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Research Article

EFFECTS OF BEE POLLEN ON ALVEOLAR BONE LOSS AND INFLAMMATORY MARKERS IN RATS WITH EXPERIMENTAL PERIODONTITIS

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ABSTRACT

Aim: This study aimed to investigate both the systemic and local anti-inflammatory effects of bee pollen in a rat model of experimental periodontitis.

Materials and Methods: A total of 24 rats were randomly divided into three experimental groups: 1) periodontally healthy (H), 2) experimental periodontitis (P), and 3) experimental periodontitis + bee pollen (P+BP). Experimental periodontitis was induced by placing ligatures on maxillary second molars. Bee pollen was administered orally to the P+BP group for 14 days. On the 15th day of the experiment, the rats were euthanized, and jaw tissues along with serum samples were collected for biochemical, histological, histomorphometric, and immunohistochemical evaluations. Serum concentrations of IL-4 and IL-6 were determined using ELISA, while RANKL and OPG expressions were evaluated through immunohistochemical staining.

Results: Bone loss was higher in the periodontitis groups than in the healthy group, but the difference was not statistically significant ($p > 0.05$). There were no significant differences in serum IL-4 and IL-6 levels between the groups ($p > 0.05$). Immunohistochemical analysis indicated a significant increase in OPG and a decrease in RANKL expression in the P+BP group compared to the P group ($p < 0.05$). Histological examination also demonstrated notably less inflammation in the P+BP group than in the P group ($p < 0.05$).

Conclusion: Within the limitations of this study, it was determined that systemic bee pollen administration had no effect on serum IL-4 and IL-6 parameters, reduced RANKL levels, increased OPG levels, and thus may prevent alveolar bone loss due to periodontitis.

Keywords: Alveolar bone loss, Bees, Interleukin-4, Interleukin-6, Periodontitis, Rats

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INTRODUCTION

Periodontitis is an multifactorial inflammation-associated condition of the periodontium that arises from an imbalance between the dental biofilm accumulating on tooth surfaces and the host immune response (1). The destruction of periodontal tissues is initiated by an inflammatory process triggered by oral bacterial infection. Bacterial plaque, the primary etiological factor, serves as a local stimulus that initiates host inflammatory responses, thereby triggering a cascade of inflammatory events. If left untreated, this dynamic host-pathogen interaction may ultimately lead to alveolar bone loss (2). Periodontitis-affected periodontal tissues exhibit a significant increase in pro-inflammatory cytokines such as IL-1, IL-12, IL-6, TNF-α and IFN-γ, while levels of anti-inflammatory cytokines, including IL-4 and IL-10, are notably diminished (3). Interactions between host cells and pathogenic microorganisms can result in the overproduction of cytokines. IL-1 and IL-6, as key pro-inflammatory cytokines, contribute substantially to the development and progression of periodontal disease, whereas anti-inflammatory cytokines are recognized for their contributions to the resolution and healing of the disease (4).

Conventional treatment approaches primarily involve the mechanical removal of microbial plaque and bacterial products; however, in certain cases, adjunctive use of chemotherapeutic agents and supportive therapies may be necessary. In recent years, emerging strategies in periodontal therapy have focused on modulating the host inflammatory response to prevent damage to the periodontal ligament and alveolar bone (5). Studies suggest that the use of antimicrobial and anti-inflammatory agents in combination with mechanical therapy may help promote periodontal health and support more effective regulation of the host immune response (6). The search for natural products that target the inflammatory response has become a promising alternative, given their broad antipathogenic effects and the potential to help prevent the development of antibiotic resistance (7).

Bee products have been widely studied for their effects on chronic inflammation, and they are generally recognized for their supportive role pathophysiological conditions (8). Bee pollen offers a range of health benefits, including antioxidant, antifungal, antimicrobial, antiviral, anti-inflammatory, immunomodulatory, antitumor, and anabolic effects on bone components (9–11). And also a study demonstrated that bee pollen supplementation increased the abundance of Lactococcus in the oral cavity of mice, along with elevated expression levels of β-defensin-2 and β-defensin-3. These components are recognized for their inhibitory effects on oral pathogens (12). Thus, bee pollen may play a role in reducing periodontal inflammation and preventing alveolar bone loss associated with periodontal disease.

