

## Resveratrol Inhibited Inflammation and Alveolar Bone Loss in Periodontitis

Research Article

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### Abstract

Resveratrol, a natural polyphenol with antioxidant, anti-inflammatory and immune regulatory properties, exists widely in many kinds of plants. Previous studies indicated that resveratrol can inhibit osteoclast differentiation and promote osteoblast formation. We hypothesized that resveratrol can influence the bone metabolism in inflammatory diseases, such as periodontitis, depending on its anti-inflammatory and bone-protective features. In the present study, the rat periodontitis model was established to investigate the effects of resveratrol on alveolar bone destruction and gingival inflammation. We found that resveratrol significantly suppressed the mRNA expression of pro-inflammatory cytokines, including IL-6, IL-1 $\beta$  and TNF- $\alpha$  in diseased periodontal tissue. RANKL, the intensive osteoclast inducer, was elevated in periodontitis tissue while significantly inhibited by resveratrol administration. The alveolar bone absorption was also significantly arrested in resveratrol treated rats, compared to vehicle treated rats. These results suggest that resveratrol can inhibit the inflammation and protect the alveolar bone from periodontitis, implying resveratrol may be considered as new adjunctive therapy in addition to traditional mechanical treatment for periodontitis.

**Keywords:** Resveratrol; Periodontitis; Inflammation; RANKL; Alveolar Bone Loss.

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### Introduction

As one of the major causes of adult tooth loss, periodontitis is attributed to inflammatory response initiated by the periodontal microorganisms in dental plaque. The supporting tissue breakdown following continuous inflammation includes connective tissue degradation and alveolar bone destruction, leading to periodontal pocket, clinical attachment loss, tooth mobility and eventually tooth loss.

Resveratrol, a natural polyphenol, exists widely in several plants and can protect plants from injury caused by pathogen attacks. Resveratrol can be found in grapes, blueberries, raspberries and peanuts. Substantial evidences have revealed that resveratrol exhibits potent antioxidant, anti-inflammatory and immune regula-

tory properties. Resveratrol protected diabetic rats from cerebral infarction and reduced malondialdehyde, an oxidative stress marker, and also inflammatory markers such as TNF- $\alpha$ , IL-6, and myeloperoxidase, while significantly increased the levels of antioxidant and anti-inflammatory markers like catalase, superoxide dismutase, and IL-10 [21]. *In vitro* study also proved its anti-inflammatory feature in that resveratrol treatment decreased the production of pro-inflammatory cytokines like IL-1 $\beta$ , IL-6, IL-8, IL-12 and TNF- $\alpha$  in human periodontal ligament cells stimulated by *P. gingivalis* LPS [24]. Resveratrol inhibited receptor activator of NF- $\kappa$ B ligand (RANKL)-induced formation of osteoclasts and bone resorption, meanwhile enhanced the expression of osteoblast markers like osteocalcin and osteopontin in human bone marrow mesenchymal stem cells, suggesting resveratrol can prevent osteoclast formation while promoting osteoblast differentiation [3]. Resveratrol also suppressed RANKL-induced acetylation and nuclear translocation of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) as well as osteoclastogenesis in high density bone cultures *in vitro* [27].

According to its significant protective properties on inflammation and bone metabolism, resveratrol was considered as a potential therapeutic agent for inflammatory diseases and related bone loss, such as periodontitis. In our study, we investigated the effects of resveratrol on the inflammation response and bone destruction in an experimental periodontitis model. The results showed that resveratrol treatment can reduce the expressions of inflammatory cytokines as well as the alveolar bone destruction in periodontitis rats.

### Materials & Methods

#### Experimental Animals and Bacteria

This study was performed in accordance with the animal protocol

approved by the ethics committee of state key laboratory of oral diseases at Sichuan University. Seven-week-old male SD rats were obtained from Animal Center of West China Center of Medical Sciences, Sichuan University. A total of 35 rats used in this study were housed in the animal care center and kept under standard conditions (room temperature of  $22 \pm 2^{\circ}\text{C}$ , 12h light/dark cycle, and free access to normal commercial food and tap water). All rats were acclimatized for 1 week prior to any experimental manipulation. *P. gingivalis* ATCC33277 strains were obtained from State Key Laboratory of Oral Diseases, Sichuan University.

