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DERMATOLOGY | SHORT COMMUNICATION

Cardamom (*Elettaria cardamomum*) essential oil significantly inhibits vascular cell adhesion molecule 1 and impacts genome-wide gene expression in human dermal fibroblasts

Xuesheng Han^{1*} and Tory L. Parker¹

Abstract: Cardamom (*Elettaria cardamomum*) essential oil (CEO) is popular in skin care, although no studies have reported its biological activity in human skin cells. We studied its effect on 17 protein biomarkers closely related to inflammation, immune responses, and tissue remodeling using a dermal fibroblast cell culture system designed to model chronic inflammation. CEO significantly inhibited the proliferation of skin cells and the expression of vascular cell adhesion molecule 1 (VCAM-1) and macrophage colony-stimulating factor (M-CSF). The CEO-induced inhibition of the production of these protein biomarkers suggests its anti-inflammatory and immunomodulatory potential, which has been largely attributed to its major active component, eucalyptol. We further studied the effect of CEO on the expression of 21,224 genes in the same cell culture system. Ingenuity pathway analysis showed that CEO affected critical genes and signaling pathways closely involved in inflammation, immune responses, and tissue remodeling. The observed overall CEO-induced inhibition of these genes and pathways supports its anti-inflammatory and immunomodulatory properties. This study provides important evidence of the biological activity of CEO in human skin cells. Further research into the mechanism of action of CEO in human skin and other systems is recommended.

ABOUT THE AUTHORS

Our group primarily studies the health benefits of essential oils. We are specifically interested in the efficacy and safety of essential oils and their active components. Our studies of essential oils in both *in vitro* and clinical settings utilize a variety of experimental approaches, including analytical, biological, biochemical, and biomedical methodologies. We work closely with research institutes, hospitals, and clinics towards developing quality essential oils with therapeutic benefits. The research work discussed in this paper represents one part of a large research project, which was designed to extensively examine the impact of essential oils on human cells. This study, along with others, will further the understanding of the health benefits of essential oils for a wide research audience. We believe that a full understanding of these health benefits will ultimately lead to the evaluation and use of essential oils as an adjunctive therapy for a variety of diseases.

PUBLIC INTEREST STATEMENT

Essential oils have been widely used globally owing to their health benefits. Our study examined the effects of cardamom (*Elettaria cardamomum*) essential oil (CEO) in a human skin disease model of chronic inflammation. We discovered the potential anti-inflammatory and immune-modulating activities of CEO in human skin cells. The effect of CEO on global gene expression was also analyzed. CEO diversely affected many genes and pathways involved in inflammation, immune responses, and tissue remodeling. These findings suggest that CEO may be a good anti-inflammatory agent and provide important evidence supporting further research on CEO and its health benefits in humans. Additional research focusing on how CEO affects these genes and processes is recommended. A comprehensive exploration of the health benefits of essential oils may lead to viable options for treating many diseases. Thus, this study provides an important stepping-stone for further research on essential oils and their health benefits for humans.

Subjects: Biochemistry; Drug Discovery; Natural Products; Biology; Cell Biology; Molecular Biology

Keywords: cardamom essential oil; *Elettaria cardamomum*; eucalyptol; 1,8-cineole; skin health; anti-inflammation; VCAM-1, vascular cell adhesion molecule 1; M-CSF, macrophage colony-stimulating factor; genome-wide gene expression

1. Introduction

Cardamom (*Elettaria cardamomum*), native to Southeast Asia, is traditionally used as a cooking spice. Cardamom essential oil (CEO) and extract are also traditionally known to be beneficial to the digestive system in various manners. Recent research on CEO has shown evidence of its antimicrobial (Elgayyar, Draughon, Golden, & Mount, 2001), insecticidal (Abbasipour, Mahmoudvand, Rastegar, & Hosseinpour, 2011), antioxidant (Misharina, Terenina, & Krikunova, 2009, 2011), and anti-inflammatory properties (Al-zuhair, El-Sayeh, Ameen, & Al-Shoora, 1996) in different settings. Specifically, 1, 8-cineole (eucalyptol), the major active constituent found in CEO has been extensively studied for its anti-inflammatory activities (Sudhoff et al., 2015; Zhao, Sun, Fang, & Tang, 2014).

