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Comparative evaluation of the effects of cape on matrix protein-dependent angiogenic and apoptotic markers in gastric and colon cancer cells

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Abstract

Cancer remains one of the most critical health issues of our era, primarily due to the unregulated growth and dissemination of abnormal cells. It is among the leading causes of mortality worldwide and is typically accompanied by chronic inflammation and a compromised immune system. For a better understanding of the mechanisms underlying cancer cell activity, it is essential to understand the distinct elements of the tumor microenvironment and the pathways through which these elements interact. In this research, we explored the potential anticancer properties of Caffeic Acid Phenethyl Ester (CAPE) in gastric and colon cancer cell lines. Our goal was to analyze and compare the expression of apoptosis markers; Apoptotic protease activating factor-1 (Apaf-1), B-cell lymphoma 2 (bcl-2), caspas 9 (cas-9) and Cytochrome c (Cyc) and angiogenesis markers; Matrix metalloproteinase-9 (MMP9), Vascular Endothelial Growth Factor (VEGF), Endostatin and thrombospondin (TSP) in environments enriched with the extracellular matrix proteins (laminin and collagen I). CAPE was administered to gastric (NCI-N87) and colon (Colo 205) cancer cells lines cultivated on matrix proteins. The amount of synthesized DNA was measured using RT-PCR by detecting absorbance at 260 nm. The comparative data indicated that CAPE enhanced apoptotic activity in colon cancer cells while promoting angiogenic responses in gastric cancer cells, particularly when laminin was present. These observations highlight laminin's significant influence in these mechanisms and show that CAPE further intensifies these effects. Follow-up studies using animal models are planned to reinforce these findings. In summary, our findings indicate that CAPE may be a potential therapeutic agent for the treatment of gastric and colorectal cancers.

Keywords: Cancer cell, apoptosis, angiogenesis, Caffeic Acid Phenethyl Ester, matrix proteins

Introduction

Cancer is a life-threatening illness caused by the unchecked growth and dissemination of cells within the body [1]. Current data show that men are most commonly affected by lung, prostate, colorectal, stomach, and liver cancers, while breast, colorectal, lung, and cervical cancers are the leading cancer types among women. [2]. Different methods and treatment approaches can be used in cancer treatment. Various treatment methods, such as immunotherapy, chemotherapy, surgery, radiotherapy, and targeted therapies, can be used alone or in combination [3]. Cancer cells exhibit many differences compared to normal cells. Among these, the most prominent are the ability of cancer cells to evade apoptosis, their ability to grow independently, their capacity for infinite division, angiogenesis, extracellular matrix degradation, and metastasis [4].

The process of forming new blood vessels, called angiogenesis, is crucial for tumor development, invasion, and metastasis [5]. The maturation and configuration of newly formed microvessels depend on the balance between proangiogenic and antiangiogenic factors. These factors may arise from surrounding cells such as tumor cells, monocytes, and fibroblasts or after the destruction of the collagen matrix. Angiogenic activity is initiated when certain

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environmental conditions trigger the dominance of angiogenic factors. Angiogenic factors are VEGF, FGF-2, TGF-β, matrix metalloproteinases (MMPs) and angiopoietins (Angs), etc. For angiogenic activity to begin, not only the increase in angiogenic factors but also the effects of antiangiogenic factors must be overcome. Antiangiogenic factors normally protect the vascular endothelium from stimuli and inhibit angiogenic activity. The most important of these are thrombospondin (TSP), angiostatin, and endostatin [6,7].

Apoptosis is programmed cell death and is also necessary for the destruction of carcinogenic cells. In apoptosis, cell death is triggered through different signaling mechanisms: The mitochondria-mediated apoptosis (intrinsic), death receptor–mediated (extrinsic) pathway and the endoplasmic reticulum-mediated pathway [8]. In intrinsic apoptosis, the release of cytochrome c from mitochondria to the cytosol activates the cell death pathway. After the release of cytochrome c (cyt-c), procaspase 9 (procas-9) and Apaf-1 assemble in the cytosol to form a complex called the apoptosome. In this complex, procas-9 is activated and turns into cas-9, which then activates caspases 3 (cas-3) and 7. Thus, cell death occurs [9]. Bcl-2 gene is a key regulator of apoptosis that helps prevent cells from apoptosis. It demonstrates its anti-apoptotic role by suppressing cyt-c release and stopping the activation of effector proteases. A reduction in cellular Bcl-2 levels triggers apoptosis, whereas elevated Bcl-2 levels inhibit cell death. Numerous anticancer agents have been shown to induce apoptosis via cas-3 and cas-9 activation, accompanied by Bax upregulation and enhanced cytosolic release of cyt-c [10].

