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Anticancer Effect of Caffeic Acid Phenethyl Ester

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Abstract: Background: Caffeic Acid Phenethyl Ester (CAPE), a bioactive component of honeybee hive propolis, is known to exhibit anti-mitogenic, anti-carcinogenic, anti-inflammatory, anti-viral and immuno-modulatory properties. **Result:** In this review study, we summarize the known effect and possible mechanism of CAPE on suppressing proliferation of different cancer cells as well as inhibiting growth and metastasis of different tumors. **Conclusion:** Recent observations suggest CAPE administration as a potential adjuvant therapy for several types of cancer.

Key words: Necrosis, hepatocarcinogensis, CAPE, anti-mitogenic

INTRODUCTION

Caffeic Acid Phenethyl Ester (CAPE) (Fig. 1), a lipophilic derivatives of caffeic acid and a phenolic antioxidant structurally related to 3, 4-dihydroxycinnamic acid, is one of the active components extracted from honeybee hive product propolis. CAPE has been used in folk medicine as a potent anti-inflammatory agent and is known to exhibit anti-mitogenic, anti-carcinogenic, anti-inflammatory, anti-viral and immuno-modulatory properties.

CAPE is well known as a NF-κB inhibitor. CAPE (50-80 μM) specifically inhibits the activation of nuclear transcription factor NF-κB induced by Tumor Necrosis Factor (TNF) and inflammatory agents as well as prevented the translocation of p65 unit of NF-κB. CAPE inhibits the binding between NF-κB and DNA but had no effect on other transcription factors (Natarajan *et al*., 1996). Reducing agent such as DTT, 2, 3-dimercaptopropanol and 2-mercaptoethanol reverses the effect of CAPE-induced inhibition of NF-κB activation (Natarajan *et al*., 1996). CAPE is also a strong antioxidant (Bhimani *et al*., 1993; Jaiswal *et al*., 1997; Sudina *et al*., 1993). CAPE dosage-dependently inhibits the oxidative stress induced by H_2O_2, oxidized bases 8-Hydroxyl-2'-Deoxyguanosine (8-OHdG), 5-Hydroxymethyl-2'-Deoxyuridine (HMdU) and 12-O-Tetradecanoylphorbol-13-acetate (TPA) in HeLa cells (Bhimani *et al*., 1993).

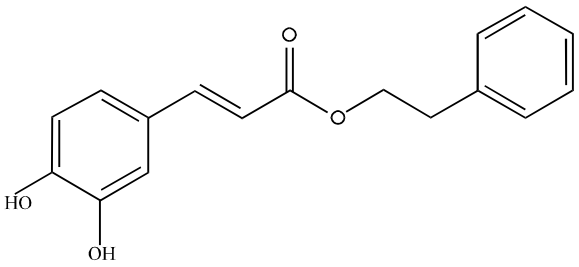

Fig. 1: Structure of caffeic acid phenethyl ester (CAPE)

CAPE also nhibits ctivity of Xanthine Oxidase (XO), which is the major source of Reactive Oxygen Species (ROS). CAPE treatment in human hepatoma HepG2 cells dramatically stimulates gene expression antioxidant response element-mediated NAD(P)H quinone oxidoreductase (NQO1) gene expression (Jaiswal *et al*., 1997). Several studies indicate that CAPE may be an alternative adjuvant therapy for several types of cancer with little or no side effect. We therefore summarized the important researches that have been done in the past 20 years and discussed the effect and anti-cancer mechanism of CAPE.

Anti-cancer effect of CAPE on different cancer cells: CAPE has been reported to inhibit transformation of normal cells to cancer cells. CAPE (10 μM) selectively inhibited cloned rat embryo fibroblast cells transformed

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by adenovirus (type 5) versus untransformed cloned rat embryo fibroblast cells (CREF cells) (Su *et al*., 1994). CAPE induces cell cycle arrest in CREF cells but induces apoptosis in type 5 adenovirus transformed Wt3A cells (Chiao *et al*., 1995). CAPE (5 μM) treatment also suppresses TPA-induced cell transformation and induces apoptosis in mouse epidermal JB6 Cl 41 cells (Nomura *et al*., 2001).

