Türkiye Klinikleri Diş Hekimliği Bilimleri Dergisi
*Turkiye Klinikleri Journal of Dental Sciences*
Turkiye Klinikleri J Dental Sci. 2022;28(4):883-9

ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/dentalsci.2022-93042

# Effect of Caffeic Acid Phenethyl Ester on Gingival Tissue Inflammation in Experimental Periodontitis: Experimental Study

## Deneysel Periodontitiste Kafeik Asit Fenetil Esterin Diş Eti Doku İnflamasyonuna Etkisi: Deneysel Çalışma

Esra DEMİR[a], Feyza OTAN ÖZDEN[b], Bahattin AVCI[c]

[a]Department of Periodontology, Bezmiâlem Vakıf University Faculty of Dentistry, İstanbul, Türkiye
[b]Department of Periodontology, Ondokuz Mayıs University Faculty of Dentistry, Samsun, Türkiye
[c]Department of Biochemistry, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye

*This study was presented as an oral presentation at EuroPerio 9, June 20-23, 2018, Amsterdam, Netherlands.*

**ABSTRACT Objective:** This study aimed to investigate the anti-inflammatory effect of two different dosages of caffeic acid phenethyl ester (CAPE) on lipopolysaccharide-induced experimental periodontitis (EP). **Material and Methods:** Forty Sprague Dawley rats were randomly divided into four groups: control, EP, EP treated with 5 µmol/kg/day of CAPE (EP+CAPE 5), and EP treated with 10 µmol/kg/day of CAPE (EP+CAPE 10). Followed by the EP, CAPE was administered intraperitoneally to the EP+CAPE groups for 28 days. Samples were investigated biochemically using an enzyme-linked immunosorbent assay kit and alveolar bone loss was measured morphometrically. **Results:** In both of the CAPE groups, the levels of interleukin-1 beta and tumor necrosis factor alpha (TNF-α) in the gingiva were significantly lower than those in the EP group ($p<0.001$). The decrease in tissue levels of TNF-α was greater in the EP+CAPE 10 group than in the EP+CAPE 5 group in a dose-dependent manner. Serum analysis of the cytokines showed no significant difference between the groups. **Conclusion:** Within the limits of this study, CAPE showed an anti-inflammatory effect and is claimed to be a novel agent in improving the results of periodontal therapy. CAPE may be valuable as an alternative host modulating agent for the treatment of periodontal disease.

**Keywords:** Caffeic acid phenethyl ester; periodontal diseases; interleukin-1 beta; tumor necrosis factor-alpha

**ÖZET Amaç:** Bu çalışma, 2 farklı dozda kafeik asit fenetil esterin (KAFE) lipopolisakkarit ile indüklenen deneysel periodontitis (DP) üzerindeki antiinflamatuar etkisini araştırmayı amaçlamıştır. **Gereç ve Yöntemler:** Kırk Sprague Dawley sıçanı rastgele 4 gruba ayrılmıştır: kontrol, DP, 5 µmol/kg/gün KAFE ile tedavi edilen DP (DP+KAFE 5) ve 10 µmol/kg/gün KAFE ile tedavi edilen DP (DP+KAFE 10). DP'yi takiben DP+KAFE gruplarına 28 gün süreyle intraperitoneal olarak KAFE uygulanmıştır. Numuneler, enzim bağlı immünosorbent tahlil kiti kullanılarak biyokimyasal olarak araştırılmış ve alveolar kemik kaybı morfometrik olarak ölçülmüştür. **Bulgular:** Her iki KAFE grubunda da diş eti interlökin-1 beta ve tümör nekroz faktörü-alfa (TNF-α) seviyeleri DP grubuna göre anlamlı derecede düşük bulunmuştur ($p<0,001$). TNF-α'nın doku seviyelerindeki düşüş, doza bağlı bir şekilde DP+KAFE 5 grubuna göre DP+KAFE 10 grubunda daha fazla olmuştur. Sitokinlerin serum analizi, gruplar arasında anlamlı bir farklılık göstermemiştir. **Sonuç:** Bu çalışmanın sınırları dâhilinde, KAFE'nin antiinflamatuar etkisi gösterilmiş ve periodontal tedavinin sonuçlarını arttırmada etkili bir ajan olabileceği ileri sürülmüştür. KAFE, periodontal hastalığın tedavisi için alternatif bir konak modüle edici ajan olarak değerli olabilir.

