painful states, such as rheumatoid arthritis, neuralgia, post-mastectomy pain syndrome and diabetic neuropathy [4] [5]. Recently, capsaicin has been evaluated for anti-carcinogenic properties. Capsaicin effects on prostate cancer using the transgenic adenocarcinoma of the mouse prostate (TRAMP) model was found to be chemopreventive [6], whereas it was also found to decrease prostate cancer cell proliferation and cell cycle progression through the inactivation of androgen receptor [7]. It was also found to modulate extracellular matrix components in an experimentally induced lung cancer model, suggesting it could also have an anti-tumor effect in lung cancer as well [8]. It was also shown to suppress the growth of leukemic cells via cell cycle arrest and apoptosis [9]. On the other hand, capsaicin was also found to be a DNA hypermethylating agent in A549 cells and is found to exhibit both anti- and pro-inflammatory effects [10]. Capsaicin is rapidly metabolized, producing three major metabolites, 16-hydroxycapsaicin, 17-hydroxycapsaicin, and 16, 17-hydroxycapsaicin, whereas vanillin is a minor metabolite.

Tea contains polyphenols, including catechins and flavonoids, however green tea contains higher quantities of catechins in comparison with other types [11]. Among the major catechins in green tea epigallocatechin-3-gallate (EGCG) is the most abundant comprising approximately 70% of the total catechin constituent [12]. It has been demonstrated that EGCG has various biologic effects such as anti-oxidant, free radical inhibition [13], anti-inflammatory [14] and anticancer. In respect to the latter, it has been shown that EGCG inhibits tumorigenesis [15] and angiogenesis [16] as well as tumor invasion and metastasis [17]. However, EGCG can also decrease the effects of drugs at some extent which limits its clinical application [18] and has a very poor bioavailability.

The aim of the study was the evaluation of Capsol-T effect on the proliferation

of various cancer cell lines representing different cancer types.

2. Materials and Methods

2.1. Cell Cultures

Cell lines that were used in the study were: DU145, a hormone insensitive prostate cancer cell line; LNCap, a hormone sensitive prostate cancer cell line; MCF7, a breast adenocarcinoma cancer cell line; HCT116, a colon cancer cell line and MOR, a lung adenocarcinoma cancer cell line. DU145 was cultured in ATCC formulated Eagle's Minimum Essential Medium (30-2003, ATCC) supplemented with 10% FBS (F9665, Sigma), LNCap was cultured in RPMI 1640 (R0883, Sigma) supplemented with 2mM Glutamine (G7513, Sigma), 1 mM sodium pyruvate (S8636, Sigma) and 10% FBS, MCF7 was cultured in RPMI 1640 supplemented with 2mM Glutamine, 1% Non-essential amino acids (M7145, Sigma) and 10% FBS, HCT116 and MOR were cultured in RPMI 1640 supplemented with 2 mM Glutamine and 10% FBS. All cells were grown until 80% - 90% confluency in T25 cell culture flasks (0030710126, Eppendorf) at 5% CO_2, 37˚C before evaluation of proliferation.

2.2. Determination of Cell Proliferation

All cells were detached using trypsin/EDTA 0.25% (T4049, Sigma) and seeded in 96 well plates (07-6096, Biologix) at 18,000 cells per well. Cells were left overnight for attachment and then treated with various concentrations of Capsol-T (7 ug/ml, 7×10^{-1} ug/ml, 7×10^{-2} ug/ml, 7×10^{-3} ug/ml, 7×10^{-4} ug/ml in DMSO) for 24 and 48 hours. After the incubation period, cell proliferation was determined using the MTT assay. Briefly, cells were incubated with 20 ul MTT (5 mg/ml; M2128, Sigma) for 3 hours at 37˚C, 5% CO_2. After incubation, supernatant was carefully removed, formazan crystals were dissolved in 100 ul DMSO (445103, Carlo Erbo Reagents) per well and absorbance was measured at 570 nm and 630 nm for noise subtraction. (uQuant; MQX200, BIOTEK).

2.3. Statistical Analysis

Every concentration was tested nine times and the average absorbance was calculated. Subsequently, the sample measurements were corrected for the measurement of the blank. For the appropriate experiments, data are presented as Mean Value ± SEM. Tests for significant differences between groups were performed using a two-tailed student' t-test. A minimal value of $p = 0.05$ was chosen as the level of significance.

