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In vitro effects of Caffeic Acid Phenethyl Ester (CAPE) on preeclamptic serum-induced endothelial dysfunction

Preeklamptik serum ile indüklenen endotel disfonksiyonunda Kafeik Asit Fenetil Esterin (CAPE) in vitro etkileri

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ABSTRACT

Aim: The aim of study was to evaluate the potential protective effects of caffeic acid phenethyl ester (CAPE), one of the major bioactive components of propolis, within an *in vitro* model of preeclampsia-induced endothelial dysfunction.

Materials and Methods: An *in vitro* endothelial dysfunction was modeled by treating Human Umbilical Vein Endothelial Cells (HUVECs) with serum from preeclamptic women (PE) and endothelial responses were then compared to normotensive pregnancy serum (N) and fetal bovin serum (FBS), which functioned as physiological and standard controls, respectively. To evaluate the effects of CAPE on PE serum-induced endothelial dysfunction, non-cytotoxic concentrations were first determined via the PrestoBlue cell viability assay. Based on these results, 10 and 25 μM CAPE were selected for subsequent experiments. The migratory and angiogenic capabilities of HUVECs were analyzed via wound healing and tube formation experiments to investigate the protective role of CAPE against preeclampsia-associated endothelial impairment.

Results: Exposure to PE serum led to a significant reduction in HUVEC viability compared to FBS and N control groups. CAPE treatment at 10 and 25 μM did not significantly alter cell viability in PE serum treated HUVECs. In functional assays, PE serum markedly impaired both endothelial migration and tube formation capacity. CAPE treatment significantly attenuated these impairments, as evidenced by enhanced wound closure and restored angiogenic tube formation in PE-treated HUVECs.

Conclusions: Our data demonstrate that CAPE treatment effectively counteracts PE serum-mediated endothelial impairment by promoting cell migration and angiogenic tube formation. These observations highlight the potential role of CAPE in maintaining endothelial integrity during preeclamptic conditions.

Keywords: Preeclampsia, endothelial dysfunction, Caffeic Acid Phenethyl Ester (CAPE)

ÖZ

Amaç: *Bu çalışmanın amacı, propolisin aktif bileşenlerinden biri olan kafeik asit fenetil esterin (CAPE), preeklampsi tanısı almış gebelerden elde edilen serum ile indüklenen in vitro endotel disfonksiyon modelinde endotel hücre fonksiyonları üzerindeki etkilerini araştırmaktır.*

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Gereç ve Yöntem: *Preeklampsi tanısı almış kadınlardan elde edilen %10 oranındaki serum (PE) kullanılarak HUVEC'lerde in vitro endotel disfonksiyon modeli oluşturuldu ve endotel hücre yanıtları %10 fetal bovine serum (FBS) ve normotansif gebelerden elde edilen %10 serum (N) ile kültüre edilen hücrelerle karşılaştırıldı. Kafeik asit fenetil esterin PE ile indüklenen endotel disfonksiyonu üzerindeki etkilerini değerlendirmek amacıyla, sitotoksik olmayan CAPE dozları PrestoBlue hücre canlılığı testi ile belirlendi ve elde edilen sonuçlara göre 10 ve 25 μM CAPE konsantrasyonları seçildi. Endotel hücre fonksiyonları, PE ile indüklenen endotel disfonksiyonu koşullarında CAPE'nin koruyucu etkilerini değerlendirmek amacıyla yara iyileşme (migrasyon) ve tüp oluşumu deneyleri ile analiz edildi.*

Bulgular: *HUVEC'lerin PE serum ile muamelesi, FBS ve N gruplarıyla karşılaştırıldığında hücre canlılığını azalttı. PE ile muamele edilen HUVEC'lerde 10 ve 25 μM CAPE uygulaması hücre canlılığında istatistiksel olarak anlamlı bir değişikliğe yol açmadı. Fonksiyonel deneylerde, PE serum endotel migrasyonunu ve tüp oluşum kapasitesini belirgin şekilde bozdu. CAPE uygulaması, PE serum ile muamele edilen HUVEC'lerde yara kapanmasını ve anjiyojenik tüp oluşumunu anlamlı şekilde artırdı.*