Recent studies have reported that bee pollen supplementation can modulate systemic cytokine levels. For example, Kösedağ et al. found that oral administration of bee pollen reduced serum IL-6 and increased IL-4 levels in a rat model of chronic inflammation (9). In terms of bone metabolism, bee pollen has demonstrated anabolic effects in ovariectomized rats, improving bone mineral density in lumbar and femoral sites (13). Yamaguchi et al. also reported that bee pollen extracts increased mineralization in trabecular and cortical bone tissues (11, 14). While these findings highlight the bone-supportive and anti-inflammatory properties of bee pollen, no prior study has specifically investigated its effects on the RANKL/OPG signaling pathway in the context of periodontitis. Given the critical role of this pathway in periodontal bone remodeling, it was selected as a key target in the current study.

The aim of this study was to investigate the effects of bee pollen on alveolar bone loss and systemic inflammation in a rat model of experimental periodontitis. Drawing on earlier research, we propose that bee pollen may have the potential to alleviate inflammation and prevent alveolar bone loss linked to periodontal disease.

MATERIALS AND METHODS

Animals and experimental periodontitis model

The animal experiment protocol was approved by the Bolu Abant Izzet Baysal University Ethics Committee (Decision number: 2024/11) and all procedures adhered to the Guide for the Care and Use of Laboratory Animals and ARRIVE guidelines. In the study, 24 male Albino Wistar rats, 10-12 weeks old, with an mean weight of 200-300 grams, were used. They were provided with unlimited food and water in a pathogen-free environment at 24°C ± 2°C and 50% humidity. All rats were housed under these conditions for one week prior to the start of the experiment. Twenty-four rats included in the study were randomly divided using the coin toss method into 3 groups:

1) Periodontally healthy (H),
2) Experimental periodontitis group (P),
3) Experimental periodontitis + bee pollen (P+BP).

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Experimental periodontitis model was created under general anesthesia in P and P-BP groups (90 mg/kg ketamine, 10 mg/kg xylazine intramuscular injection). Ligature was placed around the cervicals of the maxiller 2nd molars for each rat with 3/0 silk suture submarginally. All ligatures were placed by the same operator (NE) and ligatures were checked daily by two operators (NE, SF).

Preparation and applicatıon of pollen extract

After ligature placement, the rats in the test groups received bee pollen via oral gavage once daily at the same morning hours for a duration of 14 days. Bee pollen used in the study was obtained from Düzce University Beekeeping Research, Development, and Application Center and harvested from the Düzce region in 2024. 300 mg/kg bee pollen extract was prepared daily by dissolving in distilled water. A total of 4 ml of bee pollen was administered by oral gavage in each application. When gavage was applied to rats, considering the local effects of bee pollen, a small amount of bee pollen was administered into the mouth while the gavage syringe was withdrawn (EAY, SF).

Sample collection

Throughout the experimental process, the sutures remained secure without any signs of loosening, detachment, or displacement. Experimental periodontitis was established by maintaining them in position for a duration of 14 days. The 14-day ligature period was chosen in accordance with the study reporting that the majority of alveolar bone loss occurs within the first two weeks of ligature-induced periodontitis (15).

The rats were sacrificed by taking cardiac blood samples on the 15th day after ligation (NE, SF). The upper jaws of the rats were removed by dissecting the soft tissues. After the maxilla was separated from the skull, it was fixed in 10% neutral formaldehyde solution and sent to the histology laboratory for examination.

Morphometric analyses

Following the sacrifice, the maxillas of the rats were dissected. To assess bone loss, the distance between the cementoenamel junction (CEJ) and the alveolar bone crest (ABC) was measured. In rats, these measurements were taken from the interdental region of the second molar. Unlike in humans, where the lesion typically extends along the root surface, the most apical point of the lesion in rats was located at the center of the interdental tissue, which served as the reference point for measurement in this study (16). Linear changes in hematoxylin and eosin stained sections were examined under a light microscope (Leica DM 2000 LED) at x40 magnification. Mean alveolar bone loss was determined by taking measurements at three distinct points along the long axis of each tooth, on both the buccal and lingual surfaces. The mean of these values was then used to represent bone loss for each tooth (17). All measurements were conducted by a single calibrated examiner who was masked to the identity of samples (SED).

