Article

Discovery Medicine 2025; 37(196): 862–870
https://doi.org/10.24976/Discov.Med.202537196.76

Protective Effect of Resveratrol Against Peri-Implant Inflammation and Oxidative Stress: An *in vivo* Study

Chao Zhang[1,*], Boqiang Jiao[2], Dajun Qian[1]

[1]Department of Dentistry, Shengzhou People's Hospital, The First Affiliated Hospital of Zhejiang University Shengzhou Branch, 312400 Shengzhou, Zhejiang, China
[2]Department of Oral and Maxillofacial Surgery, Stomatology Hospital, School of Stomatology, Zhejiang University School of Medicine, Zhejiang Provincial Clinical Research Center for Oral Diseases, Key Laboratory of Oral Biomedical Research of Zhejiang Province, Cancer Center of Zhejiang University, 310000 Hangzhou, Zhejiang, China
*Correspondence: zhangchao2383@163.com (Chao Zhang)
Published: 20 May 2025

Background: Implants are commonly used to repair teeth. However, with their widespread use, the incidence of peri-implantitis has also increased. The Mitogen activated protein kinase/Protein kinase B/Nuclear factor kappa-B (MAPK/AKT/NF-κB) signaling pathway is associated with various inflammatory responses. This study aims to evaluate the role of resveratrol in managing peri-implant inflammation and its regulatory effect on the MAPK/AKT/NF-κB signaling pathway.

Methods: Peri-implant bone loss was measured by micro-computed tomography, and gingival cell apoptosis was detected by the TdT-mediated dUTP-biotin nick end labeling (TUNEL) method. The levels of apoptosis-related proteins (caspase-3, B-cell lymphoma-2 (Bcl-2)), inflammation-related proteins (caspase-1, phospho-p65 (p-p65)/p65), and MAPK/AKT/NF-κB signaling pathway-related proteins (p38 MAPK, AKT, and NF-κB) in inflammatory tissue were determined by western blotting. Enzyme-linked immunosorbent assay was used to measure the levels of tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), IL-1β, IL-4, and IL-10 in the serum of mice. Biochemical kits were used to measure the levels of malondialdehyde (MDA), nitric oxide (NO), and superoxide dismutase (SOD) in inflammatory tissue. The intercellular reactive oxygen species (ROS) content was detected by ROS staining, and the morphology of inflammatory tissue was observed by hematoxylin-eosin (HE) and tartrate-resistant acid phosphatase (TRAP) staining.

Results: The administration of resveratrol significantly reduced bone loss around the implant and prevented the apoptosis of gingival cells ($p < 0.001$). Additionally, resveratrol effectively reduced the concentration of serum inflammatory factors and inflammation-related proteins, namely caspase-1 and p-p65/p65 ($p < 0.001$). Additionally, in the resveratrol intervention group, the contents of MDA and NO, and the level of ROS decreased, while the content of SOD increased ($p < 0.05$). The HE, immunofluorescence, and TRAP staining results confirmed that resveratrol effectively reduced the number of total inflammatory cells in gingival tissue ($p < 0.05$).

Conclusion: Resveratrol has the potential to alleviate peri-implant inflammation and regulate the MAPK/AKT/NF-κB signaling pathway. This offers a novel approach for drug-based clinical interventions in peri-implant inflammation.

Keywords: resveratrol; MAPK/AKT/NF-κB signaling pathway; peri-implant inflammation

Introduction

Peri-implant inflammation, a common complication of implant repair, is the primary cause of implant failure [1]. It is characterized by inflammation around the implant and gradual loss of supporting bone tissue due to bacterial accumulation, leading to local inflammation, bone tissue absorption, and implant loosening. According to statistics, the prevalence of peri-implantitis is between 9.25% and 12.8%. In humans, the prevalence of peri-implantitis is significant, ranging from 17% to 22% [2]. The primary approach for treating peri-implantitis is to remove plaque from the implant's surface, control inflammation, and reconstruct the implant site.

With advancements in technology, new treatments for peri-implantitis are available. For instance, non-surgical approaches are diverse and generally well-accepted by patients due to minimal trauma, but they often fail to cure the condition completely [3]. Currently, antibiotics, such as tetracyclines, penicillin, nitroimidazoles, and macrolides, as well as other medications, are the main treatments for peri-implant inflammation, with minocycline, a tetracycline, being the most widely used broad-spectrum antibiotic. Therefore, understanding the pathogenesis of peri-implant inflammation is crucial for developing more effective treatments.

Resveratrol is a polyphenol plant protectant and a member of the stilbene family. It is an edible plant com-

Copyright: © 2025 The Author(s). Published by Discovery Medicine. This is an open access article under the CC BY 4.0 license.
Note: *Discovery Medicine* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

pound primarily found in grape skin and seed, wine, and other plant foods, especially peanuts, berries, and tea [4,5]. Studies have reported that resveratrol has antioxidant, anti-inflammatory, and antitumor properties [6,7]. Its preventive effect on bone loss has been confirmed in rats with periodontitis [8], although the exact mechanism remains unclear. Ginsenoside Rb3 can inhibit the proliferation of periodontal pathogenic bacteria by modulating this pathway [9]. Moreover, resveratrol reduces high glucose-induced cardiomyocyte injury by interfering with the reactive oxygen species (ROS)-Mitogen activated protein kinase-Nuclear factor kappa-B (MAPK-NF-κB) signaling pathway [10]. Therefore, we hypothesize that this pathway is related to peri-implant inflammation. This research evaluates whether resveratrol can alleviate peri-implant inflammation and modulate the MAPK/Protein kinase B (AKT)/NF-κB signaling pathway. This information may provide a new approach for the treatment of peri-implant inflammation.

Materials and Methods

Animal Model

Thirty-five male C57BL/6 mice (body weight, 18–22 g; age, 4-week-old) were provided by Hubei Provincial Centre for Disease Control and Prevention (Hubei, China). All experimental protocols were approved by the animal ethics committee of Kangtai Medical Inspection Service Hebei Co., Ltd. (No: MDL 2022-09-25-01). Mice were housed under specific pathogen-free conditions, and animal rearing was conducted in accordance with institutional standards.

