Caffeic acid phenethyl ester as an adjuvant therapy for advanced prostate cancer

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Abstract

Prostate cancer is the second most frequently diagnosed cancer of men. Androgen ablation therapy is the primary treatment for metastatic prostate cancer. However, the majority of prostate cancer patients receiving the androgen ablation therapy will ultimately develop recurrent castration-resistant tumors within 3 years. Chemotherapy shows little effect on prolonging survival for patients with metastatic hormone-refractory prostate cancer. More than 80% of prostate tumors acquire mutation or deletion of tumor suppressor phosphatase and tensin homolog (PTEN), a negative regulator of PI3K/Akt signaling. Caffeic acid phenethyl ester (CAPE) is a strong antioxidant extracted from honeybee hive propolis. Recent studies indicate that CAPE treatment suppresses tumor growth and Akt signaling in human prostate cancer cells. Combined treatments of CAPE with chemotherapeutic drugs exhibit synergistic suppression effects. Pharmacokinetic studies suggest that intraperitoneal injection of CAPE at concentration of 10 mg/kg is not toxic. CAPE treatment sensitizes cancer cells to chemotherapy and radiation treatments. In addition, CAPE treatment protects therapy-associated toxicities in animal models. We therefore propose that administration of CAPE is a potential adjuvant therapy for patients with castration-resistant prostate cancer.

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Introduction

Prostate cancer is the second most frequently diagnosed cancer of men and the fifth most common cancer overall in the world. Surgery is effective for organ-confined prostate cancer. Bones and lymph nodes are the most common metastatic sites for prostate cancer. More than 80% of prostate cancer patients die from bone metastases [1–3]. In 1941, Dr. Charles Huggins discovered that deprivation of androgen caused regression of hormone-responsive metastatic prostate cancer [4]. Since then, androgen ablation therapy has become the primary treatment for metastatic prostate cancer. Current androgen ablation therapy uses luteinizing hormone-releasing hormone agonists (LH-RH) (also known as gonadotropin-releasing hormone, GnRH) [5,6]. However, 90% of the prostate cancer patients receiving androgen ablation therapy will develop recurrent castration-resistant tumors within 1–3 years after treatment. The median overall survival time is 1–2 years after cancer relapse [6,7]. Chemotherapy is used to treat metastatic hormone-refractory prostate cancer [8,9]. Treatments with chemotherapeutic drugs may decrease serum prostate specific antigen (PSA) and improve pain and urinary symptoms. However, chemotherapy show little effect on prolonging survival [8]. Undesired side effects of chemotherapy include toxic deaths, strokes, thrombosis, neutropenia, edema, dyspnea, malaise, and fatigue [8]. Phosphatase and tensin homolog (PTEN) protein is a phosphatase dephosphorylating phosphatidylinositol (3,4,5)-trisphosphate. PTEN suppresses phosphoinositide 3-kinase/Akt signaling pathway [10]. PTEN is frequently deleted or mutated in prostate cancer, resulting in activation of PI3K/Akt signaling [11,12]. PI3K/Akt signaling plays an important role in survival and progression of prostate cancer cells [11]. Up-regulation of PI3K/Akt activity is associated with poor clinical outcome of prostate cancer [12–19].

Caffeic acid phenethyl ester (CAPE), a bioactive component extracted from honeybee hive propolis, is a strong antioxidant [20,21]. CAPE is a well known NF-κB specific inhibitor [21]. Recently, CAPE treatment has been reported to dosage-dependently suppress the cell proliferation of LNCaP, DU-145, and PC-3 cells...
with an IC\textsubscript{50} of 0.68 \textmu M, 9.54 \textmu M, and 18.65 \textmu M, respectively [22,23]. LNCaP, DU-145, and PC-3 cells are the most commonly used metastatic prostate cancer cell lines for research. The PTEN in LNCaP cells is mutated, while PC-3 cells acquire a homozygous deletion of PTEN. The growth inhibitory effect happens within 24 h and accumulates over time [22,23]. CAPE treatment (10 \textmu M) significantly inhibits the soft agar colony formation of LNCaP and PC-3 cells [22,23]. Flow cytometric analysis reveals that treatment with 3–20 \textmu M CAPE causes G1 cell cycle arrest in LNCaP and PC-3 cells [22,23]. Oral administration of CAPE (10 mg/kg per day) for six weeks causes 50\% reduction of LNCaP xenografts tumor volume in nude mice [22]. Co-treatment of CAPE (2.5–20 \textmu M) with chemotherapeutic drugs vinblastine, paclitaxel, or estramustine indicates synergistic suppression effect on PC-3 cells [23]. Treatment with 10 \textmu M CAPE for 96 h significantly decreases protein abundance of signaling protein involved in Akt signaling and cell cycle regulation in LNCaP and PC-3 cells [22,23].

CAPE treatment has been shown to sensitize cancer cells to chemotherapeutic drugs and radiation treatment in animal models [24]. CAPE treatment also protects animal from therapy-associated toxicities [24]. CAPE protects renal, heart, and brain tissues damages caused by doxorubicin treatment in rats [25–27]. CAPE treatment protects liver damage caused by cisplatin treatment [28,29], methotrexate-induced renal oxidative impairment [30], bleomycin-induced lung fibrosis [31], and liver toxicity induced by Tamoxifen treatment [32] in rats. CAPE treatment attenuates radiation treatment-induced pulmonary injury in rats [33]. CAPE treatment also sensitizes colorectal adenocarcinoma to radiation treatment in murine model [34].