Histopathological analyses

All histological analyses were conducted by a single examiner (SED), who remained blinded to the sample identities throughout the evaluation process. Following 24 hours of fixation in 10% formalin, the tissues were subjected to decalcification with 10% EDTA at pH 7.4 (Osteodec, Bio-Optica). The decalcification process was carried out for three weeks until the bone could be easily sectioned. After decalcification, the tissues were rinsed with distilled water, passed through a graded alcohol series, and cleared with xylene before being embedded in paraffin. Following this, tissue samples were sectioned into serial slices of 3 μm thickness and subjected to staining with hematoxylin and eosin (H&E), or alternatively, were immunohistochemically stained to detect RANKL and OPG.

In the histopathological examination, inflammatory cell scoring was used to assess the findings of inflammation. The scoring was based on the histopathological evaluation of inflammatory cell infiltration, with the presence of cells being scored according to predefined criteria (17). The scoring system was as follows: Score 0: No cells; Score 1: Minimal cell presence; Score 2: Moderate cell presence; Score 3: High cell presence.

Immunohistochemical analyses

Immunohistochemical staining for RANKL and OPG was performed on 3 μm thick sections obtained from paraffin-embedded tissue blocks. The RANKL and OPG antibody (BIOSS Antibodies Inc, Woburn, MA, USA) was incubated for 60 minutes at a dilution of 1:300. For antigen retrieval, the ROCHE/Cell Conditioning 1 (CC1) (EDTA) method was employed, followed by the standard 60-minute CC1 protocol. For secondary detection, the standard UltraView IHC protocol (ROCHE/UltraView Universal DAB Detection Kit) was applied. All procedures were carried out using the ROCHE/Ventana BenchMark XT IHC Stainer (Tucson, AZ, USA).

Immunohistochemical staining for RANKL and OPG was evaluated in the interradicular area and scored semiquantitatively on a scale of 0 to 3 (0: no staining, 1:

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mild staining, 2: moderate staining, 3: severe staining) (18). The sections were examined under a light microscope (LEICA DM 2000 LED). Following histomorphometric analysis, both hematoxylin and eosin-stained sections and immunohistochemically stained sections were photographed at various magnifications (INFINITY 3 ANALYZE Release 6.5 software).

Biochemical analysis

Cardiac blood samples were collected from all rats under anesthesia, followed by euthanasia. The blood samples were drawn into 5 ml gel vacuum serum separator tubes (SST) with yellow caps and subsequently centrifuged at 1200 g and 4000 rpm for 10 minutes at +4°C. The serum samples obtained were divided into aliquots and stored at -80°C for future analysis. To minimize potential preanalytical variables, identical procedures were followed for the collection, transportation, processing, and storage of all samples, and all analyses were conducted simultaneously. Serum concentrations of pro and anti-inflammatory cytokines were measured using cytokine-specific ELISA kits (BT LAB Rat Interleukin 4, IL-4 ELISA Kit, E0133Ra; BT LAB Rat Interleukin 6, IL-6 ELISA Kit, E0135Ra).

Statistical analysis

Descriptive statistics are reported as mean ± standard deviation or percentages, where appropriate. Differences in serum IL-6 (ng/L) and IL-4 (ng/L) levels among the groups were assessed using one-way (ANOVA), with group serving as the independent factor. Histomorphometric measurements were compared using the Kruskal-Wallis test. Comparative analyses of inflammatory cell infiltration scores and immunohistochemical staining intensities for RANKL and OPG were performed using Fisher's Exact Test. Statistical significance was defined as a $p < 0.05$.

RESULTS

During the 14 day experimental periodontitis period, ligatures were observed to remain around the teeth. Experimental periodontitis was successfully induced in the animals. The presence of the silk ligature around the maxillary second molar tooth was observed to cause an inflammatory reaction in the periodontal tissue. Furthermore, no apparent signs of systemic illness were observed in the animals throughout the duration of the study, and they completed the study without complications.