**Anahtar Kelimeler:** Kafeik asit fenetil ester; periodontal hastalıklar; interlökin-1 beta; tümör nekroz faktörü-alfa

Periodontitis is a chronic inflammatory disease initiated by specific plaque bacteria, resulting in gradual breakdown of supporting tissues.[1] The complex interaction between dental plaque bacteria and the host immune response induces production of inflammatory mediators such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), which are well-investigated markers that act to induce breakdown of periodontal tissues.[2] Levels of these mediators have been shown to be elevated in inflamed sites in comparison to healthy sites in both gingival tissue and gingival crevicular fluid.[3,4] Inhibition of IL-1β and TNF-α resulted in decreases in tissue breakdown and alveolar bone resorption, and antagonists of these cytokines have been reported to be potential therapeutic choices for blocking the periodontal disease process.[5]

**Correspondence:** Feyza OTAN ÖZDEN
Department of Periodontology, Ondokuz Mayıs University Faculty of Dentistry, Samsun, Türkiye
**E-mail:** feyza_otan@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Dental Sciences.

***Received:*** 23 Aug 2022 ***Received in revised form:*** 19 Sep 2022 ***Accepted:*** 19 Sep 2022 ***Available online:*** 20 Sep 2022

Host modulation therapies aim to inhibit the proinflammatory aspect of the host response as well as to increase anti-inflammatory responses. For this purpose, anti-inflammatory drugs, bone-stimulating agents, and antiproteases have been tested against periodontal diseases.[6,7] Due to the potential side effects of prolonged use of host modulators, there is now growing interest in natural products with antibacterial and anti-inflammatory effects as well as fewer side effects for periodontitis treatment.[8-12]

Caffeic acid phenethyl ester (CAPE), an active component of honeybee propolis extracts, has beneficial properties such as antibacterial, antioxidant, antitumor, anti-inflammatory, and immunomodulatory activity without any known harmful side effects.[13-16] It is commercially sold as a white powder, soluble in ethyl acetate and ethanol. CAPE has been shown to reduce proinflammatory cytokines and has antiapoptotic activity by suppressing NF-kb activation.[16,17] Dietary intake of CAPE has been suggested as an alternative therapeutic strategy for treatment of allergic disorders, bronchial asthma, and metabolic alterations caused by obesity and for prevention of atherosclerosis.[18-20] In previous in vivo studies, the anti-inflammatory and antioxidant properties of CAPE have been shown to prevent the occurrence of experimental periodontitis (EP).[21-24] However, the effects of CAPE on tissue destruction and proinflammatory responses after periodontitis has occurred are still unknown. Moreover, no studies have investigated the dose-dependent effect of CAPE on EP.

Therefore, the aim of the present study was to elucidate the immunomodulatory effect of two different dosages of CAPE on alveolar bone loss, gingival tissue, and serum levels of IL-1β and TNF-α in rats with EP.

## MATERIAL AND METHODS

### ANIMALS AND EXPERIMENTAL DESIGN

The study protocol was approved by the Ondokuz Mayıs University Ethics Committee for Animal Experimentation (no: July 24, 2014, no: 2014/29) and all the experimental procedures were conducted in accordance with the standard established guidelines of the Laboratory Animal Care Committee of the Faculty of Medicine and the Helsinki Declaration for experimental studies. All experimental procedures were performed at Ondokuz Mayıs University Laboratory of Experimental Animals Research Center. The biochemical analysis was carried out in Ondokuz Mayıs University Faculty of Medicine Department of Medical Biochemistry.

Forty adult (6-7 weeks old) male Sprague Dawley rats (≈125 to 150 g) were housed with food and water *ad libitum* at constant room temperature (22±1 °C) under a 12-h light/dark cycle in individual cages. The rats were randomly divided into four groups of ten animals each: control, EP, EP treated with 5 μmol/kg/day of CAPE (EP+CAPE 5), and EP treated with 10 μmol/kg/day of CAPE (EP+CAPE 10) based on our previous study with a similar design.[24] Proinflammatory cytokine profiles of gingival tissues were evaluated according to the IL-1β and TNF-α alterations in healthy and diseased conditions. Alveolar bone loss was measured morphometrically. For all invasive and surgical interventions, the animals were anesthetized with ketamine-HCl (75 to 100 mg/kg intraperitoneal injection) and xylazine-HCl (5 mg/kg intraperitoneal injection) sedation.

### INDUCTION OF EP

EP was induced in the left maxillary molar teeth of all rats except the control group using an endotoxin-induction model.[25,26] A commercially available *Porphyromonas gingivalis* lipopolysaccharide (LPS) (Invivogen, San Diego, CA, USA) was injected into the palatal gingiva between the first and second maxillary molars on the left side as 10 μl of endotoxin solution (1 mg/mL prepared in saline) every other day for 5 days (three injections in total). Saline was injected into the control rats in the same way and at the same times. The injections were administered using an insulin syringe equipped with a blunted edge 30-gauge needle. Periodontitis induction was verified by radiographs taken 24 days after the last injection.