Sonuç: *CAPE, preeklamptik seruma maruz bırakılan endotel hücrelerinde migrasyon ve tüp oluşumunu artırarak, PE serum ile indüklenen endotel fonksiyon bozukluklarını iyileştirmiştir. Bu bulgular, CAPE'nin preeklampsi koşullarında endotel bütünlüğünün korunmasında potansiyel bir role sahip olabileceğini göstermektedir.*

Anahtar Sözcükler: *Preeklampsi, endotel disfonksiyon, Kafeik asit fenetil ester (CAPE)*

INTRODUCTION

Preeclampsia is a prevalent pregnancy complication that affects approximately 2–10% of pregnancies worldwide. Preeclampsia is a multisystemic pregnancy complication emerging after the 20th week of gestation, clinically identified by new-onset hypertension and proteinuria (1,2). The pathogenesis is primarily driven by maternal endothelial impairment, resulting from a disrupted equilibrium between pro-angiogenic proteins (VEGF and PlGF) and anti-angiogenic antagonists (sFlt-1 and sEng). Furthermore, the release of inflammatory cytokines, reactive oxygen species (ROS), and angiotensin AT1 receptor autoantibodies into the systemic circulation exacerbates vascular damage. These combined molecular disturbances target the maternal endothelium, leading to widespread functional failure (3,4). Preeclampsia-related vascular alterations have been explored through various *in vitro* systems including standard Human Umbilical Vein Endothelial Cells (HUVECs) cultures, endothelial cells isolated from preeclamptic patients, and endothelial cell lines generated from patient-derived induced pluripotent stem cells (iPSCs). These models consistently demonstrate functional defects, characterized by a marked decline in cell migration and angiogenic potential.(5-7). Consequently, these *in vitro* models serve as essential experimental tools to investigate the underlying cellular mechanisms and evaluate the efficacy of novel protective agents against endothelial dysfunction in preeclampsia.

Caffeic acid phenethyl ester (CAPE), one of the major bioactive components of propolis, possesses potent antioxidant and anti-inflammatory properties (8,9). Previous experimental studies have demonstrated that CAPE suppresses reactive oxygen species production, modulates nitric oxide synthesis, and exerts protective effects on endothelial cell functions (10-14). These biological properties suggest that CAPE may have the potential to alleviate endothelial dysfunction associated with preeclampsia. Thus, the purpose of this study was to evaluate the effects of CAPE on endothelial cell functions in an *in vitro* endothelial dysfunction model induced by preeclamptic serum.

MATERIALS and METHODS

The study protocol was approved by the Non-Interventional Scientific Research Ethics Committee of Tokat Gaziosmanpaşa University (Approval No: 26-MOBAEK-031). Venous blood was obtained from 9 patients with preeclampsia and 10 normotensive pregnant controls. To isolate the serum, samples underwent centrifugation at 1500 ×g for a duration of 10 minutes, with the resulting supernatant being preserved at -80 °C for subsequent analysis.

Cell Culture

HUVECs were grown in a humidified environment at 37 °C with 5% CO_2, utilizing DMEM/F12

(DMEM-12-A, Capricorn, Germany) as the culture medium. This medium was prepared by adding 10% fetal bovine serum (FBS) (FBS-11B, Capricorn, Germany) and 1% antibiotic-antimycotic solution (AAS-B, Capricorn, Germany). To ensure experimental reproducibility, cells from early passages (P3–P6) were used in the study.

Characterization of HUVECs by CD31 Immunofluorescence

Cells were collected via enzymatic treatment with 0.25% Trypsin-EDTA (Capricorn, Germany) and subsequently distributed onto positively charged glass coverslips at 2 × 10^6 cells/mL. Cells were fixed with cold methanol and subsequently blocked with a protein blocking solution for 45 minutes. To visualize CD31 expression, cells were initially treated with a primary antibody (PA5-32321, Invitrogen, USA) overnight at 4 °C. Following this, a fluorescent secondary antibody was applied for 60 min at room temperature. Coverslips were mounted with a fluorescence mounting reagent including DAPI for nuclear visualization (GTX30920, GeneTex, USA) and images were acquired with a fluorescence microscope (Eclipse E600, Nikon, Germany).

Experimental design

HUVECs were assigned to three experimental groups based on the culture media: (i) 10% FBS, (ii) 10% serum from preeclamptic women (PE), and (iii) 10% serum from normotensive pregnant women (N). To investigate the potential effects of CAPE on PE-induced endothelial dysfunction, non-cytotoxic concentrations of CAPE were applied to HUVEC cultures exposed to different serum treatments. Endothelial cell functions were subsequently evaluated using cell viability, wound healing (migration), and tube formation assays. All experiments were performed in triplicate.