3. Results

The effect of Capsol-T in DU145 cell proliferation after 24 hr and 48 hr can be seen in **Figure 1** and **Figure 2** respectively. Capsol-T increased DU145 proliferation in high concentrations at 24 hr, however in 48 hr cell proliferation at low concentrations dropped significantly.

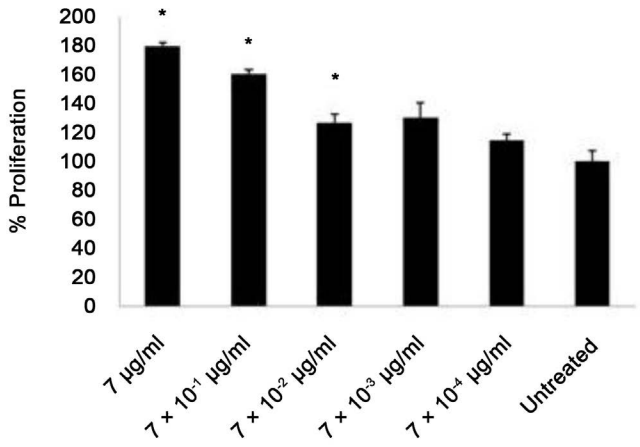

Figure 1. The effect of 24 hr incubation of Capsol-T in DU145 cell proliferation. 7 ug/ml vs Untreated $p < 0.001$; 7×10^{-1} ug/ml vs Untreated $p < 0.001$; 7×10^{-2} ug/ml vs Untreated $p = 0.015$.

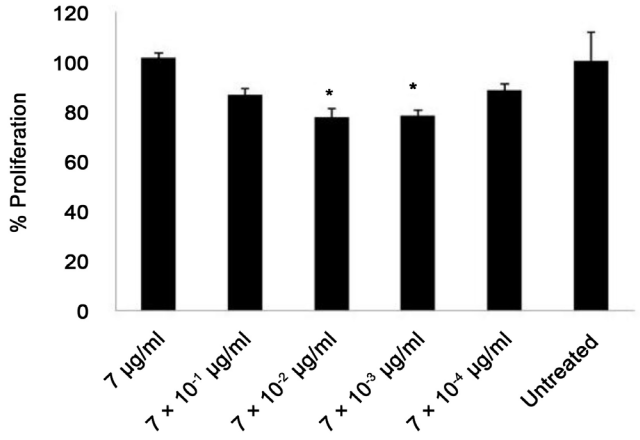

Figure 2. The effect of 48 hr incubation of Capsol-T in DU145 cell proliferation. 7×10^{-2} ug/ml vs Untreated $p < 0.001$; 7×10^{-3} ug/ml vs Untreated $p = 0.012$.

As far as LNCap, the other prostate cancer cell line is concerned; Capsol-T significantly decreases cell proliferation both at 24 hr and 48 hr (**Figure 3** and **Figure 4**).

Capsol-T incubation has differential effects on the lung cancer cell line MOR. In 24 hr the highest concentration decreases proliferation where as the lowest has proliferative effects. However, at 48 hr the effects are eradicated and there is no difference in proliferation (**Figure 5** and **Figure 6**).

As far as the hormone sensitive breast cancer cell line MCF7 is concerned, high Capsol-T concentration increased cell proliferation at 24 hr, however, at 48 hr there was a trend for a decreased proliferation which became significant at low concentrations (**Figure 7** and **Figure 8**).

Finally, the effect of Capsol-T on the colorectal carcinoma cell line HCT116 was evaluated. In was found that cell proliferation decreased in low Capsol-T concentration at 24 hr incubation. The effect was more prominent at 48 hr (**Figure 9** and **Figure 10**).

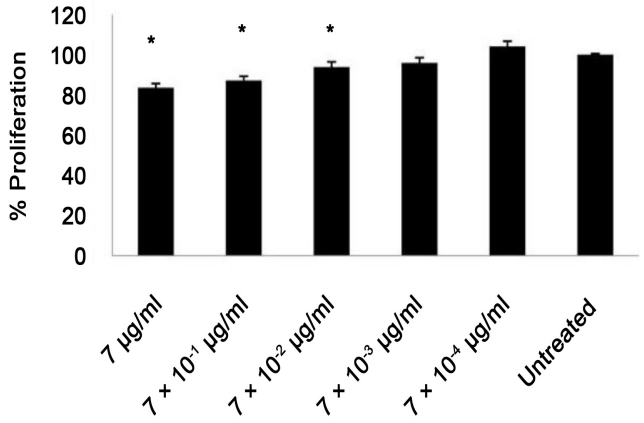

Figure 3. The effect of 24 hr incubation of Capsol-T in LNCAP cell proliferation. 7 ug/ml vs Untreated $p < 0.001$; 7×10^{-1} ug/ml vs Untreated $p < 0.001$; 7×10^{-2} ug/ml vs Untreated $p = 0.04$.