### PREPARATION AND ADMINISTRATION OF CAPE

CAPE was obtained from Sigma-Aldrich (C8221, St Louis, MO, USA), dissolved in ethanol, and subsequent dilutions were made using saline (0.9% NaCl,

w/v). Weights of the rats were determined with precision weighing scales (Precisa XB 220 A, Dietikon, Switzerland). After EP induction, the EP group did not receive any treatment, while the EP+CAPE 5 and EP+CAPE 10 groups continued with CAPE injections until the end of the experiment. CAPE in dosages of 5 and 10 µmol/kg/day was intraperitoneally administered to the EP+CAPE 5 and EP+CAPE 10 groups, respectively, once a day for 28 days.[21-24,27,28] The control and EP groups received the same volume of saline intraperitoneally at the same times. A flow chart summarizing the study is given in Figure 1. The procedures were successfully performed without any significant problems and all animals survived until sacrifice.

### GINGIVA/SERUM SAMPLES AND DETERMINATION OF CYTOKINE LEVELS

At the end of the experiment, the animals were anesthetized and blood samples were collected from each one via cardiac puncture. Serum samples were separated by centrifugation (Shimadzu UV160A, SNo: 28006648, Japan) for 10 min at 3,000×*g* and were immediately stored at -80 °C until use. The animals were sacrificed using an anesthesia overdose and neck-vertebra dislocation. Gingival tissues around the left molar teeth were excised and stored refrigerated at -80 °C until use. IL-1β (ELISA kit; eBioscience An Affymetrix Company, Cat No. BMS630/BMS630 TEN, Vienna, Austria) and TNF-α (ELISA kit; eBioscience An Affymetrix Company, Cat No. BMS622/BMS622 TWO/BMS622 TEN, Vienna, Austria) levels in the serum and gingiva were determined using ELISA kits specific to rats according to the manufacturer's instructions.

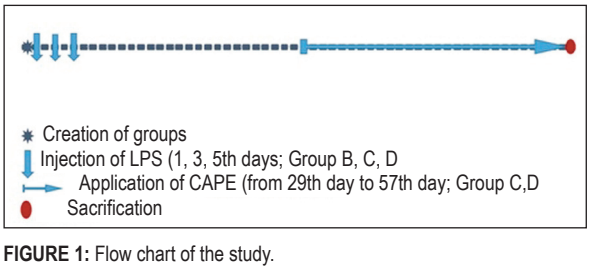


**FIGURE 1:** Flow chart of the study.
LPS: Lipopolysaccharide; CAPE: Caffeic acid phenethyl ester.

### MORPHOMETRIC ANALYSIS

The maxilla was dissected and then the left halves were boiled for 10 minutes and the soft tissue was removed manually. Then the jawbones were soaked in 0.2 N NaOH solution at room temperature for 5 minutes to remove the remaining soft tissue debris. The alveolar bone height was measured under a stereomicroscope (Olympus SZ61, Olympus Opticalco, Japan) (40× magnification) by recording the distance from the cementoenamel junction to the alveolar bone crest (Figure 2). Measurements were made at three points on the buccal and lingual sides to quantify alveolar bone level. Mean alveolar bone loss level was calculated around each tooth. Images were taken with an Olympus C-5060 digital camera. Alveolar bone loss was measured by a single examiner (ED) who was blinded to the samples.

### STATISTICAL ANALYSES

The data from all groups were imported to SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of data was analyzed with the Shapiro-Wilk normality test. One-way analysis of variance was used for comparing the values that fit a normal distribution and Tukey's HSD test was used for multiple comparisons. The data were presented as mean±standard deviation. Differences were considered statistically significant at $p<0.05$.

## RESULTS

### MEASUREMENT OF ALVEOLAR BONE LOSS

Alveolar bone loss demonstrated different values between the groups. Pairwise analysis of the groups revealed lower bone loss in the control group compared to the EP, EP+CAPE 5, and EP+CAPE 10 groups. However, the difference between the EP groups was not statistically significant (Table 1, Figure 2, Figure 3).