Mice were intraperitoneally injected with ketamine (100 mg/kg) and xylazine (5 mg/kg) for general anesthesia after 1 week of adaptive feeding. The right maxillary first molar was extracted, and the implant was implanted in the fossa of the palatine root (customized by Galway Group; size, 1.7 mm; primary diameter, 0.7 mm; crown square hexagonal side length, 0.9 mm; tip diameter, 0.4 mm) [11]. Healing occurred 4 weeks after osseointegration.

Mice were separated randomly into 5 groups (n = 7): control group (control), model control group (model), low-dose resveratrol (1602105-100MG, Sigma-Aldrich, St. Louis, MO, USA) group [model + low resveratrol (RSV) 200 mg/kg·d], medium-dose resveratrol group [model + medium RSV 400 mg/kg·d], high-dose resveratrol group [model + high RSV 600 mg/kg·d]. For two weeks, these mice were given intragastric resveratrol daily. The control and model groups were given the same amount of normal saline. The 5-0 silk thread soaked in heat extinguishing *Porphyromonas gingivalis* (P.g) was ligated in the implant neck of the model and treatment groups, and the control group was not treated. Mice were euthanized after two weeks of intervention by injecting 150 mg/kg pentobarbital sodium.

Micro-Computed Tomography

After euthanizing the mice, the right maxillary tissue was promptly isolated, with skin and muscle removed. The tissue was fixed in 4% paraformaldehyde for 24 h, ensuring the implant's head and axis were vertically positioned in both sagittal and coronal planes. Imaging was performed at isotropic voxel resolution using Dolphin 11.0 software (Dolphin Imaging and Management Solutions, Los Angeles, CA, USA). Operating parameters were as follows: a voltage of 70 kVp, a current of 200 µA, a resolution of 10 µm, an exposure time of 500 ms, and 5 frames per view. A three-dimensional analysis was performed to calculate the extent of bone loss around the implant [12,13]. To quantify peri-implant bone resorption, a cylinder with a diameter of 1.0 mm and a height of 1.7 mm was defined around the implant's axis. The bone volume fraction within the volume of interest (bone volume/total volume, BV/TV) was calculated.

The Detection of Apoptosis

Paraffin tissue sections were used for the TdT-mediated dUTP-biotin nick end labeling (TUNEL) Apoptosis Detection Kit (Beyotime, C1088, Shanghai, China). After staining with TUNEL, the sections were washed with PBS. Next, sections were stained with 4′,6-diamidino-2-phenylindole (DAPI, 2µg/mL; C1002, Beyotime, Shanghai, China) in the dark for 5 min. Fluorescence microscope (DM3000, Leica, Wetzlar, Germany) was adopted for observation and photography. Three sections were taken from each specimen, and 5 nonoverlapping high-magnification visual fields were chosen randomly for each slice. TUNEL-positive cells (apoptotic and total cells) were calculated with Image (Pro plus image, NIH, Bethesda, MA, USA) analysis software.

Western Blotting

The bicinchoninic acid method was used to estimate the protein content, and gel electrophoresis (Huzhen Industry, HZ0135, Shanghai, China) was used to separate the proteins. After electrophoresis, the proteins were transferred to polyvinyl difluoride membranes (Millipore, ISEQ00010, Boston, MA, USA). Membranes were blocked with non-fat milk (5%) at room temperature for 1 h. Next, caspase-1 (cat no. ab138483, abcam, Shanghai, China, 1:1000), caspase-3 (cat no. ab32351, abcam, Shanghai, China, 1:5000), B-cell lymphoma-2 (Bcl-2, cat no. ab182858, abcam, Shanghai, China, 1:2000), phospho-p65 (p-p65) (cat no. 3033, CST, Danvers, MA, USA, 1:2000), p65 (cat no. 8242, CST, Danvers, MA, USA, 1:2000), p38 MAPK (cat no. 9218, CST, Danvers, MA, USA, 1:5000), NF-κB (cat no. ab32536, abcam, Shanghai, China, 1:5000), phospho-Nuclear factor kappa-B (p-NF-κB, cat no. ab76302, abcam, Shanghai, China, 1:2000), AKT (cat no. 9272, CST, Danvers, MA, USA, 1:1000), phospho-Protein kinase B (p-AKT, cat no. 4058, CST, Danvers, MA, USA, 1:1000), and Glyceraldehyde-3-Phosphate De-