### Periodontitis Model

Thirty-five rats were randomly divided into 3 groups: healthy control group ( $n=9$ ), periodontitis group ( $n=14$ ) and resveratrol group ( $n=12$ ). Rats in periodontitis group and resveratrol group received a wire ligation (diameter: 0.2mm) around the cervix of the left maxillary first molar under anesthesia by intraperitoneal injection of chloral hydrate (3mg/kg). After ligation, 0.5ml *P. gingivalis* ATCC33277 broth ( $1.5 \times 10^9 \text{ CFU/ml}$ ) were inoculated in the gingival crevice of the ligated molars every other day for 3 times in total to induce periodontitis in those rats. After 21 days, three rats were randomly selected from PD group and resveratrol group to evaluate the experimental periodontitis induction. The alveolar bone loss of ligated molars was compared with the contralateral molars by the morphologic analysis, while the inflammatory infiltration and periodontal breakdown were observed by histopathological staining. The remaining rats in both groups received wire removal and normal diet for 1 week. Then the rats in resveratrol group were treated with daily resveratrol (Sigma-Aldrich, diluted by 2% alcohol into 1mg/ml, 10ml/kg) gavage, while the periodontitis group was treated with daily 2% alcohol (10ml/kg) gavage. The rats in healthy control group received neither ligation nor gavage. All animals were euthanized after 30 days.

### Real time RT-PCR, ELISA and Alveolar Bone Loss

Gingival tissues of the left maxillary first molar of all rats were collected in RNA later Tissue Protect Tubes (Qiagen, Germany) at  $4^{\circ}\text{C}$  for 12h, then stored at  $-80^{\circ}\text{C}$ .

Total RNA was isolated with the RNeasy Plus Mini Kit (Qiagen, Valencia, CA, USA) following the manufacturer's instructions, and reverse transcribed into double-stranded cDNA using the PrimeScript<sup>TM</sup> RT reagent Kit with gDNA Eraser (Takara). cDNA samples were amplified with specific primers on a ABI7300 Real-Time PCR Detection System. The relative gene expression level was quantified by the  $2^{-\Delta\Delta Ct}$  method and normalized to GAPDH expression.

The rat blood collected from the right ventricle were centrifuged at 1000g for 10 min at  $4^{\circ}\text{C}$ . The supernatant was collected into tubes and stored at  $-20^{\circ}\text{C}$ . The concentrations of serum C-reactive protein were measured via enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp, US) according to the manufacturer's guidelines.

The left maxillary bones were fixed in 10% neutral formalin at  $4^{\circ}\text{C}$  for 24 hours, then defleshed and stained with 1% aqueous methylene blue (Sigma-Aldrich). The images of both buccal and palatal sides of the first molar were taken by a stereoscopic microscope (Leica, E24HD). The alveolar bone loss was evaluated

by the mean distance from CEJ to alveolar bone crest at 6 sites (mesio-buccal, mid-buccal, disto-buccal, mesio-palatal, mid-palatal and disto-palatal) using LAS V4.2 software at 8 fold magnification for 3 times.

### Statistical Analysis

The data were presented as mean  $\pm$  SEM. Statistical analysis was administered with SPSS 17.0 software. Differences between groups were assessed by one-way analysis of variance (ANOVA) with a student's *t*-test and were considered significant when  $P < 0.05$ .

## Results

### Resveratrol inhibits inflammatory cytokine expression in periodontitis tissues

To investigate the effects of resveratrol on inflammation and bone destruction *in vivo*, an experimental periodontitis model was established by periodontal ligation and oral inoculation of *P. gingivalis*. A total of 35 SD rats were randomly assigned into control (Con,  $n=9$ ), periodontitis (PD,  $n=14$ ) and resveratrol therapy (RSV,  $n=12$ ) groups. Rats in latter two groups were treated with oral gavage of either vehicle control or resveratrol for 30 days. Histopathological examination showed alveolar bone loss, apical migration of junctional epithelium, periodontal pocket formation and inflammatory infiltration in periodontitis slides. Morphologic analysis showed obvious alveolar bone loss in ligatured side compared with the other side (Figure 1A).