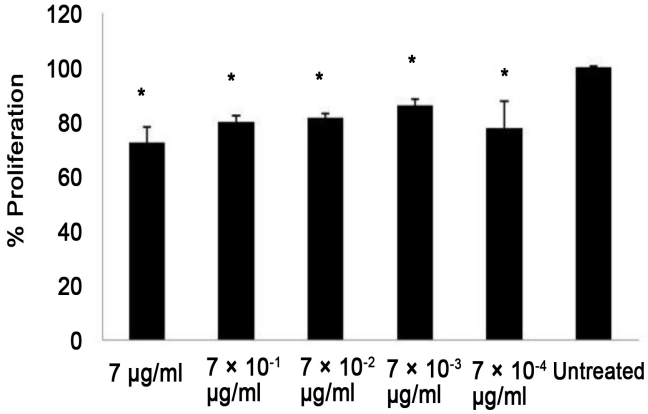

Figure 4. The effect of 48 hr incubation of Capsol-T in LNCAP cell proliferation. 7 ug/ml vs Untreated $p < 0.001$; 7×10^{-1} ug/ml vs Untreated $p < 0.001$; 7×10^{-2} ug/ml vs Untreated $p < 0.001$; 7×10^{-3} ug/ml vs Untreated $p < 0.001$; 7×10^{-4} ug/ml vs Untreated $p < 0.001$.

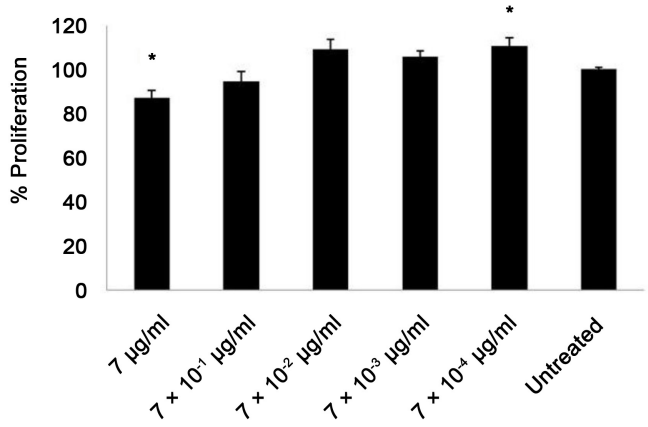

Figure 5. The effect of 24 hr incubation of Capsol-T in MOR cell proliferation. 7 ug/ml vs Untreated $p = 0.01$; 7×10^{-4} ug/ml vs Untreated $p = 0.03$.

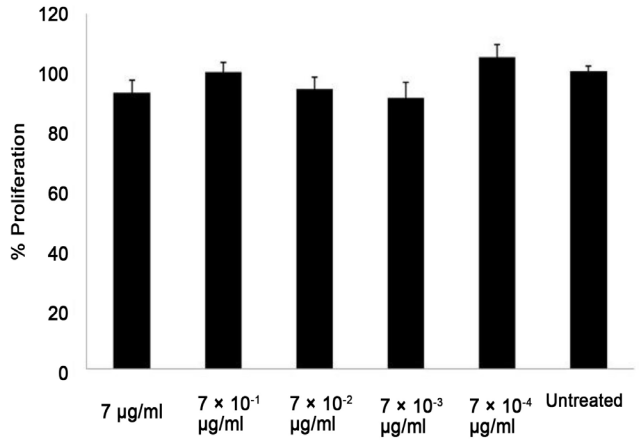

Figure 6. The effect of 48 hr incubation of Capsol-T in MOR cell proliferation. There was no statistical difference compared to untreated.