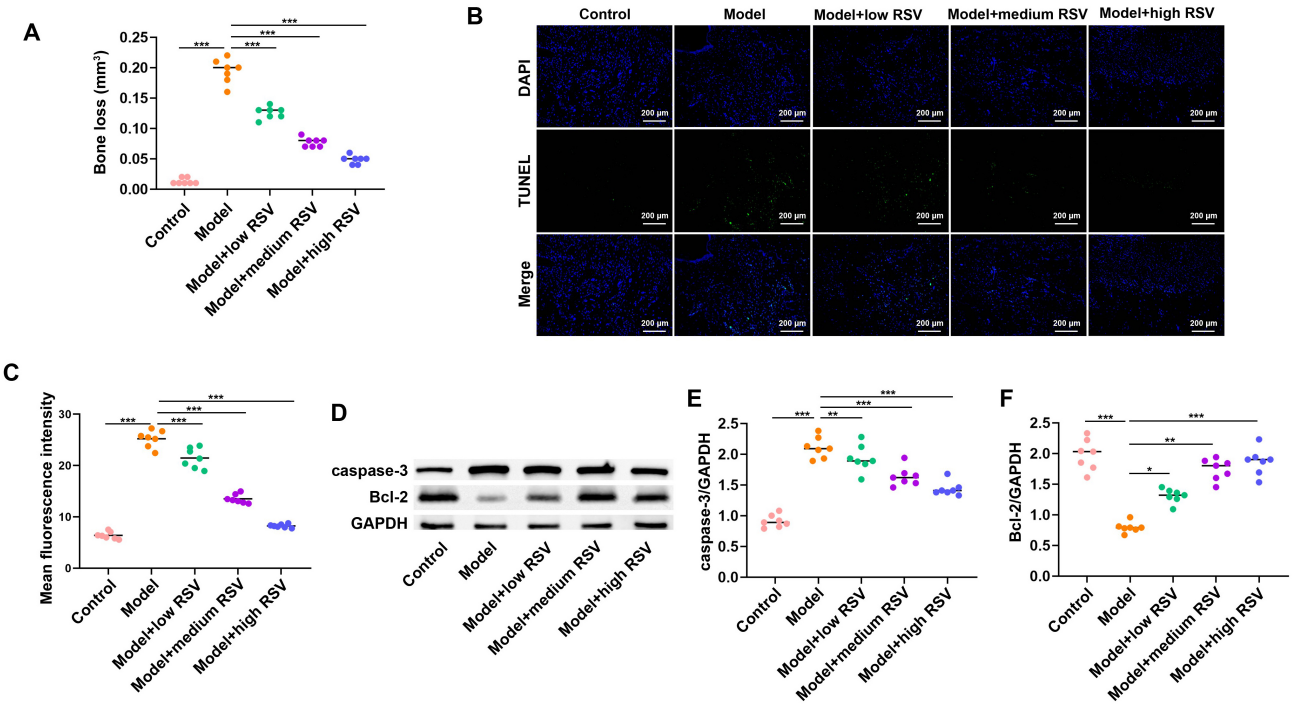

Fig. 1. The gingival tissue around the implant in mice was accompanied by significant pathological damage. (A) Amount of bone loss around the implant was calculated. (B,C) TdT-mediated dUTP-biotin nick end labeling (TUNEL) was used to estimate apoptosis. (D–F) Western blotting was used to estimate the concentrations of caspase-3 and B-cell lymphoma-2 (Bcl-2). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. N = 7. RSV, resveratrol; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase; DAPI, 4′,6-diamidino-2-phenylindole.

hydrogenase (GAPDH) (cat no. ab8245, abcam, Shanghai, China, 1:1000) were added. Membranes were incubated with horseradish peroxidase-labeled secondary antibody (1:2500, SA00001-2 and SA00001-1, Proteintech Group, Inc, Wuhan, China) at room temperature for 1 h and then developed with enhanced chemiluminescence reagents (Yisheng Biotechnology, 36208ES60, Shanghai, China). Gray-scale values were analyzed with Image J (Image J 1.8.0, National Institutes of Health, Bethesda, MA, USA).

Enzyme-Linked Immunosorbent Assay (ELISA)

According to the ELISA kits' instructions, the levels of tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), IL-1β, IL-4, and IL-10 in the serum of mice were measured. The IL-6 (A105582), IL-1β (A105612), IL-4 (A105896), and IL-10 (A105911) kits were obtained from Shanghai Fusheng Industry (Shanghai, China). The TNF-α (EK282) kit was purchased from Multi Sciences (Hangzhou, China).

Detection of Malondialdehyde (MDA), Nitric Oxide (NO), and Superoxide Dismutase (SOD)

According to the kits' instructions, the levels of MDA (GOY-0095SJ), NO (QYS-232010), and SOD (GOY-0087SJ) (Chuangsai Technology Co., Ltd., Shanghai, China) in the inflammatory tissue were measured.

Staining of Reactive Oxygen Species (ROS)

Frozen sections of gingival tissue were stained with ROS solution and incubated in darkness at 37 °C for 30 min. After washing with phosphate-buffered saline (PBS), sections were dried and stained with 4′,6-diamidino-2-phenylindole (DAPI) solution (Meng Cheng Technology, MIT-HB0747, Shanghai, China) in darkness for 10 min. Sections were then sealed with an anti-fluorescence quenching agent and observed under a fluorescence microscope (DM3000, Leica, Wetzlar, Germany).

Hematoxylin-Eosin (HE) and Tartrate-Resistant Acid Phosphatase (TRAP) Staining

For HE staining, the paraffin sections were dewaxed, rehydrated, and stained with Harris hematoxylin for 3–8 min. After rinsing, the sections were stained with eosin for 1–3 min. Gradient decolorization was performed using alcohol and xylene of varying concentrations. Sections were dried, sealed with neutral gum, and examined under a microscope (EVOS™ M7000, Thermo Fisher Scientific, Waltham, MA, USA).

Paraffin sections of periodontal tissue were taken, routinely dewaxed and hydrated, then stained with TRAP (P0332, Beyotime, Shanghai,China) and DAPI (C1002, Beyotime, Shanghai, China), blown dry, sealed with neutral gelatin, observed under the microscope (ECLIPSE Ts2, Nikon, Tokyo, Japan) and counted with osteoclasts. Five