However, we conducted a literature search that revealed no published studies on the effect of CEO in human skin cells. The topical use of CEO for skin health has gained popularity, and therefore, we decided to study its biological activity in human dermal fibroblasts. We first analyzed the effect of CEO on critical protein biomarkers involved in inflammation, immune responses, and tissue remodeling. Then, we studied the effect of CEO on regulating genome-wide gene expression. The data provide important evidence of the biological activity of CEO in human dermal fibroblasts and will likely encourage further research into the therapeutic potentials of CEO and its major active components.

2. Materials and methods

All experiments were conducted using a BioMAP system HDF3CGF, a culture of human dermal fibroblasts, which was designed to robustly and reproducibly model the pathology of chronic inflammation. The system comprises three components: a cell type, stimuli to create the disease environment, and a set of biomarker (protein) readouts to examine how the treatments affected the disease environment (Berg et al., 2010). The methodologies used in this study were essentially similar to those previously described (Han & Parker, 2017; Han, Rodriguez, & Parker, 2017; Kunkel, Dea, et al., 2004, Kunkel, Plavec, et al., 2004).

2.1. Cell culture

Primary human neonatal fibroblasts were prepared as previously described (Bergamini et al., 2012) and were plated under low-serum conditions for 24 h before stimulation with a mixture of interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , interferon (IFN)- γ , basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF). The cell culture and stimulation conditions for the HDF3CGF assays have been described in detail elsewhere and were performed in a 96-well plate (Bergamini et al., 2012).

2.2. Protein-based readouts

A direct enzyme-linked immunosorbent assay (ELISA) was used to measure the biomarker levels of cell-associated and cell membrane targets. Soluble factors in the supernatants were quantified using either homogeneous time-resolved fluorescence detection, bead-based multiplex immunoassay, or capture ELISA. The adverse effects of the test agents on cell proliferation and viability (cytotoxicity) were measured using the sulforhodamine B (SRB) assay. For proliferation assays, the cells were cultured and measured after 72 h, which is optimal for the HDF3CGF system, and the detailed procedure has been described in a previous study (Bergamini et al., 2012). Measurements were performed in triplicate wells, and a glossary of the biomarkers used in this study is provided in Supplementary Table S1.

Quantitative biomarker data are presented as the mean \log_{10} relative expression level (compared to the respective mean vehicle control value) \pm standard deviation of triplicate measurements. Differences in biomarker levels between CEO- and vehicle-treated cultures were tested for significance using the unpaired Student's *t*-test. A $p < 0.05$ outside of the significance envelope with an effect size of at least 10% (more than 0.05 \log_{10} ratio units), was considered statistically significant.

2.3. RNA isolation

Total RNA was isolated from cell lysates using the Zymo *Quick-RNA* MiniPrep kit (Zymo Research Corp., Irvine, CA, USA) according to the manufacturer's instructions. RNA concentration was determined using a NanoDrop ND-2000 system (Thermo Fisher Scientific, Waltham, MA, USA). The RNA quality was assessed using a Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA) and an Agilent RNA 6000 Nano kit. All samples had an A260/A280 ratio between 1.9 and 2.1 and an RNA integrity number score > 8.0 .

2.4. Microarray analysis of genome-wide gene expression

The effect of 0.011% CEO on the expression of 21,224 genes was evaluated in the HDF3CGF system after a 24-h treatment. The samples for microarray analysis were processed by Asuragen Inc. (Austin, TX, USA) according to the company's standard operating procedures. Biotin-labeled cRNA was prepared from 200 ng of total RNA by using an Illumina TotalPrep RNA amplification kit (Thermo Fisher Scientific) and one round of amplification. The cRNA yields were quantified using ultraviolet (UV) spectrophotometry, and the transcript size distribution was assessed using the Agilent Bioanalyzer 2100. Labeled cRNA (750 ng) was used to probe the Illumina human HT-12 v4 expression bead chips (Illumina Inc., San Diego, CA, USA). The hybridization, washing, staining with streptavidin-conjugated cyanine-3, and scanning of the Illumina arrays were carried out according to the manufacturer's instructions. The Illumina BeadScan software was used to produce the data files for each array, and the raw data were extracted using Illumina BeadStudio software.