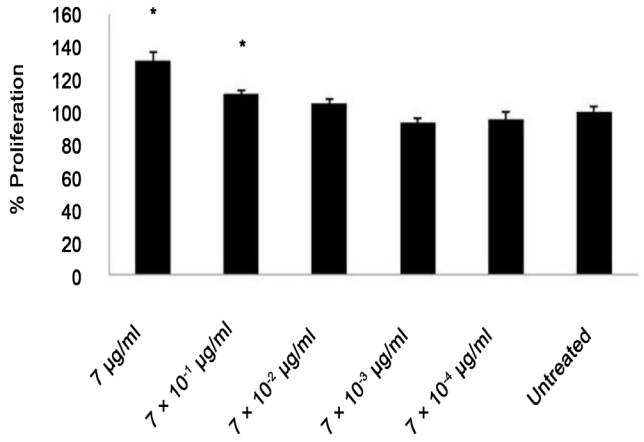

Figure 7. The effect of 24 hr incubation of Capsol-T in MCF7 cell proliferation. 7 ug/ml vs Untreated p = 0.008; 7×10^{-1} ug/ml vs Untreated p = 0.02.

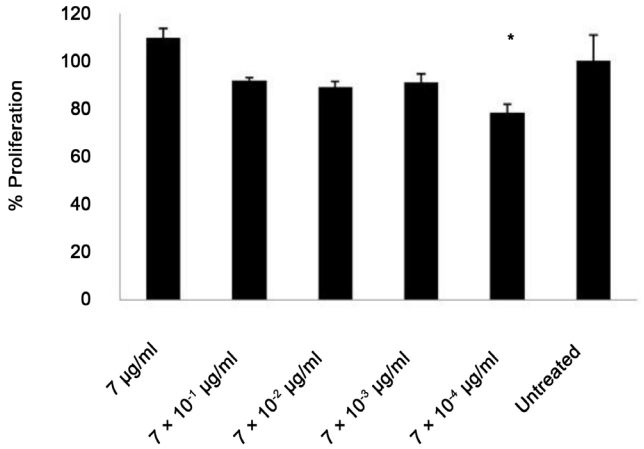

Figure 8. The effect of 48 hr incubation of Capsol-T in MCF7 cell proliferation. 7×10^{-4} ug/ml vs Untreated p = 0.03.

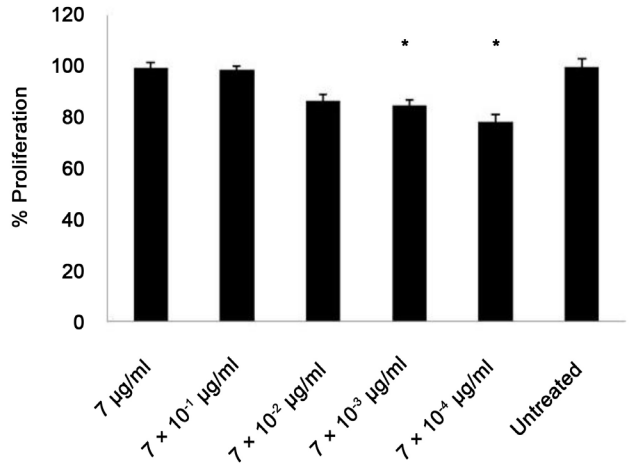

Figure 9. The effect of 24 hr incubation of Capsol-T in HCT116 cell proliferation. 7×10^{-3} ug/ml vs Untreated $p = 0.005$; 7×10^{-4} ug/ml vs Untreated $p = 0.001$.

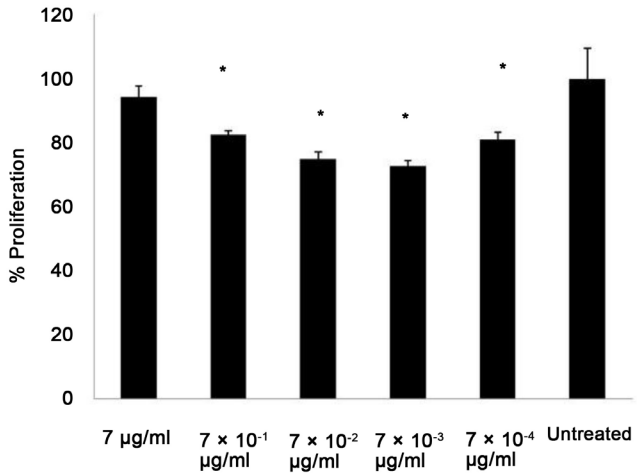

Figure 10. The effect of 48 hr incubation of Capsol-T in HCT116 cell proliferation. 7×10^{-1} ug/ml vs Untreated $p = 0.007$; 7×10^{-2} ug/ml vs Untreated $p < 0.001$; 7×10^{-3} ug/ml vs Untreated $p < 0.001$; 7×10^{-4} ug/ml vs Untreated $p = 0.01$.