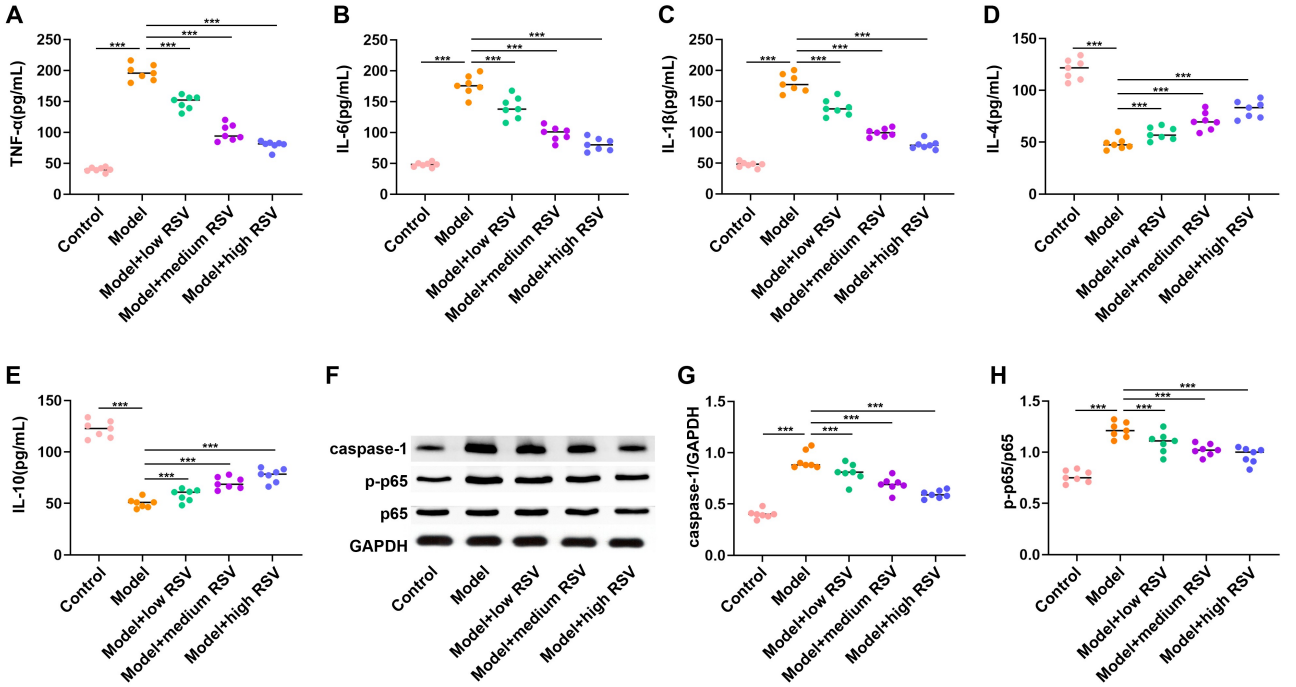

Fig. 2. Resveratrol can alleviate inflammation damage of implant-associated periodontitis tissue in mice. (A–E) Concentrations of inflammatory cytokines TNF-α, IL-6, IL-1β, IL-4, and IL-10 were estimated according to the kits' instructions. (F–H) Caspase-1, p-p65, and p65 concentrations were estimated by western blotting. ***$p < 0.001$. N = 7. TNF-α, tumor necrosis factor-α; IL-6, Interleukin-6; p-p65, phospho-p65.

fields of view were randomly selected for observation and counting of active osteoclasts in periodontal tissue specimens.

Statistical Analysis

Statistical analysis was conducted using SPSS 23.0 software (IBM, Armonk, NY, USA). All experimental data were continuous data and displayed in mean $\pm$ standard deviation. The *t*-test was used to compare two groups, while a one-way analysis of variance, followed by a posthoc Tukey test, was used to compare three or more groups. A *p*-value less than 0.05 was considered statistically significant.

Results

Resveratrol Intervention Inhibits Apoptosis of Gingival Cells

After 4 weeks, all implants were examined by percussion and showed clear metallic sounds. There was no looseness when clamped with microsurgical forceps in the mesial, distal, buccal, and lingual directions. The surrounding gums were pink, with a tough texture, and no looseness, swelling, or congestion, indicating successful bone fusion. After 2 weeks of inflammation, no mouse death or implant detachment occurred. The model and treatment groups had looseness in the near middle, far middle, buccal, and lingual directions, with deep red gums, a brittle texture, and swelling and congestion. The degree of gingival swelling in the treatment group was milder than in the model group. The survival rate of all groups of implants was 100%, with no adverse events after surgery or loss of mice during follow-up. Compared to the control group, the model group exhibited increased alveolar bone loss ($p < 0.001$). Compared to the model group, the RSV group demonstrated an improvement in alveolar bone loss, with the high-concentration RSV group showing a more significant improvement (Fig. 1A, $p < 0.001$).

As shown in Fig. 1B,C, compared to the control group, gingival cell apoptosis was increased in the model group ($p < 0.001$). Compared to the model group, resveratrol reduced cell apoptosis ($p < 0.001$). The ability to inhibit apoptosis was enhanced with the increase in resveratrol concentration. Subsequently, the concentration of apoptosis-related proteins caspase-3 and Bcl-2 in gingival tissues around implants was estimated. As shown in Fig. 1D–F, the caspase-3 concentration in the model group was increased compared to the control group ($p < 0.001$). Compared to the model group, resveratrol decreased the concentration of caspase-3 ($p < 0.01$), and the Bcl-2 level was increased ($p < 0.05$).