The raw data were uploaded into R (R Development Core Team, 2011) and analyzed for quality control metrics using the bead array package (Dunning, Smith, Ritchie, & Tavaré, 2007). The data were normalized using quantile normalization (Bolstad, Irizarry, Astrand, & Speed, 2003), and then re-annotated and filtered to remove probes that were non-specific or mapped to intronic or intragenic regions (Barbosa-Morais et al., 2010). The remaining probe sets comprised the data-set for the subsequent analysis. The fold-change expression for each set was calculated as the \log_2 ratio of CEO to the vehicle control. These fold-change values were uploaded into the Ingenuity pathway analysis (IPA) program (Qiagen, Redwood City, CA, USA, www.qiagen.com/ingenuity) to generate the networks and pathway analyses.

2.5. Reagents

CEO (dōTERRA Intl., Pleasant Grove, UT, USA) was diluted with dimethyl sulfoxide (DMSO) to $8 \times$ the specified concentrations (final DMSO concentration in culture media was no more than 0.1% [v/v]) and 25 μL of each $8 \times$ solution was added to the cell culture to a final volume of 200 μL . DMSO (0.1%, v/v) served as the vehicle control. Gas chromatography-mass spectrometry (GC-MS) analysis of CEO indicated that its major chemical constituents (i.e. $>5\%$) were alpha terpinyl acetate (38%), 1,8-cineole (eucalyptol, 36%), and linalyl acetate (5%).

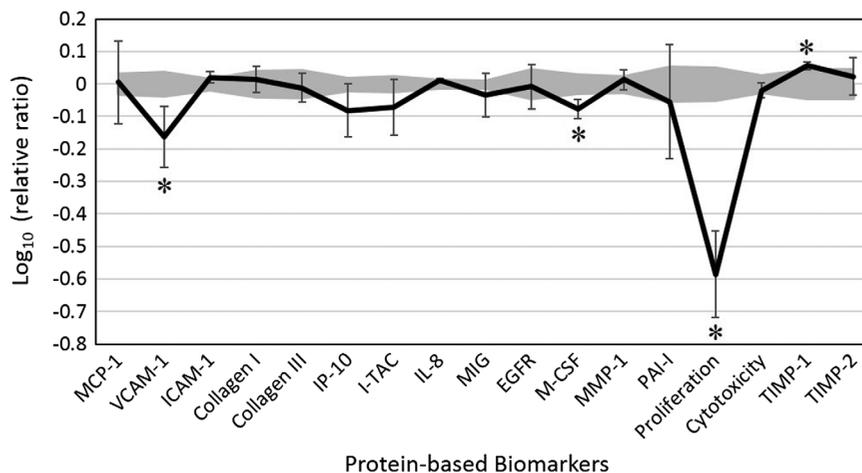
3. Results and discussion

3.1. Bioactivity profile of CEO in HDF3CGF system

We analyzed the activity of CEO in a dermal fibroblast cell culture HDF3CGF system, which comprised a microenvironment of human skin cells with a highly increased inflammation level. The four different concentrations of CEO (0.011, 0.0037, 0.0012, and 0.00041% [v/v]) initially analyzed for biological activity did not show any overt cytotoxicity, and therefore, the highest concentration (0.011%) was used for further analyses. Biomarkers were selected if their values were significantly different

Figure 1. Bioactivity profile of cardamom essential oil (CEO) 0.011% (v/v) in human dermal fibroblast culture (HDF3CGF).

Notes: X-axis denotes protein-based biomarker readouts. Y-axis denotes the relative expression levels of biomarkers compared to vehicle control values, in \log_{10} form. Vehicle control values are shaded in gray, denoting the 95% confidence level. *Indicates a biomarker designated with “key activity,” i.e., biomarker values were significantly different ($p < 0.05$) from vehicle controls outside the significance envelope with an effect size of at least 10% (more than 0.05 log ratio units). MCP-1, monocyte chemoattractant protein; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intracellular cell adhesion molecule 1; IP-10, interferon gamma-induced protein 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; IL-8, interleukin-8; MIG, monokine induced by gamma interferon; EGFR, epidermal growth factor; M-CSF, macrophage colony-stimulating factor; MMP-1, matrix metalloproteinase 1; PAI-1, plasminogen activator inhibitor 1; TIMP, tissue inhibitor of metalloproteinase.