### IL-1B AND TNF-A FINDINGS

IL-1β and TNF-α levels in the gingival tissue were significantly different between the groups ($p<0.05$). Cytokine levels were highest in the EP group followed by the EP+CAPE 5, EP+CAPE 10, and the control groups, in that order. IL-1β levels were not

**TABLE 1:** Comparison of cytokine and alveolar bone loss values between the groups.

| | Control | EP | EP+CAPE 5 | EP+CAPE 10 | p value |
|---|---|---|---|---|---|
| Alveolar bone loss (10-1 mm) | 7.2±1.3[a] | 12.2±3.7[b] | 12.2±3.2[b] | 11.1±2.0[b] | <0.001 * |
| Gingival IL-1β (pg/mg prot) | 36.7±8.3[c] | 160.2±47.2[d] | 102.3±29.4[e] | 88.4±20.8[e] | <0.001* |
| Gingival TNF-α(pg/mg prot) | 72.1±3.0[f] | 135.1±4.1[g] | 99.4±6.2[h] | 87±5.0[k] | <0.001* |
| Serum IL-1β (pg/mL) | 27.8±13.9 | 35.1±19.1 | 25.8±8.3 | 26.0±8.1 | 0.377 |
| Serum TNF-α (pg/mL) | 56.9±1.1 | 58.9±3.3 | 58.5±1.5 | 57.5±1.1 | 0.127 |

The results are presented as mean±standard deviation; EP: Experimental periodontitis; CAPE: Caffeic acid phenethyl ester; EP+CAPE 5: EP group with 5 µmol/kg/day of CAPE; EP+CAPE 10: EP group with 10 µmol/kg/day of CAPE; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; There is a significant difference between a, b, c, d, e, f, g, h, and k; There is no difference between the groups with the same letters; *Tukey's HSD test (p<0.05).*

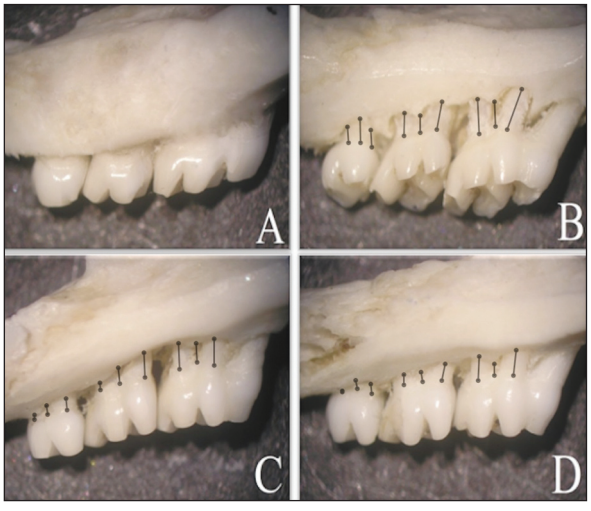


**FIGURE 2:** Representative photographs of the alveolar bone loss in the maxillary first molar tooth in the control **(A)**, EP **(B)**, EP+CAPE 5 **(C)**, and EP+CAPE 10 **(D)** groups. The distance between the cemento enamel junction and alveolar bone crest was measured to calculate the alveolar bone loss. Alveolar bone loss was lowest in the control group (a) **(A)**. The difference in bone loss was not significant between the EP, EP+CAPE 5, and EP+CAPE 10 groups **(B, C, D)**.
EP: Experimental periodontitis; CAPE: Caffeic acid phenethyl ester.

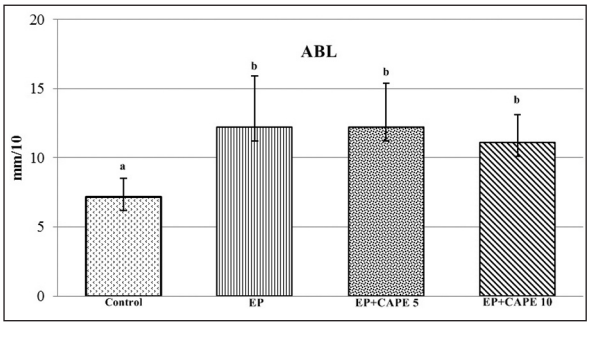


**FIGURE 3:** Comparison of the alveolar bone loss between the groups. Groups are defined on the x axis. The results are presented as mean±standard deviation. A significant difference was seen between the control and the EP, EP+CAPE 5, and EP+CAPE 10 groups (p<0.05) (a, b).
ABL: Alveolar bone loss; EP: Experimental periodontitis; CAPE: Caffeic acid phenethyl ester.

significantly different between the EP+CAPE groups ($p$>0.05). However, TNF-α levels of gingival tissue in the EP+CAPE 10 group were lower than those in the EP+CAPE 5 group ($p$<0.05). There were no statistically significant differences between the cytokine levels in serum ($p$>0.05) (Table 1, Figure 4).