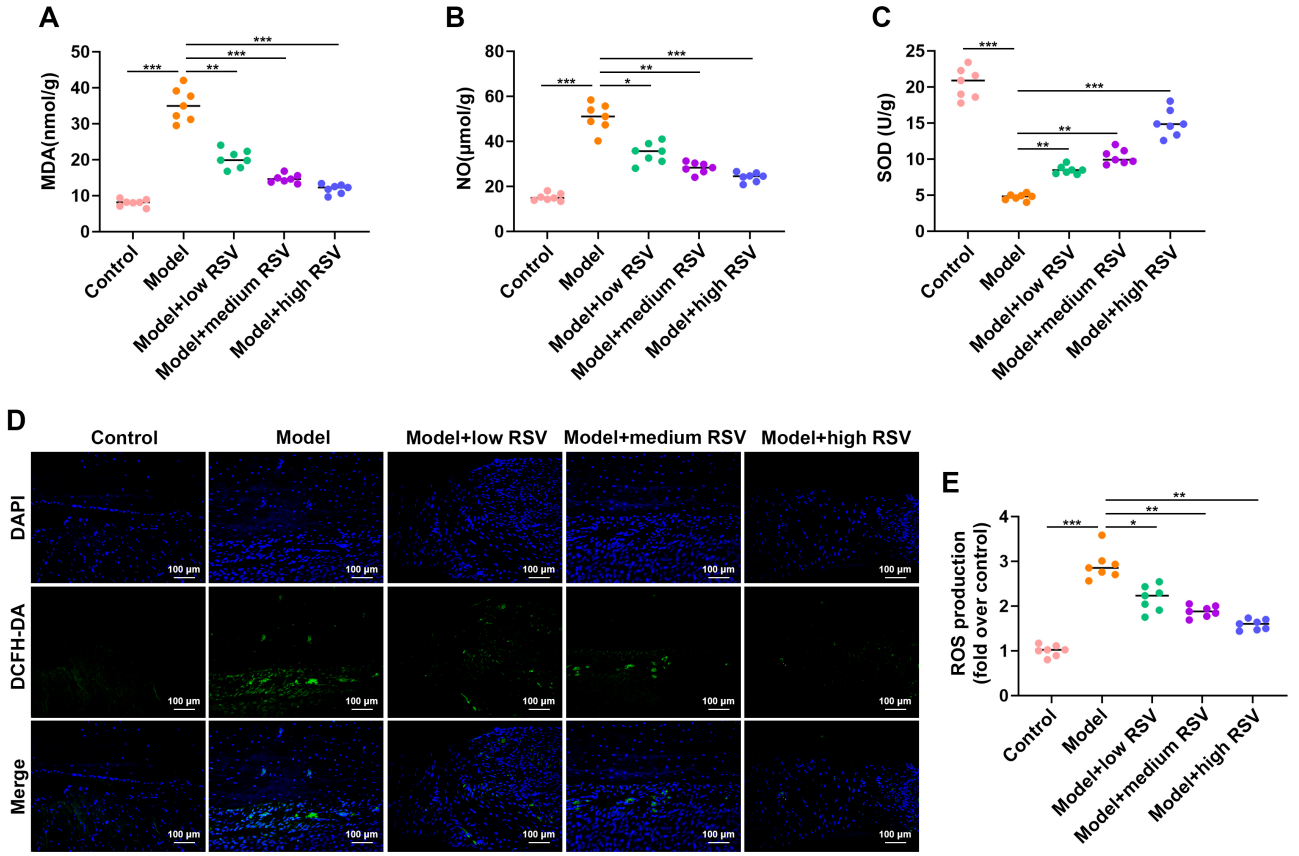

Fig. 3. Resveratrol can alleviate oxidative stress injury of peri-implant inflammation in mice. Concentrations of oxidative stress factors (A) MDA (B) NO, and (C) SOD were measured. (D) ROS staining experiment images and (E) statistical values. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; N = 7. MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase; ROS, reactive oxygen species.

Resveratrol Alleviates Inflammation of Implant-Associated Periodontitis Tissue in Mice

Compared to the control group, TNF-α, IL-6, and IL-1β concentrations in the model group increased significantly ($p < 0.001$). Compared to the model group, resveratrol decreased the concentration of serum inflammatory factors (TNF-α, IL-6, and IL-1β), and the effect was more significant with the increase of the concentration of resveratrol ($p < 0.001$). The levels of IL-4 and IL-10 were opposite to those of TNF-α, IL-6, and IL-1β (Fig. 2A–E). Additionally, we examined inflammation-related proteins in peri-implant gingival tissue (Fig. 2F,G). As shown in Fig. 2H, compared to the control group, the caspase-1 level and p-p65/p65 in the model group was significantly increased ($p < 0.001$). Conversely, the caspase-1 and p65 level in each resveratrol intervention group was markedly decreased in a dose-dependent manner ($p < 0.001$).

Resveratrol Alleviates Oxidative Stress Damage of Peri-Implantitis in Mice

MDA, NO, and SOD concentrations in inflammatory tissue around the implant were estimated. Compared to the control group, MDA and NO levels in the model group were significantly higher ($p < 0.001$) (Fig. 3A–C). After the resveratrol intervention, the MDA and NO concentrations in the model group decreased substantially ($p < 0.05$). The change in SOD concentration was opposite to those of MDA and NO. Compared to the control group, the SOD concentration in the model group declined substantially ($p < 0.001$). After the intervention of resveratrol, the SOD concentration in gingival tissue of mice increased substantially ($p < 0.01$).

According to the ROS result (Fig. 3D,E), after quantifying the fluorescence signal, it was revealed that the ROS intensity in the model group versus the control group was significantly higher ($p < 0.001$). Compared to the model group, the intensity of ROS decreased gradually after resveratrol intervention ($p < 0.05$).

Resveratrol Reduces the Osteoclast Number in Tissues Around the Implant

The results of HE staining (Fig. 4A) showed that the extent of inflammatory infiltration in the gingival tissue of the model group was remarkably increased versus the control group, and the number of inflammatory cells was significantly increased ($p < 0.001$). However, after RSV intervention, the extent of inflammatory infiltration was re-

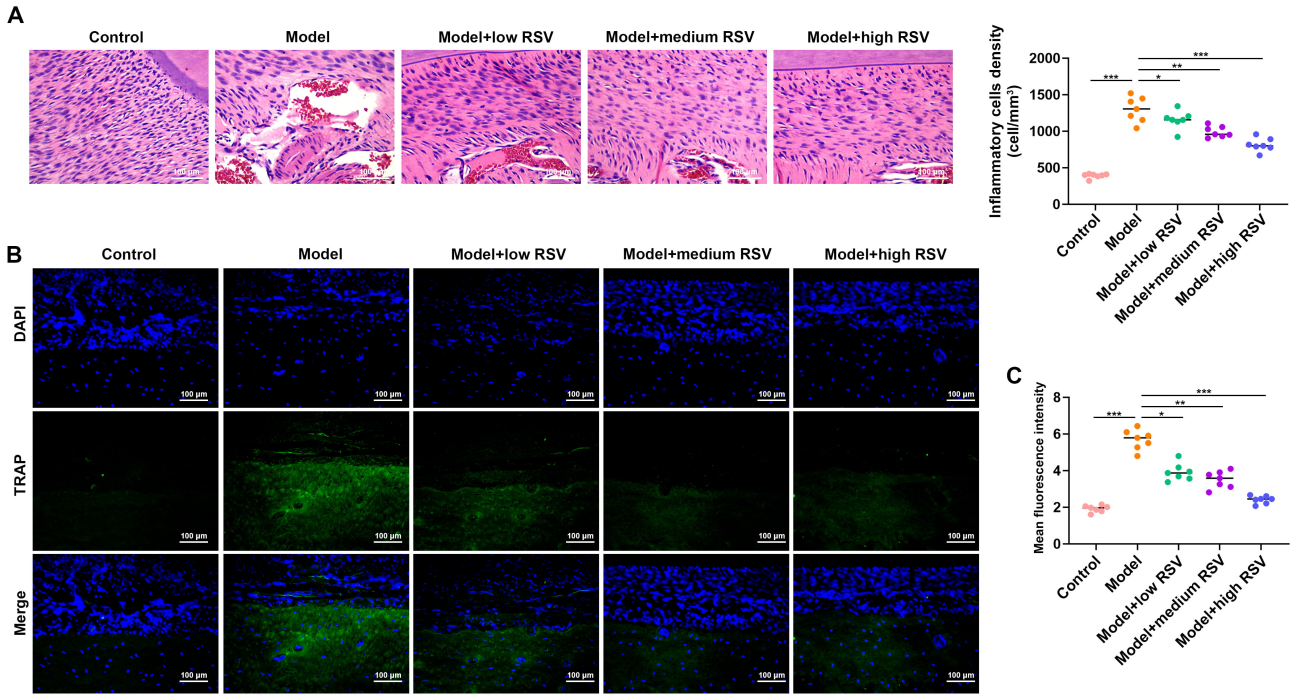

Fig. 4. Resveratrol reduces osteoclasts in peri-implant tissues. (A) HE staining and (B,C) TRAP staining results. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; N = 7. HE, hematoxylin-eosin; TRAP, tartrate-resistant acid phosphatase.

duced, and the number of inflammatory cells decreased significantly ($p < 0.05$). TRAP staining results (Fig. 4B,C) showed that the number of osteoclasts in the region of interest (ROI) of the model group was markedly higher than that of the control group ($p < 0.001$). The number of osteoclasts in the ROI of the resveratrol intervention group was considerably lower than that of the model group ($p < 0.05$).