Determination of Non-Cytotoxic CAPE Concentrations

Prior to experimental treatments, the cytotoxic effects of CAPE on HUVECs were evaluated to determine safe working concentrations. HUVECs (1 × 10^4 cells/well) were seeded in 96-well plates and treated with CAPE (1–50 µM) for 24 h. A 50 mM stock of CAPE (70750, Cayman Chemical, USA) in DMSO (M6323, Gennaxon, Germany) was used for dilutions. Post-treatment, cell viability was then determined using the PrestoBlue assay (A13261, Thermo Fisher Scientific, USA). Optical density was measured at 570 nm, and results were calculated as a percentage of the control. CAPE concentrations maintaining cell viability above 80% were considered non-cytotoxic and selected for following experiments.

Assessment of CAPE's Impact on Endothelial Cell Survival within a Preeclamptic Serum-Induced Dysfunction Model

Based on cytotoxicity screening results and previous literature, CAPE concentrations of 10 and 25 µM were selected to evaluate its protective effects against PE serum-induced endothelial dysfunction. For the viability assay, approximately 1 × 10^4 HUVECs were placed in each well of 96-well plates. After allowing the cells to attach, cells were cultured for 24 hours in medium containing 10% FBS, 10% PE serum, or 10% N serum and CAPE was applied at concentrations of 10 and 25 µM under the indicated conditions. At the end of the treatment period, 10 µL of PrestoBlue reagent was added to each well, followed by an additional 30 min incubation at 37 °C. Optical density was then recorded at 570 nm using a microplate reader. Finally, cell viability was calculated and expressed as a percentage relative to the untreated control group.

Evaluation of the Effects of CAPE on Endothelial Cell Functions

Wound Healing Assay

To perform cell migration assay, HUVECs were seeded into 12-well plates at a density of 2 × 10^5/well and grown until reaching nearly 80% confluence. A linear gap was then created in the cell monolayer using a sterile 200 µL tip. To ensure the removal of floating cells, the wells were rinsed twice with DPBS (PBS-10XA, Capricorn, Germany). The cells were subsequently maintained for 24 hours in media containing 10% FBS, 10% PE serum, or 10% N serum, either with or without CAPE. Wound closure was monitored by capturing images at 0 and 24 hours using an inverted microscope. The migratory response was quantified by measuring the change in the wound area using ImageJ software.

Tube Formation Assay

To assess the angiogenic capacity of HUVECs, a tube formation assay was performed. Initially, 96-well plates were pre-coated with 50 µL of Matrigel (354230, Corning, USA), which was left to solidify for 30 minutes at 37 °C. Following polymerization,

HUVECs were inoculated onto the Matrigel surface at a density of 2.5 × 10^4 cells per well. The cells were then maintained in media supplemented with either 10% FBS, 10% PE serum, or 10% N serum

In CAPE treatment groups, CAPE was applied at concentrations of 10 and 25 µM under the same serum conditions. Tube formation was visualized under an inverted microscope and images were acquired after 8 hours of incubation. Quantitative analysis of tube formation was performed using ImageJ software by measuring total segments length and the number of meshes within the network.

Statistical Analysis

All experimental results (viability, migration, and tube formation) are presented as mean ± SE. Inter-group variations were assessed through one-way ANOVA with Bonferroni correction. Results reaching a p-value < 0.05 were acknowledged as significant.

RESULTS

Immunofluorescence staining confirmed the endothelial phenotype of cultured HUVECs by positive CD31 expression (Figure-1). Following the confirmation of endothelial identity, the effects of CAPE on HUVEC viability were evaluated.

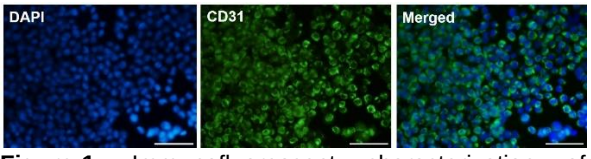

Figure-1. Immunofluorescent characterization of HUVECs via CD31 staining. HUVEC identity was confirmed by immunofluorescence staining of the endothelial marker CD31. Cell nuclei were visualized with DAPI. Scale bar: 50 µm.