($p < 0.05$) from those of the vehicle controls with an effect size of at least 10% (>0.05 log ratio units, Figure 1), and are discussed below.

CEO showed significant anti-proliferative activity against dermal fibroblasts. The inflammatory biomarker, vascular cell adhesion molecule 1 (VCAM-1), significantly and concentration-dependently decreased after CEO treatment. VCAM-1 mediates the adhesion of monocytes and T cells to endothelial cells in the inflammatory process. Macrophage colony-stimulating factor (M-CSF) levels were also significantly reduced by CEO. M-CSF is a secreted cytokine that mediates macrophage differentiation and is involved in immune modulation and tissue remodeling. Another molecule involved in tissue remodeling, tissue inhibitor of metalloproteinase 1 (TIMP1), was slightly increased by CEO treatment, which did not significantly affect the other studied biomarkers.

One major constituent of CEO, eucalyptol, has been extensively studied for its antioxidant and anti-inflammatory effects in various disease models (Bastos et al., 2011; Juergens, 2014; Khan et al., 2014; Kim, Lee, & Seol, 2015; Santos et al., 2004; Sudhoff et al., 2015; Takaishi, Uchida, Fujita, & Tominaga, 2014). The therapeutic potential of CEO may be largely attributed to eucalyptol. A study (Zhao et al., 2014) in mice showed that eucalyptol suppressed lipopolysaccharide-induced proinflammatory cytokine production through the actions of nuclear factor (NF)- κ B, TNF- α , IL-1 β , and IL-6. Another recent study (Lee et al., 2016) showed that eucalyptol inhibited the production of IL-4, IL-13, and IL-17A in bronchoalveolar lavage fluid after *Dermatophagoides pteronyssinus* (Der p) challenge of human bronchial epithelial cells, suggesting that eucalyptol also suppresses Der p-induced IL-8, IL-6, and M-CSF production. Consistent with existing studies, our current study demonstrated the inhibitory effect of CEO on VCAM-1 and M-CSF in inflamed human dermal fibroblasts, supporting the anti-inflammatory and immunomodulatory properties of CEO (and presumably that of its major component, eucalyptol). Additionally, the robust, anti-proliferative activity of CEO may have implications in tissue remodeling processes and, thus, skin health.

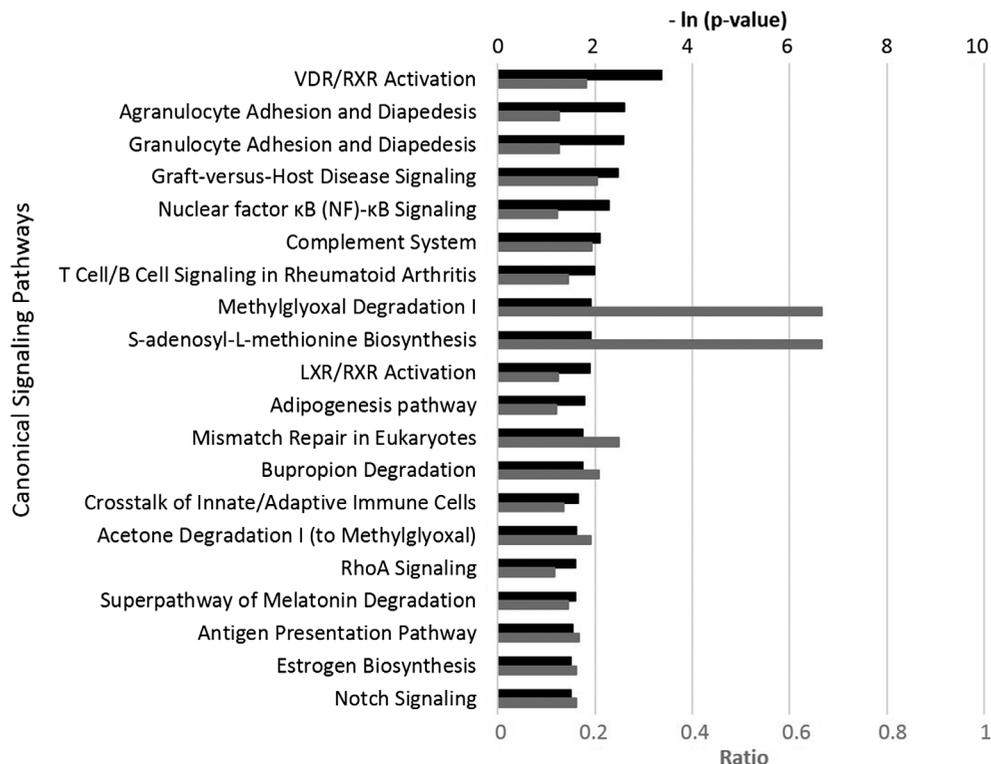
3.2. Effects of CEO on genome-wide gene expression in HDF3CGF system