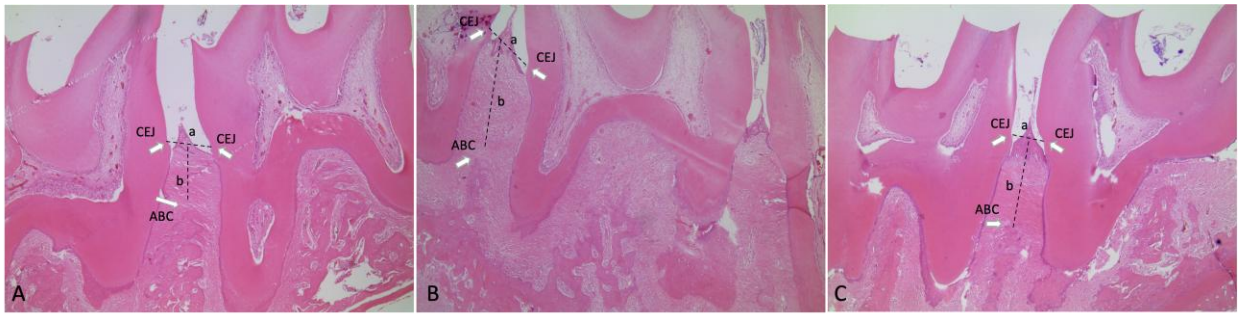

Figure 1. Representative H&E-stained sections (40×) showing CEJ–ABC measurements in A. periodontally healthy (H), B. experimental periodontitis (P), and C. experimental periodontitis + bee pollen (P+BP) groups. CEJ: Cementoenamel junction; ABC: Alveolar bone crest; a: Line between CEJs of adjacent teeth; b: Distance from CEJ to ABC.

Table 1. Distributions and comparison of morphometric measurements according to study groups.

	Min.-Max. (μm)	Mean ± S.D. (Median) (μm)	Test Statistic	p
Periodontal health	209.12 – 326.68	259,42 ± 45,79 (250,05)	5,955 ‡	0,051
Experimental periodontitis	288.34 – 534.93	363,31 ± 84,08 (335,55)		
Experimental periodontitis + Bee pollen	179,54 - 370,89	289,62 ±7 6,24 (314,84)		

‡: Kruskal Wallis test

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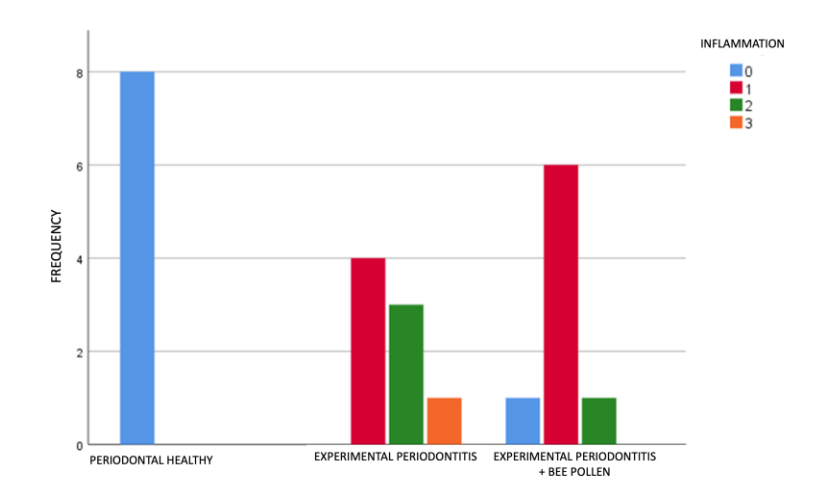

Figure 2. Box plot showing the distribution of recovery scores by study group

Morphometric analyses

In this study, to assess alveolar bone loss around the second molar, the distance values between the CEJ and ABC were measured (Figure 1). The distribution of histomorphometric measurements across the study groups is shown in Figure 2. Data obtained from histomorphometric measurements are given in the Table 1. Alveolar bone loss was more pronounced in the P group compared to the P + BP and H groups; however, there was no statistically meaningful difference among the groups ($p > 0.05$).