One of the key molecules in tumor invasion and metastasis is the extracellular matrix (ECM) elements [11]. The ECM, which forms the tumor microenvironment, is a complex and dynamic formation that not only provides structural support to organisms but also has an impact on many biological activities such as cell proliferation, differentiation and migration, adhesion and tissue morphogenesis. Increased tumor and tissue stiffness occurs mostly as a result of ECM accumulation. Type I collagen and fibronectin represent the predominant ECM components that accumulate in cancer [12]. Additionally, other ECM proteins such as fibronectin, laminin, fibromodulin and osteopontin have been shown to play a role in tumor progression by altering the properties of the tumor microenvironment. Fibronectin and laminin, in particular, are glycoproteins that enhance tumor cell migration [13]. Understanding how cancer cells behave depends on recognizing the different elements of the tumor surroundings and the pathways that regulate their interactions [11,14].

Type I collagen and fibronectin represent the predominant ECM components that accumulate in cancer [12]. Additionally, other ECM proteins including fibronectin, laminin, tenascin, decorin, fibromodulin, lumican, and osteopontin have been implicated in tumor progression by altering the biochemical and biomechanical characteristics of the tumor microenvironment.

CAPE also known as 3.4-dihydroxycinnamic acid phenethyl ester, is a bioactive compound found in propolis and is structurally related to flavonoids. It has many properties such as antimitogenic, anti-inflammatory, immunomodulatory etc [15].

The aim of our study was to comparatively investigate the effect of therapeutic dose of CAPE for cancer on angiogenesis markers; MMP9, VEGF, Endostatin, TSP and apoptosis markers; Apaf-1, bcl-2, cas-9, Cyc in the presence of matrix proteins (collagen I, Laminin) in gastric and colon Ca cell culture.

Material and Methods

Ethical committee approval is not required for our study. NCI-N87 and Colo 205 cell line were incubated with DMEM F-12, 10% FCS, 1% L-glutamine, and 1% penicillin-streptomycin and incubated at 37°C in a 5% CO_2. Cells were cultured in plates at 3 x 105 cells/3 ml medium/well for 12 hours. After the cells adhered to the surface and proliferated, CAPE stock solution was added at concentrations of 1, 0.5, 0.25, 0.12, and 0.06 µg/ml and incubated for 48 hours. The dose we calculated as an IC50 of 0.25 µg/ml was determined to be the most effective dose, and PCR was then performed. Biostatistical data analysis.

Addition of CAPE to cell lines

1 mM CAPE stock solution was dissolved in 0.5 mM DMSO and added to 9.5 mM medium.The CAPE stock solution was diluted to concentrations of 1, 0.5, 0.25, 0.12, and 0.06 µg/ml for application to cancer cell lines [16]. CAPE shows dose-dependent effects and the IC50 is 0.25 µg/ml.

Matrix Molecule Coating

Plates were coated with extracellular matrix proteins and kept at 4 °C overnight. Each well received 0.1 ml of collagen I, prepared by diluting 1 part collagen I with 9 parts of 2% (v/v) acetic acid, and 0.1 ml of laminin, diluted at a 1:10 ratio in PBS (pH: 7.4, 1 mg/ml). The total amount applied per well was adjusted to 4 µg. Density on the surface for both collagen I and laminin was kept at 6.25 µg/cm².