MAPK/AKT/NF-κB Signal-Mediated Resveratrol Improves Implant-Associated Periodontitis in Mice

The levels of MAPK/AKT/NF-κB signaling pathway-related proteins in peri-implant gingival tissue of mice were estimated by western blotting. Compared to the control group, the concentration of p38 MARK in the model group was markedly higher ($p < 0.001$) (Fig. 5A–D). Compared to the model group, the concentration of p38 MARK in tissue decreased remarkably after resveratrol intervention ($p < 0.05$). Compared to the control group, the phosphorylation concentrations of NF-κB and AKT in the model group increased significantly ($p < 0.001$). Conversely, the phosphorylation concentrations of NF-κB and AKT decreased significantly after resveratrol intervention ($p < 0.05$) (Fig. 5A–D).

Discussion

Peri-implant inflammation begins and develops as a result of the interaction between the causative organisms in the subgingival dental biofilm and the host's response, and the use of topical antibiotics can be considered an effective treatment for peri-implant inflammation [14,15]. Dental implants are essential for replacing missing teeth. However, studies indicate that peri-implant inflammation occurs in about one-third of patients and one-fifth of implants [16,17], and research on the use of plant extracts in peri-implant inflammation is limited. In this study, resveratrol intervention significantly improved bone loss around the implant and inhibited cell apoptosis in the surrounding gum tissue. This suggests a new approach for treating peri-implant inflammation with plant extract compounds.

The anti-inflammatory effects of plant extracts have been confirmed in many studies [18,19], but they are not commonly used to treat peri-implant inflammation. In this study, the control group showed a significant increase in pro-inflammatory factors (TNF-α, IL-6, and IL-1β) and a significant decrease in anti-inflammatory factors (IL-4 and IL-10). Resveratrol inhibited the increase of pro-inflammatory cytokines in the inflammatory tissue and promoted the increase of anti-inflammatory factors. Caspase-1, which processes inflammatory cytokines into mature proteins and induces apoptosis after overexpression, was also examined. Consistent with previous results [20], the concentration of caspase-1 and the degree of p65 phosphorylation were significantly higher in mice with peri-implant inflammation than those without the condition. After the resveratrol intervention, caspase-1 concentration and p65 phosphorylation decreased significantly, confirming our hypothesis.