## DISCUSSION

Based on the fact that CAPE has anti-inflammatory and antioxidant activity against many chronic diseases, our study was designed to examine the effect of CAPE on inflammatory periodontal disease.[13,14,18] For this purpose, two different therapeutic dosages based on previously published studies were selected to determine its effect on gingival tissue and serum levels of IL-1β and TNF-α.[24,27,28] The findings clearly demonstrated that CAPE reduced the levels of IL-1β and TNF-α in inflamed gingiva but had no beneficial effect on serum cytokine levels or the present alveolar bone loss. In addition, the decrease in TNF-α in gingival tissue was greater in the 10 µmol/kg/day CAPE group. This finding supports the idea that CAPE is able to reduce host inflammatory mediators (IL-1β and TNF-α) in response to both bacterial and host inflammatory signals. To the best of our knowledge, this is the first in vivo study to evaluate the host modulatory effect of two different dosages of CAPE on the inflammatory statuses of inflamed periodontal tissues.

Due to the well-known interaction between the pathogenesis of periodontitis and the host immune response, there is growing interest in natural host modulatory agents that may control periodontal disease or prevent further breakdown of the surrounding tissues.[29,30] Numerous studies have shown the antibac-

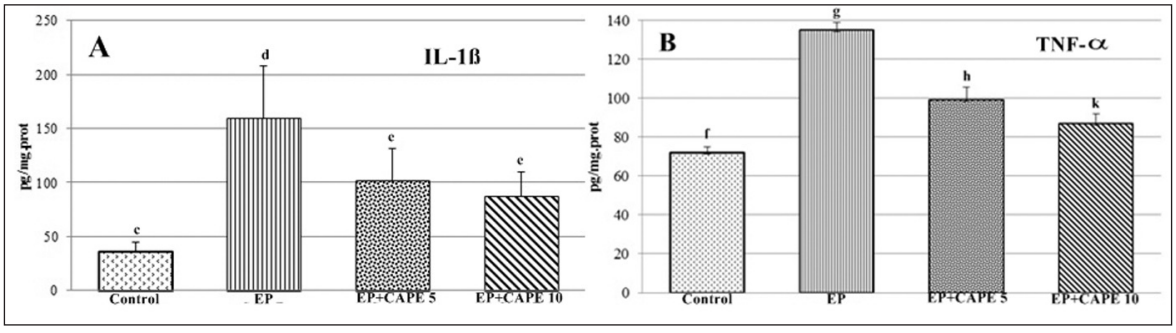


**FIGURE 4:** Comparison of the gingival tissue levels of **(A)** IL-1β and **(B)** TNF-α. The values are presented as mean±standard deviation. IL-1β and TNF-α levels in gingival tissues were significantly different between the groups ($p<0.05$) (c, d, e, f, g, h, k). IL-1β levels were not significantly different between the EP+CAPE 5 and EP+CAPE 10 groups ($p>0.05$) (e). TNF-α values were significantly different between the EP+CAPE 5 and EP+CAPE 10 groups ($p<0.05$) (h, k).
IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; EP: Experimental periodontitis; CAPE: Caffeic acid phenethyl ester.

terial, antifungal, and anti-inflammatory effects of plant extracts in maintaining gingival health.[31-33]

CAPE, one of the most abundant active components of propolis, was introduced as an antibacterial, antioxidant, anti-inflammatory, and immunomodulatory naturopathic medicine.[8,14-16] However, there is limited understanding of its potential mechanisms and there are only a few studies about its efficacy in periodontitis.[21-24,34] Choi et al. reported that CAPE exerted significant inhibitory effects on increased production of NO, IL-1β, and IL-6 and recommended it as a potential host modulatory agent for the treatment of periodontal disease.[34]

In studies involving EP, a single dosage of CAPE (10 µmol/kg/day) was administered concurrent with induction of EP.[21-23] The present study examined whether the suppressive effect of CAPE on proinflammatory cytokines was related to the dosages that were applied and the concentrations of CAPE were based on previously published studies that revealed its anti-inflammatory and antioxidative effects.[19,20,24] A previous investigation showed that CAPE suppressed the release of proinflammatory cytokines in hypertrophic adipocytes with LPS-stimulated RAW 264.7 macrophage cell lines, and a 10 µmol concentration of CAPE decreased the levels of TNF-α; however, the same effect was not observed with 5 µmol. IL-1β was significantly suppressed by both the 5 and 10 µmol CAPE concentrations.[34] Both dosages (5 µmol/kg/day and 10 µmol/kg/day) were reported to reduce tissue TNF-α levels and the higher dosage caused a significantly greater reduction in a study evaluating the anti-inflammatory activity of CAPE at two different dosages in rats with pulmonary fibrosis.[28] Consistent with these reports, both 5 and 10 µmol concentrations of CAPE were effective for reducing the tissue levels of IL-1β and TNF-α, although 10 µmol gave a more meaningful decrease in the tissue levels of TNF-α.