RNA Isolation Protocol

Tripure reagent was added to the cells and the cells were swept into the tubes.Two types of cells were used in the study: a control group and a CAPE-treated group. Cells were centrifuged, transferred to special Eppendorf tubes containing beads, and than centrifuged in a MAGNA Lyser homogenizer. The tubes were then kept in cold blocks. 200 µL of chloroform was added to the tubes, and after 5 minutes, the tubes were centrifuged at 12000 rpm for 20 min at 4°C. At the end of this process, three phases were obtained. Phase 1 contains RNA. Phase 2 contains DNA. Phase 3 contains protein. For RNA isolation, 0.5 ml of phase 1 and 0.5 ml of isopropanol were added to a new tube. The mixture was incubated at room temperature for 10 min, then centrifuged at 12.000 rpm (4°C) for 10 min.The pellet was rinsed with 100 µL of ethanol (75%) and then centrifuged at 12.000 rpm at 4°C for 5 minutes. The supernatant was discarded. The ethanol was removed at 57°C. 75 µL of RNase-free water was added to the pellet, and the mixture was homogenized.

DNA Synthesis

Absorbance was measured after adding RNase-free water. For

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each sample, a mixture containing 9.4 µL RNA and H_2O, and 2 µL Random Hexamer primer was prepared and then held in the thermal cycler at 65°C for 10 minutes. Meanwhile, the mastermix solution containing Reaction Buffer, Protective RNase Inhibitor, Deoxynucleotide Mixture, and Transcriptor Reverse Transcriptase enzyme was prepared. For each sample, master mix (8.6 µL) was prepared containing 1 µL DTT, 1.1 µL enzyme, 2 µL DNTP, 0.5 µL RNAse inhibitor and 4 µL reaction buffer. mastermix was combined with 11.4 µL of samples and than the mixture. The resulting cDNA sample volume was 20 µL. Then the samples were incubated in a thermal cycler at 55°C for 30 minutes and then at 85°C for 5 minutes.

Real Time PCR

A mixture containing dH2O (3.5 µL), primer-probe (0.5 µL) and enzyme (5 µL) was obtained for each tube, and cDNA (1 µL) sample was added to this mixture. The reaction mixture was aliquoted into plates at 10 µL per well, and absorbance was read after 1 hour.

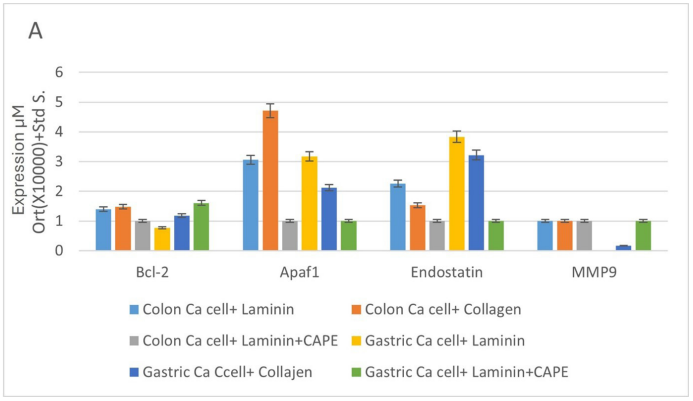
Statistical Analysis

Data collected during the study were analyzed using SPSS for Windows version 15.0. Group differences were evaluated with the Mann-Whitney U test, and a p-value of less than 0.05 was considered statistically significant.

