Resveratrol Treatment and Periodontal Disease

Subjects: Physiology

Contributor: Eric Francelino Andrade

Resveratrol is an anti-inflammatory compound found in several foods. Periodontal disease (PD) is associated to other systemic diseases, and inflammation may be responsible for the association.

Keywords: Periodontitis ; Oral Health ; Mouth Diseases ; Functional Food

1. Introduction

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol stilbene found in red wine [1], peanuts [2], apples, several vegetables and berries, and others [3]. This compound has gained attention due to the “French Paradox” that indicates a low incidence of cardiovascular diseases and even consuming a high saturated fat diet [4]. The explanation for this paradox is associated with the consumption of red wine in France that naturally contains “therapeutic doses” of resveratrol [5]. Recently, resveratrol was also linked to several other health benefits such as cardioprotective effects, antitumor activity, and a life span increase [6][7]. Consequently, resveratrol has been investigated for the prophylaxis and therapeutic treatment of periodontal disease (PD) based on its anti-inflammatory and antioxidant properties [3][8].

PD embraces a group of inflammatory conditions affecting teeth supporting tissues [9]. It may be limited to the gums (gingivitis) or may affect the alveolar bone and periodontal ligament (periodontitis), causing apical epithelial migration and alveolar bone resorption [9]. This inflammation frequently involves a host response against biofilm accumulation and is mostly clinically asymptomatic in its early stages [10]. The direct consequences of PD involve gingival bleeding, tooth mobility, and even tooth loss, leading to aesthetic impairment and a poor quality of life [10]. In addition, PD is also associated with other systemic diseases such as cardiac, renal, and respiratory dysfunction; rheumatoid arthritis; metabolic syndrome; and even cancer [11].

It is estimated that the prevalence of PD in the world population exceeds 50% of adults older than 30 year. Approximately 10% of these individuals present the more severe forms [12][13]. Population growth and aging have been contributing to an increase of severe periodontitis cases [13][14], generating a universal public health issue [13][15]. Risk factors for the development and progression of PD involve mainly genetic polymorphisms, stress, obesity and diabetes, smoking, and alcoholism [16]. Proper oral hygiene and regular dental care (including scaling and root planning) are conventional therapies employed in dental practice [17]. Alternatively, maintaining an ideal weight and consuming a high-quality diet can also help to improve periodontal health [18], besides avoiding smoking and excessive alcohol drinking.

2. Current Insights on Resveratrol Treatment and Periodontal Disease

In this work, we investigated the effects of resveratrol administration on PD progression in preclinical studies. Out of the eleven selected studies, ten evaluated ABL and nine observed improvement of this parameter after resveratrol administration [19][20][21][22][23][24][25][26][27]. Such results may be related to an improvement of oxidative stress and anti-inflammatory properties [3][8].

Resveratrol increases the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD), which are key components against reactive oxygen species (ROS) [28]. Moreover, the host response to periodontal pathogens promotes local and systemic elevations of proinflammatory cytokines that alter the expression of the receptor activator of nuclear factor-kappa B ligand (RANKL) on the osteoblast surface [29]. RANKL is responsible for activating osteoclasts through its interaction with the receptor activator of nuclear factor-kappa B (RANK), initiating bone resorption [29]. High levels of ROS acting as intracellular signal transducers result in autophagy, which plays a dual role in periodontitis by promoting cell death or blocking apoptosis in infected cells [30]. In addition, ROS may influence the activation of signaling nuclear factor-κB (NF-κB), resulting in an increase of proinflammatory cytokines and, consequently, stimulating the differentiation of osteoclasts [30]. Considering that PD can be worsened due to the increase of pro-inflammatory cytokines and ROS, resveratrol acts on both fronts attenuating the progression of this disease [8].

One of the retrieved studies, Chin et al. [31] found no significant improvement in ABL in animals treated with resveratrol (even with the largest dose of 25 mg/kg/day). However, the treatment period was maintained for only seven days. [31]. It is possible that there is some mechanism related to the time of action or even to the administration period of this (prior to or following induction of PD). More studies should be conducted to determine the effective optimal dose and duration needed to attenuate ABL. Regarding toxicity, no side effects were reported for resveratrol consumption in any of the selected studies.

Regarding administration route, only two studies evaluated the injectable administration of resveratrol [21][27]. Even a single 0.001% (*w*/*w*) dose delivered one day prior to PD induction promoted ABL reduction, inflammatory profile, and oxidative stress improvements in C57BL/6J wild-type mice [27]. The highest percentages of ABL reduction were observed in studies where resveratrol was injected [21][27]. This fact may be related to the reduction of resveratrol bioavailability after gastrointestinal absorption [32].

The mechanisms involved in resveratrol regulation in periodontal inflammation have not yet been fully elucidated [21]. It is known that resveratrol can decrease the expression of toll-like receptor type 4 (TRL4) which is activated by lipopolysaccharides (LPS) [21]. An activation of TLR4 observed in chronic periodontitis increases the production of proinflammatory cytokines [33]. Another possible mechanism is by increasing anti-inflammatory mediators such as IL-4 [26], as well as a suppression of both matrix metalloproteinase (MMP-2 and MMP-9) and cyclooxygenase-2 (COX-2) [21]. IL-4 suppress the production of IL-17 and IL-1β [26], which play an important role in the periodontitis pathogenesis and inhibit both Th1 pro-inflammatory response and bone resorption [34].