Some studies have shown that serum proinflammatory cytokine levels increase or do not change with periodontal disease.[4,35] In our study, no difference was observed between the experimental groups in terms of serum cytokine levels after CAPE application, in contrast to previous studies reporting a positive effect of CAPE on serum levels of IL-1β in EP.[21,23] The stability of the serum cytokines in our study can be explained by the systemically homeostatic states with no fluctuations in the serum markers. In our experimental model, LPS from *P. gingivalis* was locally injected into the gingiva rather than being reflected in circulation. Therefore, no serumal changes were expected to appear regardless of what was happening in tissue locally or changes were too small to be detected by the assay kit. The LPS groups had pronounced bone loss in comparison to the control group; however, the serum levels of IL-1β and TNF-α remained unchanged in these groups. Another reason for the same serum levels might be the time that the serum samples were collected. The fact that these samples were collected 52 days after the final injections of LPS might explain why the

serum levels of these cytokines subsided. In the present study, the ineffectiveness of CAPE application on serum cytokine levels was also consistent with the unchanged bone destruction in the experimental groups.

In contrast to previous studies, our study found that CAPE had no effect on alveolar bone healing, even though the proinflammatory challenge in tissue was diminished. These different results in comparison to the other studies can be explained by the difference in the timeline of the CAPE application and the induction of the EP.[21-23] In previous studies CAPE was applied at the same time as the EP stimulus. However, clinically, patients with periodontitis generally present to clinics with existing alveolar bone loss, and for this reason it is important to find out how CAPE affects alveolar bone after the disease has occurred. The same alveolar bone loss among EP and EP+CAPE groups was the result of existing breakdown prior to CAPE application. These results may indicate that CAPE has a positive effect when administered before bone destruction, but shows no positive therapeutic effect on existing alveolar bone loss.

Differently from the previous studies, the effect of two different dosages of CAPE were evaluated on gingival tissue IL-1β and TNF-α levels as well as serum levels.[21-23] The present study confirms the results of our previous study showing the antioxidative effect of CAPE in the same experimental procedure and is the first report showing the gingival tissue levels of the inflammatory markers IL-1β and TNF-α after CAPE application.[24]

Our study has a number of potential limitations, such as the same dosages of CAPE might also have been applied to another experimental group prior to EP induction and the conservative effect of CAPE might have been followed using different dosages. There is a need for additional studies with other relevant inflammatory markers and other underlying mechanisms for alveolar bone loss in comparison with other host modulatory agents.

This is the first study to evaluate the anti-inflammatory effect of systemically administered CAPE on gingival tissues after EP has occurred, and the results clearly indicate that the effects of CAPE can be dose-dependent with regard to attenuating LPS-induced periodontitis in rats. The underlying mechanisms of the protective effect of CAPE may be attributed to modulation of the IL-1β and TNF-α levels. Therefore, CAPE could be considered a valuable novel agent for the prophylaxis or treatment of periodontitis.

## CONCLUSION

Host modulation therapies are an area of considerable interest in periodontal therapy. In conclusion, CAPE reduced IL-1β and TNF-α in this experimentally induced periodontitis rat model. The 10 µmol concentration of CAPE appeared to have a greater reducing effect on gingival TNF-α. The modulation of host response by CAPE may represent an attractive strategy for the treatment of periodontal disease and may be valuable as an alternative host modulating agent without any known side effects. However, further work is required to better understand the possible mechanisms behind its clinical success.

***Source of Finance***

*This study supported by Scientific and Technological Research Council of Türkiye (TÜBİTAK) (Project no: 115S805).*

***Conflict of Interest***

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

***Authorship Contributions***

***Idea/Concept:*** *Esra Demir, Feyza Otan Özden;* ***Design:*** *Esra Demir, Feyza Otan Özden, Bahattin Avcı;* ***Control/Supervision:*** *Feyza Otan Özden, Bahattin Avcı;* ***Data Collection and/or Processing:*** *Esra Demir, Bahattin Avcı;* ***Analysis and/or Interpretation:*** *Feyza Otan Özden, Bahattin Avcı;* ***Literature Review:*** *Esra Demir, Feyza Otan Özden;* ***Writing the Article:*** *Esra Demir, Feyza Otan Özden;* ***Critical Review:*** *Bahattin Avcı;* ***References and Fundings:*** *Feyza Otan Özden, Esra Demir;* ***Materials:*** *Esra Demir.*