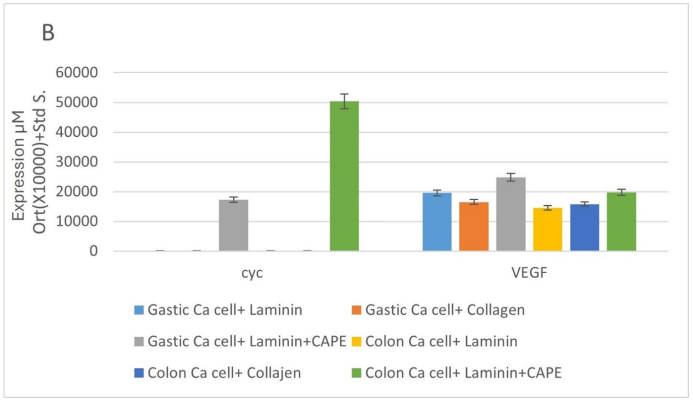
Results

When colon cancer cells + laminin and stomach cancer cells + laminin were compared, there was no statistically significant difference between cys and Apaf-1 ($p>0.05$), while bcl-2 and cas-9 increased more in gastric cancer compared to colon cancer ($p<0.005$) (Graphic A,C). When colon cancer cells + collagen were compared with gastric cancer cells + collagen, there was no statistically significant difference in bcl-2, while there was a statistically significant decrease in cys and Apaf-1 (Graphic B,A), and cas-9 increased more in gastric cancer compared to colon cancer ($p<0.005$) (Graphic C). Colon and gastric cancer cell lines supplemented with CAPE in the presence of laminin matrix protein are shown in Figure 1 and Figure 2. When these cells were compared, there was no statistically significant difference in Apaf-1, while there was a statistically significant decrease in cys and cas-9, and a statistically significant increase in bcl-2 levels ($p<0.005$) (Graphic A,B,C). Therefore, it appears that apoptosis increases more in colon cancer cells with the addition of matrix proteins and CAPE. Specifically, the colon cancer cell group exhibited the greatest increase in apoptosis when laminin and CAPE were added. Thus, we can conclude that the addition of CAPE to the laminin matrix protein is more effective in increasing apoptosis.

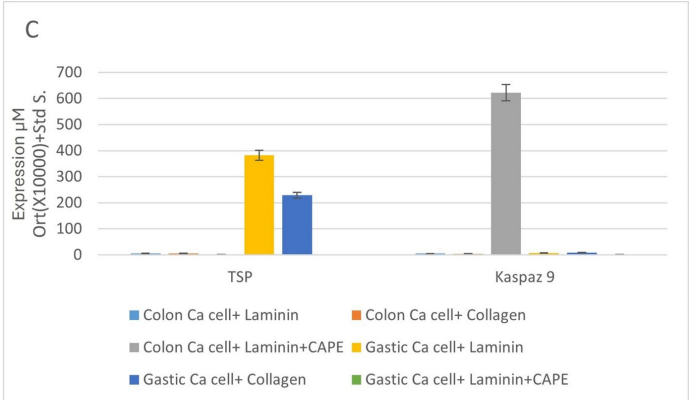
When comparing colon cancer cells + laminin and stomach cancer cells + laminin, MMP9, VEGF, and Endostatin levels increase in gastric cancer, while TSP statistically decreases ($p<0.005$) (Graphic A,B,C). When comparing colon cancer cells + collagen with stomach cancer cells + collagen, MMP-9, Endostatin, and VEGF increase in gastric cancer, while TSP statistically decreases ($p<0.005$) (Graphic A,B,C). When comparing colon cancer cells + laminin + cape and stomach cancer cells + laminin + cape, there is no statistical difference between Endostatin and MMP-9, while TSP and VEGF statistically increase in gastric cancer ($p<0.005$) (Graphic A,B,C). As a result, angiogenesis was found to be more significantly enhanced by the addition of matrix proteins and CAPE in gastric cancer compared to colon cancer. In particular, gastric cancer cells exhibit the greatest increase in angiogenesis when supplemented with laminin and CAPE. Thus, we can conclude that adding CAPE to the laminin matrix protein is more effective in increasing angiogenesis.



Graphic A. Graphical representation of Real Time PCR results for Bcl-2, Apaf1, Endostatin, MMP9 in gastric and colon cancer cells treated with CAPE on laminin- and collagen I–coated culture plates



Graphic B. Graphical representation of Real Time PCR results for cyc, VEGF in gastric and colon cancer cells treated with CAPE on laminin- and collagen I–coated culture plates



Graphic C. Graphical representation of Real Time PCR results for TSP and Cas-9 in gastric and colon cancer cells treated with CAPE on laminin- and collagen I–coated culture plates