Histopathological analyses

A significantly elevated inflammation score was observed in the P group relative to both the P+BP and H groups. Statistical analysis revealed a significant correlation between all study groups and inflammation levels ($p < 0.05$). No inflammation was observed in the healthy group, while the periodontitis group exhibited an increase in inflammation severity. In the P+BP group, the majority of inflammation scores were rated as 1 (Figure 2). Hematoxylin & Eosin staining images of the experimental groups are presented in Figure 3.

Immunohistochemical analyses

The intensity of RANKL staining was found to be significantly lower in the P+BP group compared to the P group ($p < 0.05$). Additionally, RANKL staining intensity in the H group was significantly lower than in both the P and P+BP groups. The intensity of OPG staining was significantly higher in the P+BP group than in the P group

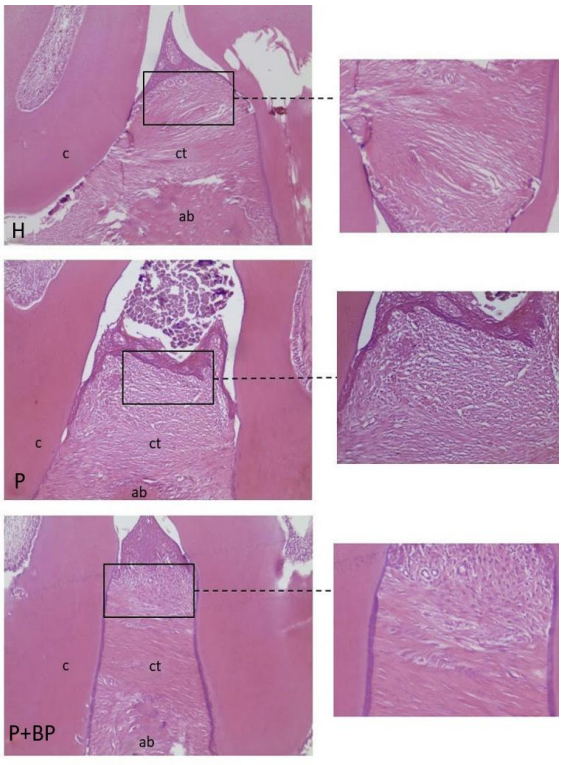

Figure 3. Inflammation and alveolar bone loss by groups under light microscope, H&E staining, 100x magnification. A. H: Periodontally Healthy, B. P: Experimental Periodontitis, C. P+BP: Experimental Periodontitis + Bee Pollen, ct: connective tissue, ab: alveolar bone, c: cementum.

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($p < 0.05$). Furthermore, OPG staining intensity in the H group was higher than in both the P and P+BP groups, with the difference was observed between the three groups ($p < 0.05$) (Figure 4a, Figure 5a). Histological sections showing RANKL and OPG immunostaining are presented in Figure 4b and Figure 5b.

and administration method used in this study (300 mg/kg/day via oral gavage) were determined based on previous experimental models, particularly the study by Kösedağ et al., which demonstrated significant anti-inflammatory effects of bee pollen at this dose (9). The 14-day ligature period was chosen in accordance with the