Different cancer cell lines showed different sensitivity to CAPE treatment (Table 1). CAPE treatment suppresses proliferation of several human cancer cell lines, including MCF-7 breast cancer cells (Nomura *et al*., 2001), PC-3 prostate cancer cells (Watabe *et al*., 2004), HL-60 leukemia cells (Chen *et al*., 2001b; McEleny *et al*., 2004), A549 and H1299 non-small cell lung cancer cells (Chen *et al*., 2004; Chen *et al*., 2001a; Lin *et al*., 2011; Usia *et al*., 2002), HT-1080 fibrosarcoma cells (Chen *et al*., 2004), HeLa cervical cancer cells (Chen *et al*., 2004), CT26, HCT116, SW480 colon cancer cells (Liao *et al*., 2003, Shigeoka *et al*., 2004; Wang *et al*., 2005), GNM neck metastasis of *Gingiva carcinoma* (Xiang *et al*., 2006), TSCC tongue squamous carcinoma cells (Xiang *et al*., 2006), SAS oral squamous carcinoma cells (Lee *et al*., 2000), Meng 1 oral epidermal carcinoma cells (Lee *et al*., 2000), Daoy medulloblastoma cells (Lee *et al*., 2005), Nalm6, Farage, Pfeiffer, Ramos, HDMAR lymphoma cells (Lin *et al*., 2006) and U973 myeloid leukemia cells (Berger *et al*., 2007). Among the different type of cancer cell lines being tested, cervical cancer HeLa cells (Usia *et al*., 2002) and multiple lymphoma cell lines (Berger *et al*., 2007) are relative sensitive to CAPE treatment, suggesting the possibility that cervical cancer and lymphoma cancer patients may benefit from CAPE treatment. Non-cancer cells, such as human immortal lung fibroblast WI-38 cells (Chen *et al*., 2004), Human Normal Umbilical Vein Epithelial Cells (HUVEC) (Usia *et al*., 2002), or Human Normal Oral Fibroblast (NHOF) cells (Lee *et al*., 2005) are much more resistant to CAPE treatment, indicating potential selective cytotoxic effect against cancer cells of CAPE treatment.

CAPE treatment causes apoptosis and cell cycle arrest. CAPE induce apoptosis in many cancer types through stimulation of Bcl-2-associated X protein (Bax) (Chen *et al*., 2001a; Jin *et al*., 2008; Lee *et al*., 2003; Watabe *et al*., 2004), Bak (Lee *et al*., 2003), p53 (Hung *et al*., 2003; Lee *et al*., 2003; Nomura *et al*., 2001), $p21^{cip}$ (Hung *et al*., 2003), extracellular signal-regulated kinase (ERKs) (Lee *et al*., 2003), c-Jun (Hung *et al*., 2003), c-Jun N-terminal kinase (JNK) (Watabe *et al*., 2004), p38 mitogen-activated protein kinase (p38 MAPK) (Lee *et al*., 2003; Watabe *et al*., 2004), Fas ligand (Watabe *et al*., 2004), caspase activity (Chen *et al*., 2001a; Hung *et al*., 2003; Jin *et al*., 2008; Lee *et al*., 2003), down-regulation of Bcl-2 (Jin *et al*., 2008; Su *et al*., 1994), the cellular inhibitor of apoptosis proteins 1 and 2 (cIAP-1 and cIAP-2, respectively) and X-linked Inhibitor of Apoptosis Protein (XIAP) (Chen *et al*., 2001a; McEleny *et al*., 2004), release of cytochrome C (Jin *et al*., 2008; Lee *et al*., 2003), loss of mitochondrial transmembrane potential (Hung *et al*., 2003), decrease in Mcl-1 (Hung *et al*., 2003), as well as by inhibiting the functions of NF-κB (McEleny *et al*., 2004; Watabe *et al*., 2004). Treatment of p38 MAPK inhibitor SB203580 partially suppresses CAPE-induced p53 activation, Bax expression and apoptosis (Watabe *et al*., 2004). Expression of dominant negative c-Jun which inhibits the JNK signal, also suppresses CAPE-induced apoptosis, suggesting MAPKs are involved in CAPE-induced