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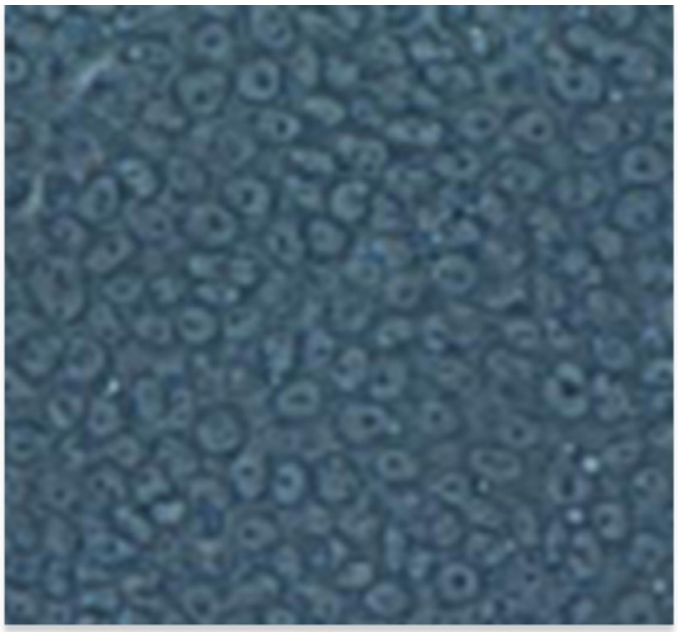

Figure 1. Gastric cancer cell line supplemented with CAPE in the presence of laminin matrix protein

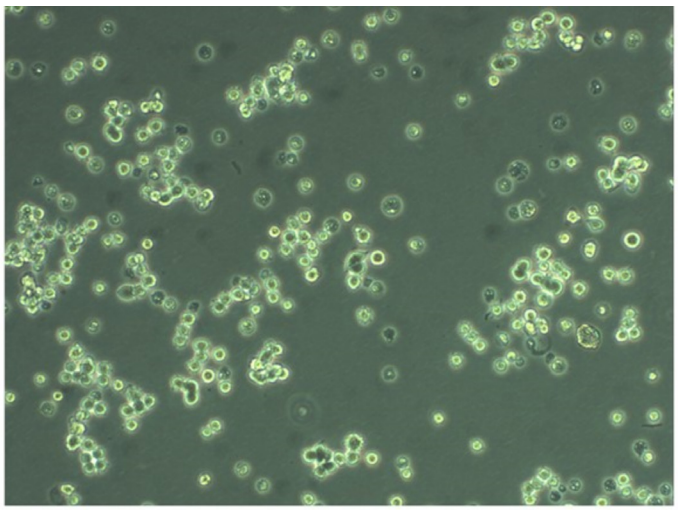

Figure 2. Colon cancer cell line supplemented with CAPE in the presence of laminin matrix protein

Discussion

Gastric Ca is the type of cancer that causes the most deaths. It ranks second among men and third among women, and is resistant to drug therapy. Colorectal cancer ranks as the third most prevalent cancer globally. In the etiology of gastric and colorectal cancers, in addition to genetic predisposition, factors such as age, environmental influences, dietary habits, and certain predisposing conditions that facilitate cancer development play significant roles. Although significant progress has been made in the diagnosis and treatment of these diseases over the past decade, the prognosis remains poor [17,18]. Despite advancements in surgical techniques and multimodal therapies, survival rates remain low. Oncogenes with the potential to cause cancer through mutation regulate cell proliferation, invasion, and metastasis via angiogenesis [19,20]. A decreased rate of apoptotic cell death has also been shown to contribute to malignancy in cancer development. Cells that do not undergo apoptosis when necessary may have the potential to transform into malignant cells [21]. Arresting the cell cycle and inducing apoptosis are potential strategies for cancer treatment.

In recent years, reports indicating that natural compounds may reduce cancer risk have increased interest in their potential use in cancer therapy and stimulated related research. CAPE is one of the major active components of propolis, and has many biological and pharmacological effects [22,23]. CAPE has antiproliferative, proapoptotic and antiinvasive effects on various cancer cell lines, supporting its potential as an anticancer agent [24,25]. CAPE's lack of harmful effects on healthy cells and its absence of side effects further support its potential as a cancer therapeutic [26]. Considering the side effects of chemotherapy and radiotherapy, this feature of CAPE is particularly significant [27]. CAPE is an active compound derived from propolis and demonstrates anti-inflammatory, antioxidant, immunomodulatory and anticancer effects across various biological systems [28]. It also has properties that inhibit cell division and has been shown to reduce the proliferation of different cancer cells, including the gastric, colon, and breast [29]. It also possesses antimitogenic effects and has been demonstrated to suppress the growth of several transformed cell types, such as gastric, colon, and breast cancer cells. CAPE shows strong cytotoxic activity against multiple tumor cell lines.