4. Discussion

In recent years the use of natural products for the prevention and treatment of cancer have attracted much attention. While the lack of clinical trials suggests there is little scientific evidence for the anti-tumor effect for the majority of these products, many patients adopt natural supplements as a complementary therapy in order to prevent, treat or delay recurrence of cancer or reduce chemotherapy toxicity. One of the natural products used as an anti-cancer supplement is Capsol-T.

Capsol-T contains de-caffeinated green tea concentrate and *Capsicum* powder. Its anti-tumor effect is attributed mainly to the inhibition of tNOX protein [19]. tNOX, also known as tumor-associated NADH oxidase, is a cell membrane protein that catalyses hydroquinone/NADH oxidation and protein disulfide-thiol

interchange [20]. Although the physiological significance of membrane NADH oxidases is not clear, it is postulated that they are involved in cell growth since they are activated by hormones or growth factors and are inhibited by quinone analogs [21]. *Capsicum* extract possesses quinone reductase inductive activity and therefore can have an effect on NADH oxidase [22].

It has been demonstrated that capsaicin can decrease cancer cell proliferation through tNOX down-regulation [23] [24]. However, on the other hand in has also been shown that in low concentrations, capsaicin can increase cell proliferation by tNOX upregulation [25]. The role of *Capsicum* powder in cancer is therefore unclear since both cancer cell proliferation and growth arrest have been demonstrated. One of the reasons for this discrepancy can be found in p53 status. Chen *et al*. (2018) [26] studied the diverse therapeutic results of oxaliplatin in gastric cancer patients and found that its anti-cancer activity can also be due to tNOX binding. They found that NAD+ generation can enhance p53 acetylation and apoptosis. However, in p53-mutated cell lines there was little apoptosis evident. Therefore p53 status plays a key role in tNOX-mediated apoptosis.

The anti-cancer effects of green tea have been well documented [27]. Not only does green tea possess anti-oxidant and anti-inflammatory properties, but it also has been associated with amelioration of anti-cancer therapy side-effects [28]. The major constituent of green tea is epigallocatechin-3-gallate (EGCG). It has been found that EGCG can induce ROS generation and that EGCG oxidation can generate catechol-quinone formation [29]. Therefore the second ingredient of Capsol-T—green tea extract—can also decrease cell viability by two mechanisms: a direct one by which EGCG can induce growth arrest and apoptosis and an indirect one through the oxidation of EGCG and subsequent formation of catechol-quinones which in turn can bind to and inhibit tNOX. However, studies have shown that EGCG can decrease both bortezomib anticancer effects [30] and sunitinib bioavailability [31]. Therefore caution should be exercised when using green tea extracts as adjuvant therapy in cancer.

In this paper, the anti-proliferative effect of Capsol-T on various cancer cell lines was studied. Capsol-T was used in concentrations ranging from 7×10^{-4} ug/ml to 7 ug/ml for 24 and 48 hr. The cell lines used covered a range of cancer types including prostate (both hormone sensitive and insensitive), colon, lung and breast. According to the results there was not a common anti-proliferative pattern demonstrated in all cancer cells. In some cell lines (DU145, MCF7, MOR) and certain concentrations, Capsol-T caused a significant increase in cell proliferation, although this effect was not seen in 48 hr. In some cell lines (HCT116, MOR, LnCAP) and in certain Capsol-T concentrations, cell growth was significantly decreased at 24 hr. Decrease in viability became more evident at 48 hr. It is possible that at 72 hr the decrease in cell proliferation would be more prominent, although one cannot postulate a linear relationship. It would be interesting to study the effects of green tea and *Capsicum* extract in signaling pathways classically associated with cancer progression, other than tNOX.

Our results suggest that an anti-proliferative effect in certain types of cancer should not be generalized to other types as well. Even in the same type of cancer results may vary as it was demonstrated in the case of prostate cancer with the androgen dependent and androgen independent cell lines. This could be due to the inherent differences in the signaling pathways different cells utilize for proliferation or other unknown factors as it was demonstrated with p53 status. Different concentrations also affect the net result often having opposite effects. Overall, caution should be taken when using natural supplements for their anti-cancer effects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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