CAPE Maintains Endothelial Integrity at Non-Cytotoxic Concentrations

The cytotoxicity profile of CAPE on HUVECs was established across a range of 1 to 50 µM via the PrestoBlue assay in order to determine non-cytotoxic working concentrations for subsequent experiments. Initial assessments indicated that doses of 1 and 5 µM did not alter cell survival rates relative to the control. While a marginal increase in viability was noted at 10 µM CAPE, this change failed to reach statistical significance. Conversely, exposure to 50 µM CAPE resulted in a significant decline in cell viability, with an approximate reduction of 22% compared to untreated cells ($p = 0.015$) (Figure-2). Consequently, 10 and 25 µM were identified as the highest non-cytotoxic concentrations and were selected for subsequent experimental procedures to ensure sufficient biological activity without compromising cell viability.

Assessment of HUVEC viability under various serum conditions revealed a decrease in survival rates within the PE serum group compared to both the FBS and N groups ($p < 0.001$). In contrast, no statistically significant difference was detected between the FBS and N groups. The effects of the selected CAPE concentrations (10 and 25 µM) on HUVEC viability were further examined under FBS, N, and PE serum conditions, and no significant change in cell viability was observed following CAPE treatment in any of the groups (Figure-3).

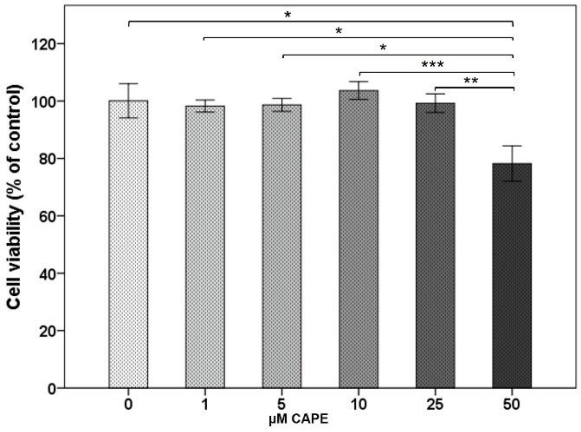

Figure-2. Determination of optimal CAPE concentrations in HUVECs. HUVECs were exposed to 1, 5, 10, 25, and 50 µM concentrations of CAPE and cell viability was assessed via PrestoBlue assay. Data are presented as percent of control (mean ± SE). $p < 0.05$ (*), $p < 0.01$(**), $p < 0.001$ (***).

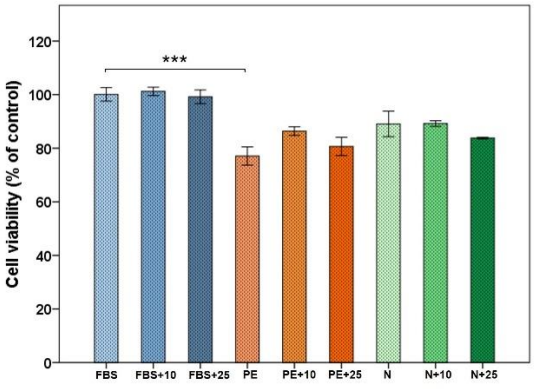

Figure-3. Effect of 10 and 25 µM CAPE on the viability of HUVECs treated with FBS, PE, and N serum. Data are expressed as means ± SE. $p < 0.001$ (***).

CAPE Enhances the Migratory Ability of PE-induced HUVECs

Quantitative analysis of the wound healing assay demonstrated that endothelial migration was significantly reduced in HUVECs treated with PE serum compared with the FBS and N groups ($p < 0.001$ for both comparisons) (Figure-4A). In PE-induced HUVECs, administration of 10 µM CAPE significantly promoted the wound closure process ($p = 0.043$) (Figure-4B). In HUVECs cultured with FBS or N serum, CAPE supplementation at 10 and 25 µM exerted no significant influence on the on the migratory capacity of the cells (Figure-4C).