Table 1: Effect of CAPE on proferation of different cancer cells lines. Either IC_{50} of the dosages being used to show suppressive effect of CAPE on cancer are shown in table

Cell lines	Cancer type	IC_{50} (μM)	Dosage (μM)
MCF-7	Breast cancer	-	10-100
PC-3	Prostate cancer	-	88
HL-60	Leukemia	-	21
A549	Lung cancer	20.9	-
H1299	Lung cancer	21.2	-
HT-1080	Fibrosarcoma	9.5	-
HeLa	Cervical cancer	2.4	-
CT26	Colon cancer	35.0	3.5-24
HCT116	Colon cancer	-	9-182
SW480	Colon cancer neck metastasis of	-	9-182
GNM	Gingiva carcinoma tongue squamous cell	-	25-200
TSCCa	Carcinoma oral squmous cell	-	25-200
SAS	Carcinoma oral cell epidermiod	-	-
Meng 1	Carcinoma	-	50-200
Daoy	Medulloblastoma acute lymphoblastic	-	1-100
Nalm6	Lymphoma diffuse large cell	3.1	-
Farage	Lymphoma diffuse large cell	2.0	-
Pfeiffer	Lymphoma	1.2	-
Ramos	Buzrkkit's lymphoma	4	-
HDMAR	T-cell lymphoma	2.1	-
U937	Myeloid leukemia	-	0.4-53

apoptosis (Watabe *et al*., 2004). Overexpression of Bcl-2 rescues apoptosis induced by CAPE (Su *et al*., 1994).

In addition, CAPE treatment induces G1 or G2 cell cycle arrest in several cancer cells through suppression of cyclin B1 (Chen *et al*., 2004; Lin *et al*., 2006), cyclin D1 (He *et al*., 2006; Kuo *et al*., 2006), cyclin E (Kuo *et al*., 2006), c-myc expression (He *et al*., 2006), phosphorylation of Rb (Kuo *et al*., 2006), cytoplasmic and total and nuclear β-catenin (Wang *et al*., 2005; Xiang *et al*., 2006) and increased expression of the cyclin dependent kinase inhibitors $p21^{waf1/cip1}$ (Kuo *et al*., 2006), $p27^{Kip1}$ (Kuo *et al*., 2006) and $p16^{INK4A}$ (Kuo *et al*., 2006). CAPE may also induces necrosis (Berger *et al*., 2007).

CAPE treatment also suppresses cancer cell motility and invasiveness via suppression of Akt phosphorylation (Shigeoka *et al*., 2004), phosphorylation of Focal Adhesion Kinase (FAK) (Weyant *et al*., 2000), expression of matrix metalloproteinase MMP-2 and MMP-9 (Usia *et al*., 2002), Vascular Endothelial Growth Factor (VEGF) (Usia *et al*., 2002) and disrupts the arrangement of actin cytoskeleton (Weyant *et al*., 2000).

Inhibition of tumor growth and metastasis by CAPE: Several animal studies suggest that CAPE can prevent carcinogenesis *in vivo*. C57BL/6J-Min/+mice bear a germ line mutation in the Apc gene and spontaneously develop several intestinal adenomas by 15 weeks of age. A dietary level of 0.15% CAPE decreases 63% of tumor formation in these mice. Examination of intestinal tissue from the treated animals reveals that CAPE treatment increases apoptosis and cell proliferation of enterocyte and decreases expression of the oncoprotein β-catenin in the enterocytes (Mahmoud *et al*., 2000). Rats treated with 50 mg kg^{-1} CAPE i.p., reduced the formation of aberrant crypt foci and colon-rectal carcinoma induced by azoxymethane (Borrelli *et al*., 2002). Male Wistar rats are medium-term rat hepatocarcinogenesis model. These rats will generate Altered Hepatic Foci (AHF), an early sign of hepatocarcinoma, when subjected to a carcinogenic treatment (diethylnitrosamine (DEN), 2-AAF) to. A single 20 mg kg^{-1} dosage treatment of CAPE given 12 h before initiation of the carcinogenic treatment reduces γ-glutamyl transpeptidase (GGT) positive AHF by 84%, possibly through an anti-oxidative and free-radical scavenging mechanism (Carrasco-Legleu *et al*., 2006). Gavage of CAPE (20 mg kg^{-1}) decreases the number and area of GGT-positive AHF in Male Wistar rats exposed to diethylnitrosamine by 91 and 97%, respectively (Carrasco-Legleu *et al*., 2004). Nuclear localization of the p65 subunit of Nf-κB was decreased by 85% by CAPE treatment as well (Carrasco-Legleu *et al*., 2004).