To further explore its biological activities, we studied the effect of 0.011% CEO (the highest tested noncytotoxic concentration) on the RNA expression of 21,224 genes in the HDF3CGF system. Among the top 49 genes affected by CEO (with an absolute value of the ratio of expression to vehicle control ≥ 1.5), approximately half of them (22 out of 49) were significantly downregulated (Table S2). It is noteworthy that a cross comparison of the results indicated that CEO significantly inhibited both VCAM-1 protein and gene expression levels.

IPA showed that the bioactivity of CEO significantly overlapped with that of numerous canonical signaling pathways from the literature-validated database (Figure 2). Many of these pathways are

Figure 2. Top 20 canonical pathways matching bioactivity profile of cardamom essential oil (CEO) 0.011% (v/v) in gene expression in HDF3CGF system produced using ingenuity pathway analysis (IPA, Qiagen, www.qiagen.com/ingenuity).

Notes: Each p -value was calculated using the right-tailed Fisher's Exact Test. The p -value measures the likelihood that the observed association between a specific pathway and the data-set is due to random chance. The smaller the p -value (the bigger $-\ln(p\text{-value})$, indicated by the black bars) of the pathway, the more significantly it matches the bioactivity of CEO. A ratio, indicated by each gray bar, was calculated by dividing the number of genes from the CEO data-set that participate in a canonical pathway by the total number of genes in that pathway. VDR, vitamin D receptor; RXR, retinoid X receptor; LXR, liver X receptor; RhoA, Ras homolog gene family member A.



critically involved in inflammatory, immune response, and tissue remodeling processes. The overall inhibitory effect of CEO on these pathways and critical genes highly supports its anti-inflammatory and immunomodulatory properties (See Supplementary Material for more information).

Eucalyptol, a major active component of CEO, has been shown to suppress the action of NF- κ B and numerous cytokines in several settings (Khan et al., 2014; Kim et al., 2015; Seol & Kim, 2016). This is consistent with the results of our present study, where CEO significantly affected the NF- κ B signaling pathway and many other critical pathways closely involved in inflammatory and immune responses (Figure 2). Collectively, the results of our study provide the first evidence to support the anti-inflammatory and immunomodulatory properties of CEO in human dermal fibroblasts. Further research is needed to extensively reveal the biological mechanism of action of CEO in human cells.

This study has some limitations worth mentioning. The *in vitro* study results cannot be directly translated to more complex human skin systems. The effect of CEO on genome-wide gene expression was evaluated after a short-term treatment intervention. However, the mechanisms underlying the long-term effects of CEO on global gene expression are still unclear. Nevertheless, based on the protein and gene expression data, this study provides important evidence of the biological effect of CEO on human skin cells, and will likely encourage further research into the mechanisms of action of CEO.

4. Conclusions

This study showed that CEO significantly inhibited the production of VCAM-1 and M-CSF in an *in vitro* skin disease model. CEO also showed significant anti-proliferative activity against skin cells and robustly affected various important genes and signaling pathways. This study provides the first evidence of biological activities of CEO in human skin cells, and consistent with the findings of existing studies, and these results support the anti-inflammatory and immunomodulatory potential of CEO.

Supplemental data

Supplemental data for this article can be accessed at <http://dx.doi.org/10.1080/2331205X.2017.1308066>.

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Competing Interest

X.H. and T.P. are employees of dōTERRA, where the study agent CEO was manufactured.

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