Research indicates that CAPE suppresses VEGF-induced activation of several intracellular signaling pathways, including PI-3K/AKT, ERK, E-cadherin, β-catenin, and FAK. This inhibition leads to a reduction in cell proliferation, tube formation, migration, focal adhesion, and cell-to-cell adhesion [30]. Additionally, CAPE has been demonstrated to impede the growth of various transformed cell types [24]. CAPE treatments have demonstrated that it inhibits angiogenesis by preventing MMP and VEGF expression and reducing neovascularization [16]. Considering current studies, CAPE exerts its effects on cancer cells not through cytotoxicity but by inducing apoptosis [31]. The various effects of CAPE may be attributed to its ability to pass through the cell membrane. CAPE is capable of inhibiting the activities of enzymes such as lipoxygenase, cyclooxygenase, glutathione S-transferase, and xanthine oxidase. It is also a potent and specific inhibitor of nuclear transcription factor-kB (NF-κB) activation [32]. CAPE may reduce chemotherapeutic drug-related toxicity in normal tissues while enhancing the cytotoxicity of chemotherapeutic agents on cancer cells through mechanisms such as apoptosis induction. Additionally, CAPE has been reported to offer protection against nephrotoxicity, ototoxicity, and periodontal diseases [33-35]. Propolis and CAPE inhibit the TLR4 signaling pathway and suppress the proliferation of breast cancer cells

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in the inflammatory microenvironment by inducing apoptosis and autophagy [36]. Wu et al. demonstrated that CAPE induces apoptosis and modulates NF-κB, leading to the inhibition of growth in human breast cancer cell lines MDA-MB-231 and MCF-7 through mechanisms involving cell cycle arrest and suppression of angiogenesis [37].

Cancer cell behavior is affected by ECM proteins like Laminin and Collagen I. Laminin-1, a major component of the basement membrane, is implicated in many biological activities such as cell adhesion, differentiation, proliferation, tissue morphogenesis. High laminin-1 levels have been associated with increased tumor growth [38,39]. Laminins are molecules typically present in basement membranes (BMs) and facilitate cell adhesion and migration via integrins and other cell surface receptors. However, the BM barrier is compromised during tumor invasion. In carcinomas, tumor cells at the invasive edge show strong intracellular expression of the γ2 chain, a part of laminin-5. Vascular BM undergoes remodeling during angiogenesis, and multiple BMs are penetrated during tumor spread and metastasis. Consequently, abnormal interactions between cells and laminins are key features of malignancies [40]. Collagen I is found within ECM, playing a key role in providing tissue stiffness and serving as a biomechanical platform for the attachment of macromolecules. In animal experiments, Collagen I serves as a favored substrate for ovarian cancer cell adhesion and migration, facilitating their invasive properties [41,42]. Both Collagen I and laminin play roles in controlling the malignant characteristics of cells [37]. Tumor-associated angiogenesis relies on particular growth factors, the activation of angiogenic processes, and alterations in ECM components [6].

Conclusion

In our comparison between gastric and colon Ca cells, we found that the addition of matrix proteins and CAPE caused a greater increase in apoptosis in colon Ca cells, while angiogenesis increased more significantly in gastric Ca cells. Literature studies have also reported that aberrant cell-laminin interactions are key characteristics of malignancies. In light of this information, we observed that laminin is the main matrix protein responsible for these phenomena and that the addition of CAPE further triggered both angiogenesis and apoptosis. Based on the results obtained from our study, we believe that CAPE may be a promising treatment agent for patients with stomach and colorectal cancer. We think it would be meaningful to support this study with animal experiments.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Due to the public availability of the data, ethical committee approval was unnecessary for this study.

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