We found that the expression of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were significantly increased in gingival tissues from rats with periodontitis ( $P < 0.05$ ). Compared with the highly increased cytokine profiles in periodontitis rats, the gingival expression levels of the cytokines in resveratrol treated animals were significantly down-regulated (Figure 1B) ( $P < 0.05$ ). The ELISA results revealed that serum CRP concentrations of periodontitis animals ascended to nearly 3 folds of healthy rats ( $P < 0.05$ ). However, resveratrol and vehicle treated rats had almost similar serum CRP levels, suggesting that resveratrol treatment show no significant effects on serum CRP (Figure 1C).

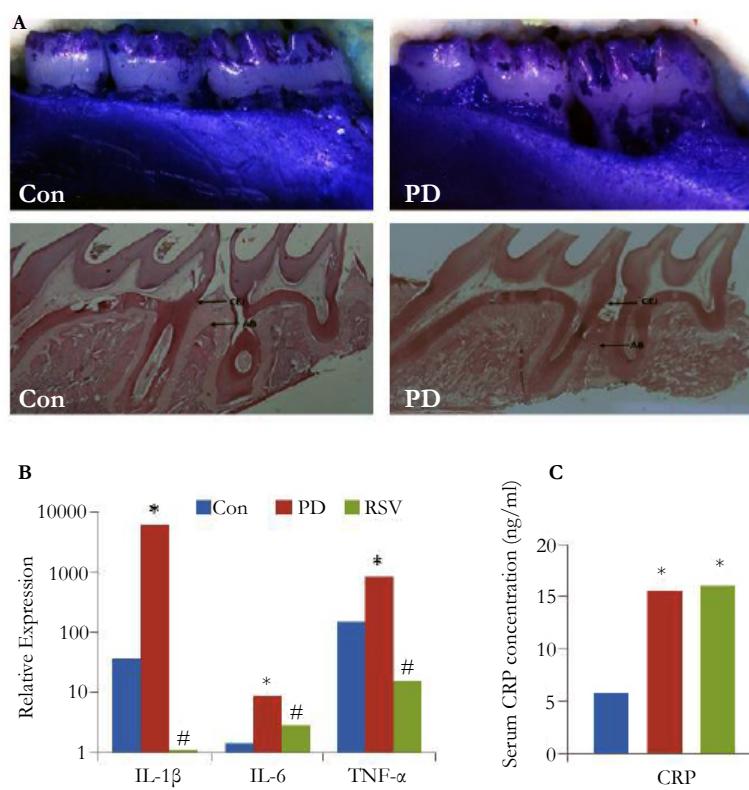
### Resveratrol reduces RANKL expression and alveolar bone loss in periodontitis

RANKL, which is well known for its pivot role in destructive bone diseases, is significantly elevated in the diseased tissues in accordance with the alteration of gingival cytokine profiles. The enhanced RANKL expression in the periodontitis tissues was significantly neutralized by resveratrol treatment ( $P < 0.05$ ) (Figure 2B), suggesting protective effect of resveratrol against inflammation and bone destruction. Morphometric analysis showed advanced alveolar bone resorption in the periodontitis group (Figure 2A) and histological results showed interproximal bone destruction and inflammatory infiltration in the periodontitis and resveratrol groups (Data not shown). As a specific feature of periodontitis, the alveolar bone loss of the control, periodontitis, and resveratrol groups was  $0.46 \pm 0.10 \text{ mm}$ ,  $1.15 \pm 0.27 \text{ mm}$ , and  $0.87 \pm 0.19 \text{ mm}$ , respectively. Resveratrol treatment significantly reduced the bone destruction caused by periodontitis ( $P < 0.05$ ) (Figure 2C).