## REFERENCES


1. Cho MI, Garant PR. Development and general structure of the periodontium. Periodontol 2000. 2000;24:9-27. [Crossref] [PubMed]
2. Graves DT, Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J Periodontol. 2003;74(3):391-401. [Crossref] [PubMed]
3. Yavuzyilmaz E, Yamalik N, Bulut S, Ozen S, Ersoy F, Saatçi U. The gingival crevicular fluid interleukin-1 beta and tumour necrosis factor-alpha levels in patients with rapidly progressive periodontitis. Aust Dent J. 1995;40(1):46-9. [Crossref] [PubMed]
4. Górska R, Gregorek H, Kowalski J, Laskus-Perendyk A, Syczewska M, Madaliński K. Relationship between clinical parameters and cytokine profiles in inflamed gingival tissue and serum samples from patients with chronic periodontitis. J Clin Periodontol. 2003;30(12):1046-52. [Crossref] [PubMed]
5. Assuma R, Oates T, Cochran D, Amar S, Graves DT. IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. J Immunol. 1998;160(1):403-9. [PubMed]
6. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. Periodontol 2000. 2007;43:294-315. [Crossref] [PubMed] [PMC]
7. Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. J Periodontol. 2000;71(4):521-32. [Crossref] [PubMed]
8. Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Rainsford KD, Lanas A. Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. Gastroenterology. 2018;154(3):500-14. [Crossref] [PubMed]
9. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al; American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007;22(10):1479-91. [Crossref] [PubMed]
10. Slots J, Rams TE. Antibiotics in periodontal therapy: advantages and disadvantages. J Clin Periodontol. 1990;17(7 ( Pt 2)):479-93. [Crossref] [PubMed]
11. Preshaw PM. Host modulation therapy with anti-inflammatory agents. Periodontol 2000. 2018;76(1):131-49. [Crossref] [PubMed]
12. Palaska I, Papathanasiou E, Theoharides TC. Use of polyphenols in periodontal inflammation. Eur J Pharmacol. 2013;720(1-3):77-83. [Crossref] [PubMed]
13. Velazquez C, Navarro M, Acosta A, Angulo A, Dominguez Z, Robles R, et al. Antibacterial and free-radical scavenging activities of Sonoran propolis. J Appl Microbiol. 2007;103(5):1747-56. [Crossref] [PubMed]
14. Chen YJ, Shiao MS, Wang SY. The antioxidant caffeic acid phenethyl ester induces apoptosis associated with selective scavenging of hydrogen peroxide in human leukemic HL-60 cells. Anticancer Drugs. 2001;12(2):143-9. [Crossref] [PubMed]
15. Akyol S, Ozturk G, Ginis Z, Armutcu F, Yigitoglu MR, Akyol O. In vivo and in vitro antineoplastic actions of caffeic acid phenethyl ester (CAPE): therapeutic perspectives. Nutr Cancer. 2013;65(4):515-26. [Crossref] [PubMed]
16. da Cunha FM, Duma D, Assreuy J, Buzzi FC, Niero R, Campos MM, et al. Caffeic acid derivatives: in vitro and in vivo anti-inflammatory properties. Free Radic Res. 2004;38(11):1241-53. [Crossref] [PubMed]
17. Orban Z, Mitsiades N, Burke TR Jr, Tsokos M, Chrousos GP. Caffeic acid phenethyl ester induces leukocyte apoptosis, modulates nuclear factor-kappa B and suppresses acute inflammation. Neuroimmunomodulation. 2000;7(2):99-105. [Crossref] [PubMed]
18. Park SG, Lee DY, Seo SK, Lee SW, Kim SK, Jung WK, et al. Evaluation of anti-allergic properties of caffeic acid phenethyl ester in a murine model of systemic anaphylaxis. Toxicol Appl Pharmacol. 2008;226(1):22-9. [Crossref] [PubMed]
19. Jung WK, Lee DY, Choi YH, Yea SS, Choi I, Park SG, et al. Caffeic acid phenethyl ester attenuates allergic airway inflammation and hyperresponsiveness in murine model of ovalbumin-induced asthma. Life Sci. 2008;82(13-14):797-805. [Crossref] [PubMed]