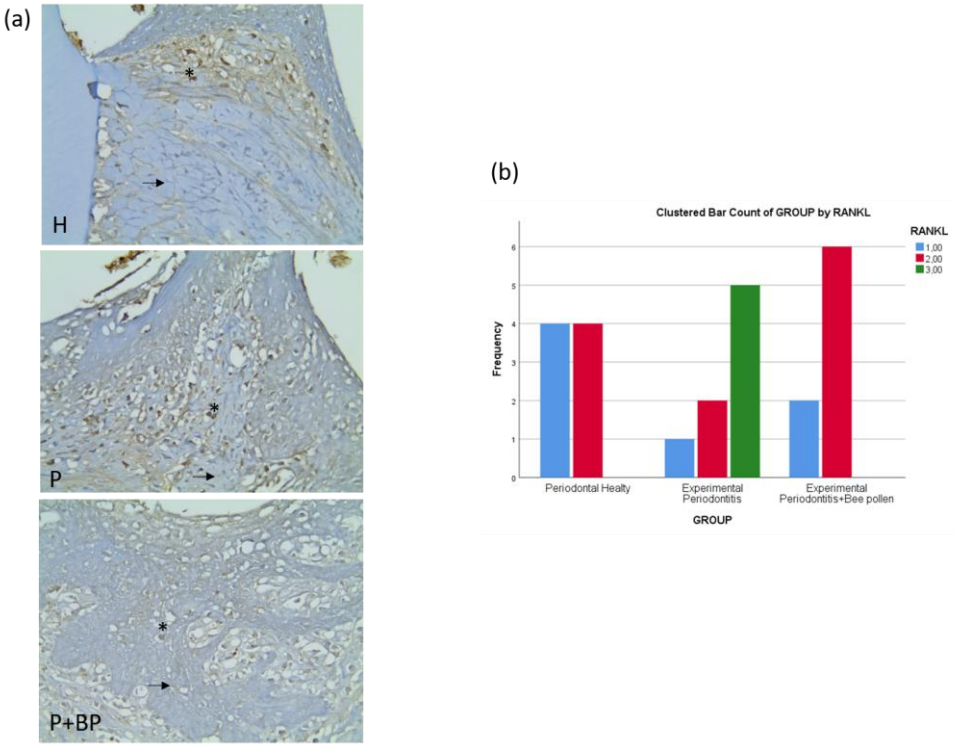

Figure 4. (a) Light microscope images of RANKL immunostaining in different groups at 400× magnification; (b) box plot showing the distribution of RANKL staining intensity across study groups; H, Periodontally Healthy; P, Experimental Periodontitis; P+BP, Experimental Periodontitis + Bee Pollen; asterisk (*) : Intensely immunopositive RANKL-cells, horizontal arrow: Weakly immunopositive stained RANKL-cells.

Biochemical analysis

The serum IL-4 (ng/L) level was highest in the P+BP group. In the H group, IL-4 levels were lower than those in the P+BP and P groups, although the differences were not statistically significant ($p > 0.05$). Similarly, serum IL-6 (ng/L) levels were highest in the P+BP group, followed by the P and H groups, with no statistically significant differences observed ($p > 0.05$). Serum levels of IL-4 (ng/L) and IL-6 (ng/L) are shown in Table 2.

DISCUSSION

This research investigated the impact of bee pollen on alveolar bone loss and inflammation using a rat model of induced periodontitis. To the best of our knowledge, it is the first to explore the potential of bee pollen in preventing periodontal tissue destruction in this context. The dose

study reporting that the majority of alveolar bone loss occurs within the first two weeks of ligature-induced periodontitis. As a result of our study, when the inflammation scores were compared in the histopathological examination, a statistically significant difference was observed among all groups. The level of inflammation in the periodontitis group treated with bee pollen was significantly lower than in the group with periodontitis alone. As anticipated, bee pollen supplementation led to a reduction in inflammatory cell infiltration compared to the untreated periodontitis group. Several studies in the literature have explored the effects of bee pollen on inflammation, and their findings align

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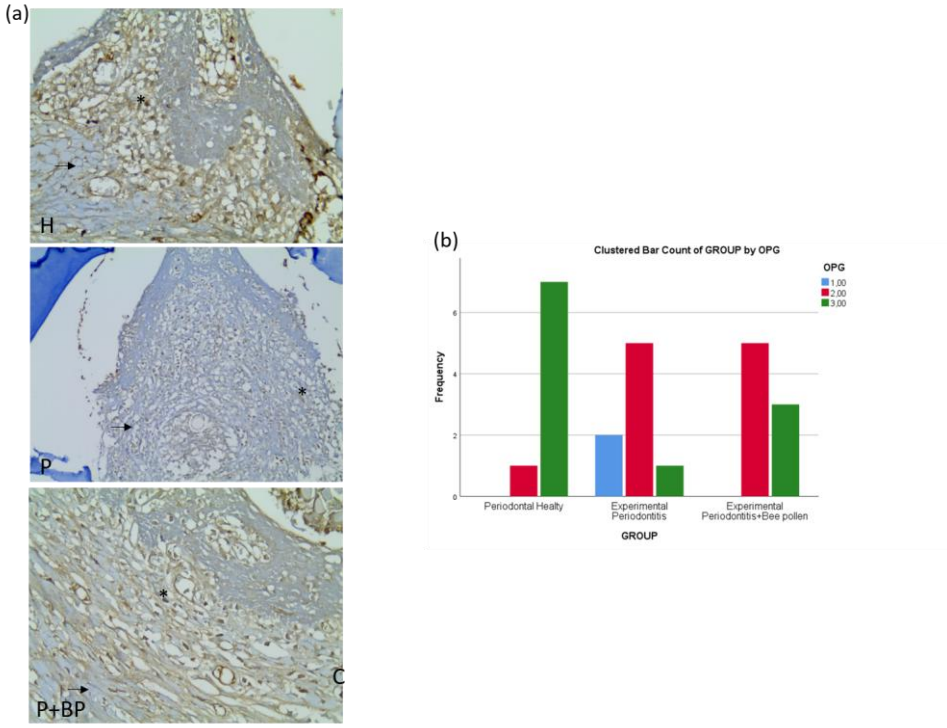