**Figure 1. Resveratrol inhibits inflammatory cytokine expression in periodontitis tissues.**

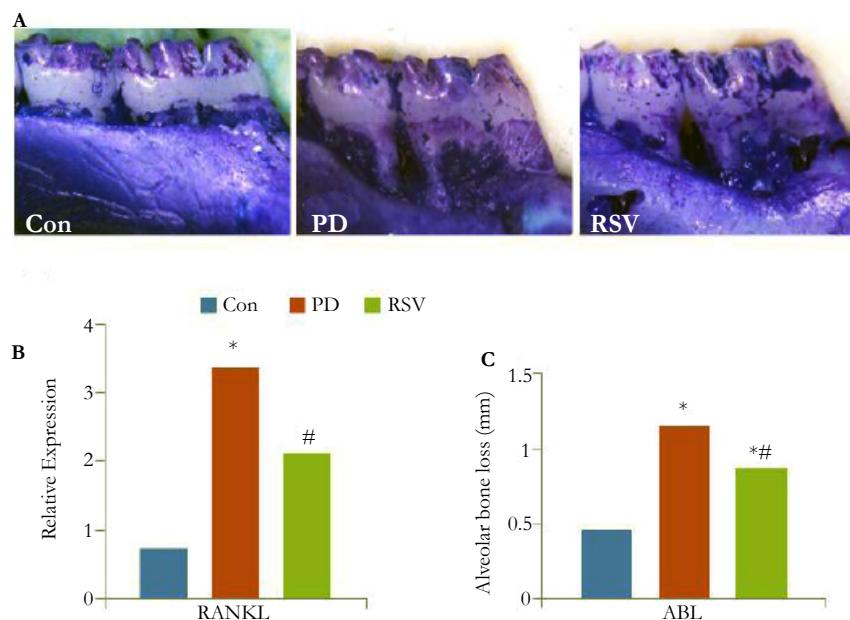
Morphological and HE staining results from ligated molars and the healthy control are shown (A). Resveratrol inhibited pro-inflammatory gene expressions in periodontitis tissue. Gene expressions relative to GAPDH in gingival tissues were shown in groups (B). Serum CRP showed no significant difference in PD and RSV groups (C).

\*P < 0.05 between Con and PD or RSV; # P < 0.05 between PD and RSV. Con, blue; PD, red; RSV, green.



**Figure 2. Resveratrol reduces RANKL expression and alveolar bone loss in periodontitis.** Morphological staining results from different groups are shown (A). RSV inhibited RANKL expression in diseased periodontal tissue (B). The alveolar bone loss was  $0.46 \pm 0.10$  mm (Con),  $1.15 \pm 0.27$  mm (PD) and  $0.87 \pm 0.19$  mm (RSV), respectively (C).

\*P < 0.05 between Con and PD or RSV; # P < 0.05 between PD and RSV. Con, blue; PD, red; RSV, green.



## Discussion

In the present study, we established an experimental periodontitis model by periodontal ligation and oral inoculation of *P. gingivalis*. Animals in periodontitis and resveratrol groups were treated with oral gavage of either vehicle control or resveratrol for 30 days. The resveratrol administration significantly suppressed the en-

hanced expression of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  mRNA in inflammatory gingivae. The increased RANKL production in periodontitis tissues was significantly neutralized by resveratrol treatment, while alleviated alveolar bone loss was observed in resveratrol treated rats.

Dental plaque biofilm is the initiating factor of periodontal dis-

ease, which can be aggravated by factors conductive to plaque deposition. Ligaturing silk or wire around molars was widely applied to establish periodontitis models [15, 16]. Kara et al. showed alveolar bone loss as well as the formation of periodontal pocket in rats with cotton wire ligatured around the cervix of first molar after 4 weeks [9]. Obvious alveolar bone loss can be observed in rats receiving tube feeding with *P. gingivalis* [5]. In our study, we established periodontitis model successfully in 3 weeks, in accordance with studies which combined ligation with *P. gingivalis* vaccination and high-sugar drink and diet [15].

The anti-inflammatory effects of resveratrol have been confirmed by substantial studies. Kim et al. revealed that the expression levels of IL-4, IL-5, prostaglandin D synthase, and leukotriene C4 synthase were significantly decreased by the administration of resveratrol [11], while other researchers showed that resveratrol and its derivatives could decrease IL-17 production in human mononuclear cells and gingival tissue of rats with periodontitis [4, 14]. The production of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-8, IL-12 and TNF- $\alpha$  and NO production of HPLCs stimulated by *P. gingivalis* LPS were decreased by the treatment of resveratrol [24]. Resveratrol could decrease IL-1 $\beta$ , TNF- $\alpha$  and other pro-inflammatory mediators in liver from old mice [32]. Similarly, we can see a decrease in the level of IL-6, IL-1 $\beta$  and TNF- $\alpha$  in the gingival tissue of rats with periodontitis by the therapy of resveratrol in our study, reflecting its anti-inflammatory character.