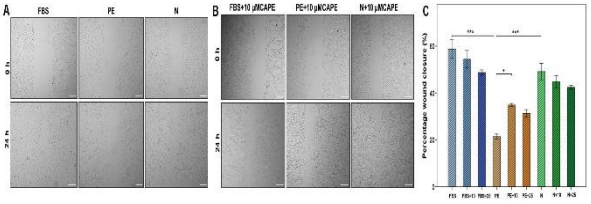

Figure-4. Effect of CAPE on HUVEC migration under FBS, PE, and N serum conditions in the scratch wound healing assay. (A) Representative micrographs showing wound closure in HUVECs treated with FBS, PE, and N at 0 and 24 h. (B). Representative micrographs showing wound closure in HUVECs treated with FBS, PE, and N serum in the presence of 10 µM CAPE. (C) Quantification of percentage wound closure. Data are expressed as mean ± SE. Significance levels are indicated as $p < 0.05$ (*), $p < 0.001$ (***). Scale bar: 200 µm.

Restoration of Endothelial Tube Formation by CAPE Treatment

Quantitative assessment of the tube formation assay demonstrated that PE serum significantly compromised the angiogenic potential of HUVECs. This was evidenced by a substantial decline in both mesh number and total segment length compared to the FBS and N control groups (mesh number: $p < 0.001$ for both comparisons; total segment length: $p < 0.001$ vs. FBS and $p = 0.005$ vs. N). Importantly, no discernible difference was found between the FBS and N groups, confirming the specific inhibitory effect of PE serum.

Notably, CAPE treatment effectively rescued the impaired angiogenic phenotype induced by PE serum. At concentrations of 10 and 25 µM, CAPE led to a robust restoration of both mesh number ($p = 0.008$ and $p = 0.006$, respectively) and total segment length ($p = 0.042$ and $p = 0.026$, respectively). Morphological evaluation further supported these findings, revealing improved network organization and enhanced cell density within the intertubular areas following CAPE administration, with no significant variation between the two dosage groups.

In contrast, CAPE supplementation (10 and 25 µM) in HUVECs cultured with N serum did not significantly alter the quantitative tube parameters. However, qualitative observations suggested that tubular structures appeared wider particularly in the N + 25 µM CAPE group (Figure-5). Collectively, these results indicate that while CAPE has a neutral effect under healthy conditions, it possesses a potent protective capacity against PE-induced disruption of the endothelial capillary-like network.

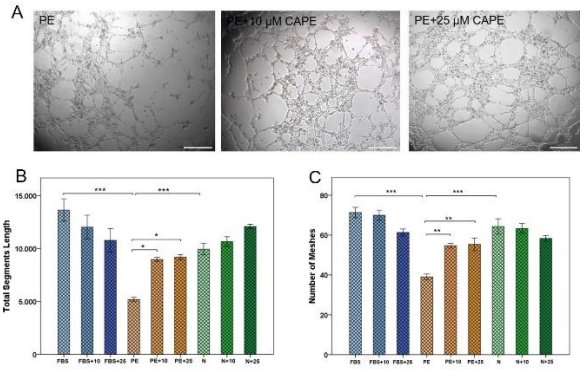

Figure-5. Effects of CAPE on tube formation in HUVECs cultured with FBS, PE, and N serum. (A) Representative tube formation images of PE group (B) Quantification of total segment length (C) Quantification of the number of meshes. Data are expressed as mean ± SE. Significance levels are indicated as $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Scale bar: 200 µm.

DISCUSSION

In the present study, we investigated endothelial cell functions in an *in vitro* model of PE serum-induced endothelial dysfunction and evaluated the effects of CAPE on endothelial cell behavior.Our data demonstrate that PE serum exposure not only compromises HUVEC viability but also induces a profound impairment in migratory and tube-forming capacities. Importantly, CAPE treatment significantly rescued these functional deficits in PE serum treated HUVECs. Our findings represent the first report describing the effects of CAPE in an *in vitro* endothelial dysfunction model generated by PE serum.

Maternal endothelial dysfunction is widely recognized as a pathophysiological hallmark of preeclampsia (3,4). To investigate the