The achievable concentration of CAPE in human serum is approximately 17 \textmu M [35]. The pharmacokinetic profile of CAPE has been determined in rats after intravenous (i.v.) administration of 5–20 mg/kg [36]. Total body clearance values for CAPE range from 42.1 to 172 ml/min/kg and decrease with the increasing dose of CAPE. The volume of distribution values for CAPE range from 1555 to 5209 ml/kg, decrease with increasing dose. The elimination half-life for CAPE range from 21.2 to 26.7 min and is independent of dose [36]. This study suggests that CAPE is distributed extensively into tissues and is eliminated rapidly with a short half life. Intraperitoneal (i.p.) injection of CAPE at 10–30 mg/kg for 7 days does not affect mice body weight [37]. Seven days of i.p. injection of 10 mg/kg of CAPE shows no toxicity to liver and kidney while i.p. injection of 20 or 30 mg/kg CAPE for seven days causes mild dose-dependent liver and kidney toxicity in mice [37].

**Hypothesis**

According to the following facts: (1) CAPE treatment significantly suppresses growth of prostate cancer cells both in vitro and in vivo, (2) CAPE treatment significantly suppresses Akt signaling in prostate cancer cells, (3) Akt signaling is up-regulated in the majority of prostate tumors, (4) Co-treatment of commonly used chemotherapeutic drugs with CAPE exhibits synergistic suppressive effect, (5) CAPE treatment has been shown to sensitize cancer cells to chemotherapeutic drugs and radiation treatment, (6) CAPE treatment protects animal from therapy-associated toxicities, (7) The achievable concentration of CAPE in human serum is approximately 17 \textmu M (8) The IC\textsubscript{50} of CAPE to suppress proliferation of human prostate cancer cells ranging from 0.68 to 18.65 \textmu M, we hypothesize that administration of CAPE (10 mg/kg) can suppress tumor growth of advanced prostate tumors targeting Akt signaling in patients with no toxicity to liver and kidney. As CAPE causes G1 cell cycle arrest but not cell death in human prostate cancer cells [22,23], we predict that CAPE treatment can only retard tumor growth but not eradicate cancer cells in patients. Therefore, chemotherapy or radiation therapy should be applied in combination of CAPE treatment to eliminate prostate cancer cells in patients. Co-treatment of chemotherapy drugs with CAPE will reduce the dosage of chemotherapy drugs needed, and therefore avoid or trim down the undesired side effects of these chemotherapeutic agents. To prove our hypothesis, we propose to design a clinical trial recruiting patients having recurrent castration-resistant prostate cancers undergoing chemotherapy or radiation therapy. Patients should be randomly separated into four groups. In addition to their current chemotherapeutic or radiation treatment, three groups receive different dosage of CAPE pellets daily while the other group receives placebo only for one year. We therefore suggest the CAPE treatment groups to include low (50 mg/day), medium (300 mg/day), and high dosage (600 mg/day) group. Most male have body weight around 60–90 kg, 600 mg CAPE equals dosage of 6.7–10 mg/kg and should be safe for prostate cancer patients. As intra-peritoneal injection of 20–30 mg/kg CAPE in mice significantly increases plasma alanine aminotransferase (ALT) levels as well as lipid peroxidation in liver and kidney [37], we recommend that patients with history of liver or kidney diseases should be excluded from this clinical trial. We predict that the CAPE treatment groups will show lower serum PSA level and smaller tumor burden. Since CAPE treatment has been shown to protect damage in brain, heart, liver, and kidney from chemotherapies in animal models [25–33], we predict that co-treatment with CAPE may reduce incidence of toxic deaths, strokes, thrombosis, edema, dyspnea, malaise, or fatigue in prostate cancer patients under chemotherapy treatments. Propolis is widely sold as health food in United States and European countries. The LD\textsubscript{50} of propolis for different strains of mice ranges from 300 to 2050 mg/kg [38]. However, treatment with 100–2000 mg/kg propolis to mice causes a dose-responsive decrease in spontaneous movement [38,39]. Since CAPE is the main active component of propolis, propolis treatment should also suppress proliferation of prostate cancer cells. Indeed, propolis treatment enhances apoptosis in human prostate cancer cells induced by TRAIL [40]. We also predict that people routinely eating propolis will have lower incidence of prostate cancer and taking propolis will reduce incidence of tumor recurrence in prostate patients receiving androgen ablation therapy. Unfortunately, currently there is no study investigating the relationship between propolis intake and incidence of any cancers in human. Propolis has only been reported to be effective in combination with \beta-interferon for treating cervical human papillomavirus (HPV) infection in women with cervical lesions [41]. Further studies are needed to investigate the relationship between propolis diet and prostate cancer incidence.

**Conclusion**

We provide several evidences to support the hypothesis that administration of CAPE, a natural compound extracted from honey-bee hive propolis, is an effective adjuvant therapy for advanced prostate cancers targeting Akt signaling. CAPE treatment may reduce the dosage of chemotherapeutic agents required and protect organ damages and toxicity induced by various kinds of cancer chemotherapeutic drugs or radiation therapy. Propolis has already been marketed by health food stores as a traditional medicine with beneficial effects for human health. We believe that CAPE is a safe natural compound and a potential adjuvant therapy for patients with advanced prostate cancer.

**Conflicts of interest statement**

There is no conflict of interest for all authors.
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References


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