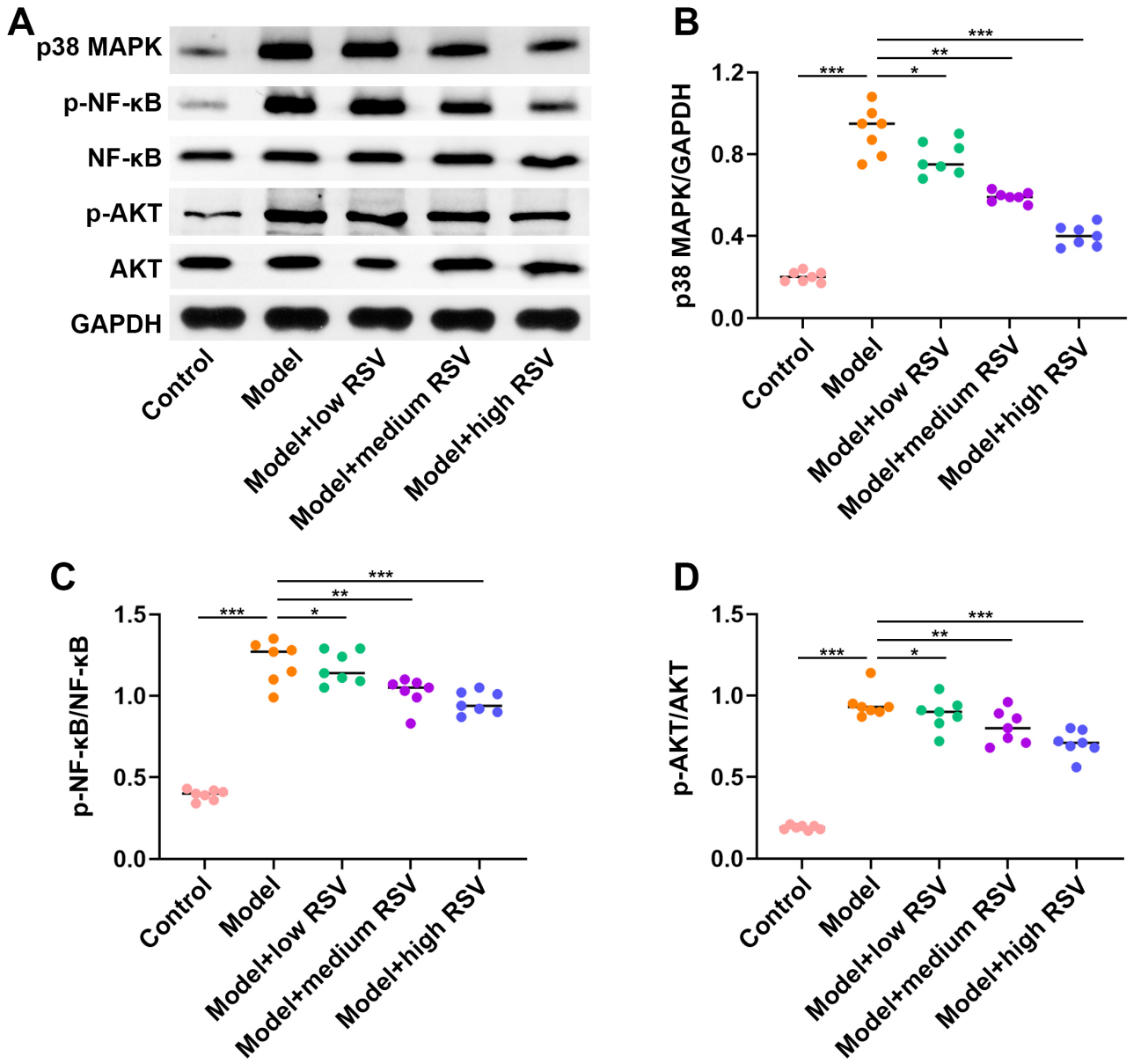

Fig. 5. MAPK/AKT/NF-κB-signal mediated resveratrol improves implant-associated periodontitis in mice. (A–D) Concentrations of p38 MAPK, p-NF-κB, NF-κB, p-AKT, and AKT were estimated by western blotting. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; N = 7. MAPK/AKT/NF-κB, Mitogen activated protein kinase/Protein kinase B/Nuclear factor kappa-B; p-NF-κB, phospho-Nuclear factor kappa-B; p-AKT, phospho-Protein kinase B.

MDA and SOD are crucial indicators of the body's antioxidant capacity [20–22]. Studies have demonstrated that resveratrol protects the spinal cord from injury by reducing ROS levels, including that of MDA, and increasing SOD activity [23,24]. *In vitro* and *in vivo* experiments show that oxidative stress is involved in bone resorption. Maintaining a balance between ROS and antioxidants is essential for periodontal health [25]. Another study has reported that, after resveratrol intervention, ROS production is reduced, membrane potential is increased, and cytochrome c release in the mitochondrial inner membrane is inhibited [26]. In this study, resveratrol effectively reduced the levels of MDA, NO, and other ROS in the inflammatory tissue, and increased the SOD level, suggesting resveratrol improved the body's antioxidant capacity.

Biopsies of human peri-implant inflammation reveal that inflammatory infiltration is twice as extensive as in periodontitis, with a higher number and density of plasma cells and macrophages [27]. Histologically, peri-implant inflammation sites tend to associate with larger inflammatory lesions compared to periodontitis sites. Consistent with these results, our experiment showed a significant increase in the number of inflammatory cells in the model group, which was effectively alleviated by resveratrol.

One study has shown that MAPK, AKT, and NF-κB signaling pathways are involved in the induction of apoptosis [28]. Additionally, ROS-induced oxidative stress may activate the MAPK/AKT pathway [29]. Yue *et al*. [30] reported increased NF-κB levels in patients with periodontitis. At the same time, Jung *et al*. [31] demonstrated that the NF-κB signaling pathway plays a role in the immune response to peri-implant inflammation. In this study, resveratrol intervention altered the levels of MAPK/AKT/NF-κB signaling pathway-related proteins. However, to confirm whether resveratrol can alleviate peri-implantitis through this signaling pathway, further studies that interfere with the MAPK/AKT/NF-κB signaling pathway are needed.

Conclusion

In conclusion, this study demonstrates that resveratrol effectively alleviates bone loss caused by peri-implant inflammation and regulates associated inflammatory factors through the MAPK/AKT/NF-κB signaling pathway. These findings suggest a promising avenue for drug-based clinical interventions in peri-implant inflammation.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

CZ has been involved in drafting the manuscript or revising it critically for important intellectual content. CZ, BQJ and DJQ have made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data. DJQ has helped perform the analysis with constructive discussions and supervision and has been involved in drafting the manuscript and revising it critically for important intellectual content. All authors have given final approval for the version to be published. Each author have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed significantly to editorial changes of important content.

Ethics Approval and Consent to Participate

All animal experiments complied with the ARRIVE reporting. All experimental protocols were approved by the Beijing Biocisco Biomedical Technology Co., Ltd. Ethics Committee (No: MDL 2022-09-25-01).

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Korsch M, Walther W. Peri-Implantitis Associated with Type of Cement: A Retrospective Analysis of Different Types of Cement and Their Clinical Correlation to the Peri-Implant Tissue. Clinical Implant Dentistry and Related Research. 2015; 17: e434–43.

[2] Stacchi C, Troiano G, Rapani A, Lombardi T, Sentineri R, Speroni S, *et al*. Factors influencing the prevalence of peri-implantitis in implants inserted in augmented maxillary sinuses: A multicenter cross-sectional study. Journal of Periodontology. 2021; 92: 1117–1125.

[3] Shafizadeh M, Amid R, Mahmoum M, Kadkhodazadeh M. Histopathological characterization of peri-implant diseases: A systematic review and meta-analysis. Archives of Oral Biology. 2021; 132: 105288.

[4] Chudzińska M, Rogowicz D, Wołowiec Ł, Banach J, Sielski S, Bujak R, *et al*. Resveratrol and cardiovascular system-the unfulfilled hopes. Irish Journal of Medical Science. 2021; 190: 981–986.

[5] Lin Q, Banu K, Ni Z, Leventhal JS, Menon MC. Podocyte Autophagy in Homeostasis and Disease. Journal of Clinical Medicine. 2021; 10: 1184.

[6] Xu D, Li Y, Zhang B, Wang Y, Liu Y, Luo Y, *et al*. Resveratrol alleviate hypoxic pulmonary hypertension via anti-inflammation and anti-oxidant pathways in rats. International Journal of Medical Sciences. 2016; 13: 942–954.

[7] Rauf A, Imran M, Butt MS, Nadeem M, Peters DG, Mubarak MS. Resveratrol as an anti-cancer agent: A review. Critical Reviews in Food Science and Nutrition. 2018; 58: 1428–1447.

[8] Yang R, Yan Y, Wu Z, Wei Y, Song H, Zhu L, *et al*. Resveratrol-loaded titania nanotube coatings promote osteogenesis and inhibit inflammation through reducing the reactive oxygen species production via regulation of NF-κB signaling pathway. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 131: 112513.

[9] Sun M, Ji Y, Li Z, Chen R, Zhou S, Liu C, *et al*. Ginsenoside Rb3 Inhibits Pro-Inflammatory Cytokines via MAPK/AKT/NF-κB Pathways and Attenuates Rat Alveolar Bone Resorption in Response to *Porphyromonas gingivalis* LPS. Molecules. 2020; 25: 4815.