Figure 5. (a) Light microscope images of OPG immunostaining in different groups at 400× magnification; (b) box plot showing the distribution of OPG staining intensity across study groups. H, Periodontally Healthy; P, Experimental Periodontitis; P+BP, Experimental Periodontitis + Bee Pollen; asterisk (*) : Intensely immunopositive OPG-cells, horizontal arrow: Weakly immunopositive stained OPG-cells.

Table 2. Serum IL-6 (ng/L) and IL-4 levels (ng/L) across study groups.*

		Min.-Max.	Mean ± S.D. (Median)	Test Statistic	p
IL-6 (ng/L)	Periodontal healthy	3,52-6,79	5,02 ± 1,13 (4,72)	1,316	0,289
	Experimental Periodontitis	3,91-5,91	5,22 ± 0,67 (5,28)		
	Experimental periodontitis + Bee pollen	5,03-7,11	5,69 ± 0,66 (5,62)		
IL-4 (ng/L)	Periodontal healthy	25,18-67,81	51,77 ± 13,46 (54,28)	1,046	0,369
	Experimental Periodontitis	35,73-80,13	57,15 ± 16,47 (62,47)		
	Experimental periodontitis + Bee pollen	47,46-76,13	61,68 ± 10,6 (63,15)		

*One way ANOVA

with the results observed in our study (19, 20). In our study, the highest histomorphometric values were identified within the P group, followed by the P+BP and H groups, respectively. However, the absence of a statistically significant difference among the groups is likely due to measurements being taken from a single point and the lack of standardization in tissue sectioning (21).

The RANKL-OPG interaction plays a key role in alveolar bone destruction associated with periodontal disease. Under normal physiological conditions, bone formation and resorption are balanced; however, this balance is disrupted in periodontitis, where an increased RANKL/OPG ratio due to elevated RANKL and reduced OPG levels leads to pathological bone loss (22). In our study, consistent with this mechanism, RANKL expression was substantially higher in the P group compared to the H group. Additionally, RANKL levels in

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the P+BP group were significantly lower than in the P group. Conversely, OPG expression was highest in the H group, in line with existing literature, and was significantly higher in the P+BP group than in the P group ($p < 0.05$).

Numerous studies in the literature have demonstrated that bee pollen has a beneficial effect on bone metabolism (11, 23). Considering the findings of our study, it was concluded that bee pollen reduces alveolar bone destruction associated with periodontal disease by decreasing RANKL levels and increasing OPG levels.