The anti-inflammatory effects may be attributed to the inhibition of NF- $\kappa$ B expression [23]. As a member of transcription factor protein family, NF- $\kappa$ B can be activated by LPS of most gram-negative bacteria through the Toll like receptor-4 and plays an pivot role in regulation of inflammatory cytokines [6, 18]. Cytokines participating the early immune response and inflammatory reaction, such as IL-6 and TNF- $\alpha$ , are regulated by the NF- $\kappa$ B signaling pathway [6, 18]. However, the NF- $\kappa$ B activation induced by LPS was inhibited by resveratrol [31]. Resveratrol can significantly attenuated the *P. gingivalis* LPS-induced monocyte adhesion to the endothelium by suppressing the expression of the NF- $\kappa$ B-dependent cell adhesion molecules [19]. According to these studies, we speculated that the decrease of IL-6, IL-1 $\beta$  and TNF- $\alpha$  in our study may be affected by the suppression of NF- $\kappa$ B signaling pathway by resveratrol.

In our study, the bone destruction mitigated by resveratrol may depend on RANKL expression, which was proved to be down-regulated by resveratrol. Zhao et al. found resveratrol reduced OPG/RANKL ratio and subsequent osteoclastogenesis, and prevented bone loss in the osteoporosis mice [33]. Resveratrol blocked RANKL-induced acetylation and nuclear translocation of NF- $\kappa$ B, leading to inhibition of NF- $\kappa$ B transcriptional and osteoclastogenesis [27]. Boissy et al. reported that resveratrol arrested RANKL-induced TRAP positive multinucleated cells, namely osteoclasts, which mediate bone absorption [3]. Similar with our results, Bhattacharai et al. also proved resveratrol could prevent bone loss by inhibiting inflammatory responses [2].

However, our data showed that resveratrol decreased the level of IL-6, IL-1 $\beta$  and TNF- $\alpha$  in periodontitis tissues, which may alleviate the bone absorption in another way. TNF- $\alpha$  can regulate the formation and differentiation of osteoclasts [12, 26]. IL-6 and IL-1 $\beta$  also stimulate bone destruction mediated by osteoclast indirectly through regulating the expression of RANKL [1]. Casati et al. suggested resveratrol alleviated the bone absorption through

reducing IL-17 expression [4], for IL-17 can not only promote the formation of inflammatory mediator and osteoclastogenesis related factors [30], but also increase RANKL production [25]. In addition to its anti-osteoclastogenesis effect, resveratrol may promote osteoblast differentiation to further orchestrate the bone metabolism [3, 13].

As an indicator of inflammation, serum CRP in rats with periodontitis raised to nearly 3 times higher than healthy animals, in accordance with a previous research [28]. Periodontal treatment was believed to decrease the CRP in serum [20]. However, resveratrol treated rats and periodontitis rats showed no significant difference in serum CRP levels in our study. Resveratrol, a stilbene type of phytoestrogen, combines with estrogen receptor and possesses some estrogen-like effects. Previous studies showed that estrogen treatment in postmenopausal women decreased the expression of inflammatory factors, but resulted in a raise of CRP by oral administration. The serum CRP enhancement may be explained by the first-pass hepatic effect [8, 10]. Oral hormone therapy had pronounced effects on hepatic protein synthesis, such as C-reactive protein and fibrinolytic markers [7]. However, transdermal or transmucosal estrogen administration had no such effects on serum CRP levels [22, 29]. Therefore, further studies will be needed to explore a surrogate way for resveratrol therapy to avoid serum CRP increase.

## Conclusion

Our results showed that resveratrol inhibited the inflammatory cytokine production in periodontitis gingivae, as well as the alveolar bone destruction. Therefore, resveratrol could be considered as a potential therapeutic agent against periodontitis.

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