[10] Cao G, Fan J, Yu H, Chen Z. Resveratrol attenuates high glucose-induced cardiomyocytes injury via interfering ROS-MAPK-NF-κB signaling pathway. International Journal of Clinical and Experimental Pathology. 2018; 11: 48–57.

[11] Ribeiro S, Carvalho AM, Fernandes EM, Gomes ME, Reis RL, Bayon Y, *et al*. Development and characterisation of cytocompatible polyester substrates with tunable mechanical properties and degradation rate. Acta Biomaterialia. 2021; 121: 303–315.

[12] Shiba T, Komatsu K, Sudo T, Sawafuji R, Saso A, Ueda S, *et al*. Comparison of Periodontal Bacteria of Edo and Modern Periods Using Novel Diagnostic Approach for Periodontitis With Micro-

CT. Frontiers in Cellular and Infection Microbiology. 2021; 11: 723821.

[13] Nakao Y, Fukuda T, Zhang Q, Sanui T, Shinjo T, Kou X, *et al*. Exosomes from TNF-α-treated human gingiva-derived MSCs enhance M2 macrophage polarization and inhibit periodontal bone loss. Acta Biomaterialia. 2021; 122: 306–324.

[14] Hernández-Vargas P, Muñoz M, Domínguez F. Identifying biomarkers for predicting successful embryo implantation: applying single to multi-OMICs to improve reproductive outcomes. Human Reproduction Update. 2020; 26: 264–301.

[15] Niringiyumukiza JD, Cai H, Xiang W. Prostaglandin E2 involvement in mammalian female fertility: ovulation, fertilization, embryo development and early implantation. Reproductive Biology and Endocrinology. 2018; 16: 43.

[16] Renvert S, Persson GR, Pirih FQ, Camargo PM. Peri-implant health, peri-implant mucositis, and peri-implantitis: Case definitions and diagnostic considerations. Journal of Clinical Periodontology. 2018; 45: S278–S285.

[17] Berglundh T, Armitage G, Araujo MG, Avila-Ortiz G, Blanco J, Camargo PM, *et al*. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Journal of Clinical Periodontology. 2018; 45: S286–S291.

[18] Sangiovanni E, Fumagalli M, Pacchetti B, Piazza S, Magnavacca A, Khalilpour S, *et al*. Cannabis sativa L. extract and cannabidiol inhibit *in vitro* mediators of skin inflammation and wound injury. Phytotherapy Research. 2019; 33: 2083–2093.

[19] Khaksarian M, Mahmoudvand H, Alipour M, Naizi M, Hasanvand KH, Nadri S. Effect of Nectaroscordum koelzi Methanolic Extract on Acute and Chronic Inflammation in Male Mice. Current Drug Discovery Technologies. 2021; 18: 525–531.

[20] Che C, Liu J, Yang J, Ma L, Bai N, Zhang Q. Osteopontin is essential for IL-1β production and apoptosis in peri-implantitis. Clinical Implant Dentistry and Related Research. 2018; 20: 384–392.

[21] Reastuty R, Haryuna TSH. Correlation of SOD and MDA Expression in the Organ of Corti and Changes in the Function of Outer Hair Cells Measured by DPOAE Examination in Noise-Exposed Rat Cochlea. Reports of Biochemistry & Molecular Biology. 2021; 10: 41–49.

[22] Yin Y, Han W, Cao Y. Association between activities of SOD, MDA and Na^+-K^+-ATPase in peripheral blood of patients with acute myocardial infarction and the complication of varying degrees of arrhythmia. Hellenic Journal of Cardiology. 2019; 60: 366–371.

[23] Fu S, Lv R, Wang L, Hou H, Liu H, Shao S. Resveratrol, an antioxidant, protects spinal cord injury in rats by suppressing MAPK pathway. Saudi Journal of Biological Sciences. 2018; 25: 259–266.

[24] Chen W, Zhao Z, Zhao S, Zhang L, Song Q. Resveratrol and Puerarin loaded polymeric nanoparticles to enhance the chemotherapeutic efficacy in spinal cord injury. Biomedical Microdevices. 2020; 22: 69.

[25] Araújo AAD, Pereira ADSBF, Medeiros CACXD, Brito GADC, Leitão RFDC, Araújo LDS, *et al*. Effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of periodontitis. PLoS ONE. 2017; 12: e0183506.

[26] Yang G, Chang CC, Yang Y, Yuan L, Xu L, Ho CT, *et al*. Resveratrol Alleviates Rheumatoid Arthritis via Reducing ROS and Inflammation, Inhibiting MAPK Signaling Pathways, and Suppressing Angiogenesis. Journal of Agricultural and Food Chemistry. 2018; 66: 12953–12960.

[27] Jepsen S, Berglundh T, Genco R, Aass AM, Demirel K, Derks J, *et al*. Primary prevention of peri-implantitis: managing peri-implant mucositis. Journal of Clinical Periodontology. 2015; 42: S152–S157.

[28] Sheng YN, Luo YH, Liu SB, Xu WT, Zhang Y, Zhang T, *et al*. Zeaxanthin Induces Apoptosis via ROS-Regulated MAPK and AKT Signaling Pathway in Human Gastric Cancer Cells. OncoTargets and Therapy. 2020; 13: 10995–11006.

[29] Zhu M, Miao S, Zhou W, Elnesr SS, Dong X, Zou X. MAPK, AKT/FoxO3a and mTOR pathways are involved in cadmium regulating the cell cycle, proliferation and apoptosis of chicken follicular granulosa cells. Ecotoxicology and Environmental Safety. 2021; 214: 112091.

[30] Yue Y, Liu X, Li Y, Xia B, Yu W. The role of TLR4/MyD88/NF-κB pathway in periodontitis-induced liver inflammation of rats. Oral Diseases. 2021; 27: 1012–1021.

[31] Jung HJ, Lee W, Shin JS, Lee SK, Lee JH. The Effects of NF-kB Inhibition with p65-TMD-Linked PTD on Inflammatory Responses at Peri-implantitis Sites. Inflammation. 2021; 44: 2291–2301.