mechanisms underlying this process, conventional HUVEC cultures, endothelial cells isolated from preeclamptic pregnancies, and patient-specific endothelial cells derived from iPSCs have been used to investigate the endothelial alterations associated with preeclampsia. In one study, treatment of HUVECs with 10% PE serum resulted in a significant decrease in cell viability, which was attributed to increased apoptotic activity (5). HUVECs isolated from preeclamptic pregnancies have been reported to exhibit reduced migration and tube formation capacity without a significant change in proliferation compared with cells obtained from healthy pregnancies (6). In another study designed to investigate patient-specific mechanisms, endothelial cells differentiated from iPSC obtained from normotensive pregnancie were exposed to maternal sera obtained from both preeclamptic and normotensive pregnancies. Within this model, exposure to PE serum did not significantly affect endothelial cell viability. Although endothelial cell viability was not significantly affected, PE serum significantly impaired endothelial wound closure and tube formation capacity (7). These observations suggest that the impact of PE serum on endothelial viability may be model-specific. While conventional HUVEC cultures often show reduced survival following PE serum exposure, studies utilizing patient-specific or pregnancy-isolated endothelial cells frequently report preserved viability despite significant functional impairments. This divergence can likely be attributed to differences in cellular origin or intrinsic adaptive mechanisms to the circulating factors found in PE serum. In our study, PE serum led to a modest reduction in HUVEC viability, alongside a marked suppression of migration and tube formation. This reinforces the consensus that PE serum induces a profound state of endothelial dysfunction. Caffeic acid phenethyl ester (CAPE), a prominent bioactive derivative of propolis, is well-recognized for its antioxidant, anti-inflammatory, and cytoprotective activities across diverse cellular environments (8,9). However, its potential effects on endothelial dysfunction associated with preeclampsia remain largely unexplored. In our study, CAPE administration at 10 and 25 μM significantly restored the migratory and angiogenic capacity of HUVECs exposed to PE serum, suggesting a robust protective effect.

Preeclampsia is characterized by increased oxidative stress and inflammatory signaling, both of which contribute to endothelial injury and impaired endothelial function. Although the direct molecular pathways were not elucidated in the present study, the functional recovery observed following CAPE treatment aligns with its established roles in other oxidative stress models. For instance, in a menadione-induced oxidative stress model, 17.6 μM CAPE restored approximately 65% of the oxidative stress-induced loss in cell viability, and CAPE at 20 μM significantly reduced intracellular ROS levels in HUVECs (10). Similarly, another study using a menadione-induced oxidative stress model demonstrated that CAPE and its derivatives at 20 μM exerted cytoprotective effects and reduced ROS levels (11). Consistently, our study demonstrated that 10 and 25 μM CAPE improved migration and tube formation in preeclamptic serum-induced HUVECs, suggesting that these concentrations may contribute to the restoration of endothelial function under conditions of increased oxidative stress. The consistency of our effective dose range with previous reports further supports the potential of CAPE at these concentrations without evident cytotoxicity. Furthermore, in endothelial injury models triggered by homocysteine or ox-LDL, propolis-derived compounds have been reported to attenuate lipid peroxidation and modulate apoptotic signaling-specifically by downregulating Bax and inhibiting caspase activation (12–14). Given that PE serum is known to contain a complex mixture of pro-oxidant factors, it is highly probable that CAPE exerts its protective effects in our model by neutralizing oxidative stress and stabilizing endothelial survival pathways.

These results indicate that CAPE enhances endothelial functional responses without markedly altering cell viability, suggesting that its protective effects are primarily driven by the modulation of intracellular signaling rather than the stimulation of cell proliferation. Considering that oxidative stress is a central hallmark of preeclampsia pathophysiology, these observations further suggest that CAPE alleviates PE-induced endothelial dysfunction through its potent antioxidant and cytoprotective properties. Collectively, this study highlights CAPE as a promising agent for preserving endothelial function, though further research into specific

pathways is required to fully elucidate its therapeutic mechanism.

CONCLUSION

In conclusion, the present study demonstrates that PE serum exposure compromises the migratory and angiogenic capacity of HUVECs, providing an *in vitro* model that reflects endothelial dysfunction observed in preeclampsia. Our findings reveal that CAPE treatment effectively restores these essential endothelial functions without inducing significant changes in cell viability. While the underlying molecular pathways remain to be fully elucidated, the observed functional recovery is likely mediated by the potent antioxidant and cytoprotective properties of CAPE. By identifying CAPE as a potential modulator of endothelial function, this study provides a basis for future studies investigating the underlying signaling pathways and its possible therapeutic relevance in preeclampsia.

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Conflicts of interest: Authors declared no conflict of interest.

Ethics statement: This study was approved by the Non-Interventional Scientific Research Ethics Committee of Tokat Gaziosmanpaşa University (Approval No: 26-MOBAEK-031).

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