The literature indicates that both microbial and host-derived factors contribute to bone resorption and remodeling in inflammatory periodontal disease, with various chemical mediators playing complex roles in this process (2). Studies have shown that low levels of immunoregulatory cytokines such as IL-2 and IL-4 are associated with increased bone loss in periodontal disease (7). Similarly, Lorenzo et al. reported that cytokines like IL-4, IFN-γ, and TGF-β inhibit osteoclastogenesis. In our study, higher IL-4 levels and elevated OPG scores in the bee pollen group compared to the experimental periodontitis group support this regulatory mechanism.
In this study, serum IL-6 as a pro-inflammatory and IL-4 as a anti-inflammatory cytokine levels were evaluated. Previous research has shown that nonsurgical periodontal therapy reduces systemic IL-6 levels in parallel with clinical improvement (24). Kösedağ et al. also reported a decrease in serum IL-6 following oral administration of bee pollen in a model of chronic inflammation (9). In line with previous reports, our findings showed that Both the P and P+BP groups exhibited increased IL-6 levels in comparison to the H group, although this difference did not reach statistical significance. The increase in IL-6 levels with periodontitis is consistent with the literature, but unlike other studies, bee pollen was ineffective in reducing inflammation in our study. Qing et al. reported that acute stress, induced by standard laboratory procedures such as cage changes and social isolation, significantly increased circulating IL-6 levels (25). In this study, only the bee pollen-supplemented group underwent daily oral gavage for 14 days, while the other groups were not subjected to this procedure. The elevated IL-6 levels observed in this group may therefore be attributed to gavage-induced stress. This finding aligns with previous study showing that oral gavage can trigger a stress response in rats, including increased plasma corticosteroid levels (26). In our study, serum IL-4 levels were higher in rats with experimental periodontitis receiving bee pollen compared to those without supplementation. Although this finding aligns with previous studies demonstrating a statistically significant anti-inflammatory effect of bee pollen (9, 20), we did not observe statistical significance. This discrepancy may be attributed to variations in the chemical composition of bee pollen, which is known to possess anti-inflammatory properties. However, its composition—and consequently its therapeutic potential—can vary depending on regional origin, ecological conditions, and seasonal factors (27). Additionally, the lack of a significant difference between the periodontitis groups and the healthy group may be explained by the fact that IL-4 interacts with multiple cytokine pathways and plays a complex role in the regulation of inflammation (28).

The reason for the lack of difference between the periodontitis groups and the healthy groups can be explained by the fact that IL-4 interacts with more than one cytokine release and its role in inflammation is complex (28). However, in our study, it was observed that the IL-4 levels of the P+BP group were higher than the P group, although not statistically significant. This result is parallel with the studies in the literature showing the a statistically significant anti-inflammatory effect of bee pollen (9, 20).

This study has several limitations. Firstly, only two-dimensional histomorphometric techniques were used to evaluate alveolar bone loss, which may not fully represent the complexity of bone alterations. And also, the effect of different bee pollen doses on alveolar bone loss and inflammatory parameters was not assessed. Serum IL-4 and IL-6 levels were measured, but local cytokine levels in the tissue were not evaluated. Additionally, the use of 3.0 silk suture may have accelerated the inflammatory process, resulting in more rapid tissue destruction. Future studies may consider employing alternative ligature materials or modified protocols to establish more gradual and chronic models of experimental periodontitis. Lastly, oral gavage was not performed with a placebo in the control and periodontitis groups to account for potential stress-induced effects. These limitations should be taken into account when evaluating the findings, and additional research is required to explore these areas more thoroughly.

CONCLUSION

In our study, the effects of bee pollen administration on inflammatory parameters and alveolar bone destruction were investigated for the first time in a rat model of experimental periodontitis. The findings demonstrated that bee pollen reduced bone loss associated with

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periodontitis through modulation of the RANKL/OPG pathway; however, this was not supported by histomorphometric measurements, and also decreased tissue inflammation as observed in histopathological analysis. Given its ability to reduce both inflammation and alveolar bone destruction, systemic bee pollen administration may be considered a potential adjunctive therapy for host modulation in the management of periodontal disease.

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Authorship contributions
Senem Filiz: Surgical and medical practices, data collection or processing, analysis or interpretation, literature search, writing
Nuray Ercan: Surgical and medical practices, concept, design, data collection or processing, literature search, writing
Esra Ateş Yıldırım: Surgical and medical practices, data collection or processing, analysis or interpretation
Selma Erdoğan Düzcü: Concept, design, data collection or processing, analysis or interpretation

Data availibity statement
All data are available in the article, and raw data can be provided upon request.

Declaration of competing interest
The authors report no conflicts of interest related to this study.

Ethics
The experimental protocol of the present study was approved by the Ethics Committee at Bolu Abant Izzet Baysal University (Decision number: 2024/11).

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