20. Bezerra RM, Veiga LF, Caetano AC, Rosalen PL, Amaral ME, Palanch AC, et al. Caffeic acid phenethyl ester reduces the activation of the nuclear factor κB pathway by high-fat diet-induced obesity in mice. Metabolism. 2012;61(11):1606-14. [Crossref] [PubMed]
21. Yiğit U, Kırzıoğlu FY, Uğuz AC, Nazıroğlu M, Özmen Ö. Is caffeic acid phenethyl ester more protective than doxycycline in experimental periodontitis? Arch Oral Biol. 2017;81:61-8. [Crossref] [PubMed]
22. Kızıldağ A, Arabacı T, Albayrak M, Taşdemir U, Şenel E, Dalyanoglu M, et al. Therapeutic effects of caffeic acid phenethyl ester on alveolar bone loss in rats with endotoxin-induced periodontitis. J Dent Sci. 2019;14(4):339-45. [Crossref] [PubMed] [PMC]
23. Kızıldağ A, Arabacı T, Albayrak M, Balseven HM, Aksu Kızıldağ C, Tasdemir U. A biochemical and immunohistochemical study of the effects of caffeic acid phenethyl ester on alveolar bone loss and oxidative stress in diabetic rats with experimental periodontitis. Biotech Histochem. 2020;95(6):456-63. [Crossref] [PubMed]
24. Otan Özden F, Lütfioğlu M, Demir E, Bilgici B. Antioxidant effect of caffeic acid phenethyl ester in experimentally induced periodontitis. Clin Oral Investig. 2021;25(8):4959-66. [Crossref] [PubMed]
25. Graves DT, Kang J, Andriankaja O, Wada K, Rossa C Jr. Animal models to study host-bacteria interactions involved in periodontitis. Front Oral Biol. 2012;15:117-32. [Crossref] [PubMed] [PMC]
26. Kador PF, O'Meara JD, Blessing K, Marx DB, Reinhardt RA. Efficacy of structurally diverse aldose reductase inhibitors on experimental periodontitis in rats. J Periodontol. 2011;82(6):926-33. [Crossref] [PubMed]
27. Sud'ina GF, Mirzoeva OK, Pushkareva MA, Korshunova GA, Sumbatyan NV, Varfolomeev SD. Caffeic acid phenethyl ester as a lipoxygenase inhibitor with antioxidant properties. FEBS Lett. 1993;329(1-2):21-4. [Crossref] [PubMed]
28. Larki-Harchegani A, Hemmati AA, Arzi A, Ghafurian-Boroojerdnia M, Shabib S, Zadkarami MR, et al. Evaluation of the effects of caffeic acid phenethyl ester on prostaglandin E2 and two key cytokines involved in bleomycin-induced pulmonary fibrosis. Iran J Basic Med Sci. 2013;16(7):850-7. [PubMed] [PMC]
29. Kantarci A, Hasturk H, Van Dyke TE. Host-mediated resolution of inflammation in periodontal diseases. Periodontol 2000. 2006;40:144-63. [Crossref] [PubMed]
30. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. J Clin Periodontol. 2005;32 Suppl 6:108-29. [Crossref] [PubMed]
31. Stoyell KA, Mappus JL, Gandhi MA. Clinical efficacy of turmeric use in gingivitis: a comprehensive review. Complement Ther Clin Pract. 2016;25:13-7. [Crossref] [PubMed]
32. Casati MZ, Algayer C, Cardoso da Cruz G, Ribeiro FV, Casarin RC, Pimentel SP, et al. Resveratrol decreases periodontal breakdown and modulates local levels of cytokines during periodontitis in rats. J Periodontol. 2013;84(10):e58-64. [Crossref] [PubMed]
33. Corrêa MG, Pires PR, Ribeiro FV, Pimentel SP, Cirano FR, Napimoga MH, et al. Systemic treatment with resveratrol reduces the progression of experimental periodontitis and arthritis in rats. PLoS One. 2018;13(10):e0204414. [Crossref] [PubMed] [PMC]
34. Choi EY, Choe SH, Hyeon JY, Choi JI, Choi IS, Kim SJ. Effect of caffeic acid phenethyl ester on Prevotella intermedia lipopolysaccharide-induced production of proinflammatory mediators in murine macrophages. J Periodontal Res. 2015;50(6):737-47. [Crossref] [PubMed]
35. Zekeridou A, Mombelli A, Cancela J, Courvoisier D, Giannopoulou C. Systemic inflammatory burden and local inflammation in periodontitis: what is the link between inflammatory biomarkers in serum and gingival crevicular fluid? Clin Exp Dent Res. 2019;5(2):128-35. [Crossref] [PubMed] [PMC]