CAPE treatment also suppresses tumor growth and metastasis in animal models. Growth of rat C6 glioma xenografts in nude mice are dose-dependently inhibited by CAPE treatment (1-10 mg/kg/day, i.p.). CAPE treatment significantly reduces the number of mitotic cells and Proliferating Cell Nuclear Antigen (PCNA)-positive cells (Lee *et al*., 2005). Oral administration of CAPE (100-250 mg/kg/day) for 7 days after murine colon 26-L5 cancer cells inoculation decreases the tumor weight and the number of tumor nodules in the lung by around 50 and 50%, respectively, compared to the control (Nagoaka *et al*., 2003). CAPE treatment (10 mg/kg/day, i.p.) in Balb/c mice reduces 80% of the pulmonary metastatic foci of CT26 murine colon tumors, decreased 60% plasma VEGF level and prolonged the survival of mice (Liao *et al*., 2003). Gauge of single dosage (50 or 150 mg kg^{-1}) of CAPE 15, 10 and 5 days before metastases in the lung generated by intravenous (i.v.) injection of transplantable mammary carcinoma in CBA mice reduces 50-67% of lung metastases (Orsolic *et al*., 2004). Subcutaneous or oral administration of CAPE (5 mg kg^{-1}) three times a week suppresses 45-55% of the tumor volume and 70-85% of number of liver metastasis of HepG2 xenografts in nude mice (Chung *et al*., 2004).

DISCUSSION

The possible mechanism involved in the anti-cancer effect of CAPE is summarized in Fig. 2. As we discuss

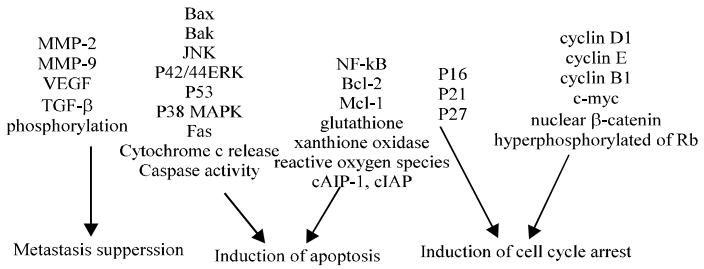

Fig. 2: Potential mechanism of the anti-cancer activity of CAPE. The signaling molecules being activated by CAPE are shown in red and those being suppressed by CAPE are shown in blue

above, CAPE can induce apoptosis, G1 or G2 cell cycle arrest and necrosis while it can reduce motility and invasiveness in cancer cells depends on the concentration of CAPE being used and the types of cancer cells being treated. CAPE also suppresses development, growth and metastasis of tumors in animal models. These observations suggest that CAPE might be a potential therapeutic agent for cancers. The achievable concentration of CAPE in human serum is around 5.0 μg mL^{-1} (17 μM) (Celli *et al*., 2007). This concentration (17 μM) is not enough to eradicate all types of cancer cells (Table 1), However, CAPE can be used in combination with current standard treatments. We believe that further clinical trials should be performed to determine if caffeic acid phenethyl ester can be used as a safe and effective adjuvant therapy for variable types of cancers.

Disclosure of Potential Conflicts of Interest: No potential conflicts of interest were disclosed.

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