All analyzed studies used rat or mice. Rodent periodontium has a good similarity with humans [35]. The induction of periodontitis involved the ligature in all experiments. This model has several advantages such as low cost and the possibility of investigation in a wide genetic variety of rodents, besides allowing the exploration of the interaction between the oral microorganisms and host response during the development of periodontitis [7]. Even though rats are not natural hosts for some bacteria found in human oral cavity, both *A. actinomycetemcomitans* and *P. gingivalis* have been reported in rodents' microbiota after ligature [36][37][38].

Regarding the quality assessment of studies, most of the categories were classified as excellent or average. A previous systematic review [39] using the ARRIVE guidelines reported that most animal studies lack a clear indication of the reasons for choosing a particular animal model, contributing to a lower score for this item. This item also received the lowest score. This aspect is considered an important criterion for preclinical animal trials [39]. Thus, even if it is already well-known that some results of studies in rodents can be extrapolated to humans, it is important to highlight the relevance of the model used.

Another ARRIVE item that scored as low in several studies was the "interpretation/scientific implications" since only a few articles commented about the limitations and bias as well as mentioned the 3Rs (replacement, refinement, and reduction) principles adopted in experiments with animal studies. Similar results were also reported by Dereka et al. [40], in which only 10% of the studies attended this question.

Among the risk of bias assessed, the domains "allocation concealment", "random housing", "blinding of participants and personnel", "random outcome assessment", and "blinding of outcome assessment domains" presented a high risk of bias or were not clearly described. These same domains were classified as unclear or with a high risk of bias according to the Syrcle tool in previous study [41]. In a systematic review of animal studies [39], 40% and 60% of studies presented a high risk of bias and an unclear risk in the "allocation concealment" domain, respectively. Randomized housing during the experiment reduces the bias risk once these conditions (such as lighting, humidity, temperature, etc.) are known to influence study outcomes [42]. An implementation of a blind evaluation in animal studies is also crucial, especially for subjective measurements [43].

This systematic review was conducted according to the PRISMA criteria [44] and the protocol for the preparation, registration, and publication of systematic reviews of animal intervention studies [45]. In order to minimize bias, each step of searching or ranking was performed by two independent researchers. Additionally, to prevent the exclusion of any article, a careful search was conducted. It is important to emphasize that, in the searches performed, we have not found previous systematic review or meta-analysis studies involving the main question addressed in this study.

The results of meta-analysis demonstrated that, in rats, bone loss was significantly lower due to resveratrol administration. However, only a few studies were eligible for the meta-analysis (seven), and it was not possible to assess the publication bias. Considering the potential benefits of resveratrol on periodontal health, further studies should be conducted investigating the effects of this compound in PD models. In addition, future studies should focus on reducing the risk of

bias, especially in the areas related to “allocation concealment” and "blinding of participants and personnel" which contributed to the greatest risk of bias.

3. Conclusions

We concluded from preclinical studies that resveratrol can improve periodontal disease probably due to the modulation of both oxidative stress and inflammatory profile. The results obtained through ARRIVE showed a good quality of the studies overall. However, the analysis by the Syrcle tool demonstrated that some aspects related to randomization and blinding should be considered to reduce the risk of bias.

The findings of this systematic review and meta-analysis demonstrated promising effects of resveratrol on periodontal disease, which may stimulate future studies in humans. Because of species-specific variables such as oral microbiota, dose-response effect, and the route of administration, the results in humans may vary from those observed in animals. Clinical studies are essential to confirm the results observed in animal studies.

References

1. Pastor, R.F.; Restani, P.; Di Lorenzo, C.; Orgiu, F.; Teissedre, P.-L.; Stockley, C.; Ruf, J.C.; Quini, C.I.; Garcìa Tejedor, N.; Gargantini, R.; et al. Resveratrol, human health and winemaking perspectives. Crit. Rev. Food Sci. Nutr. 2017, 5, 1–19.
2. Sales, J.M.; Resurreccion, A.V.A. Resveratrol in Peanuts. Crit. Rev. Food Sci. Nutr. 2014, 54, 734–770.
3. Baur, J.A.; Sinclair, D.A. Therapeutic potential of resveratrol: the in vivo evidence. Nat. Rev. Drug Discov. 2006, 5, 493–506.
4. Catalgol, B.; Batirel, S.; Taga, Y.; Ozer, N.K. Resveratrol: French Paradox Revisited. Front. Pharmacol. 2012, 3, 1–18.
5. Biagi, M.; Bertelli, A.A.E. Wine, alcohol and pills: What future for the French paradox? Life Sci. 2015, 131, 19–22.
6. Weiskirchen, S.; Weiskirchen, R. Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy? Adv. Nutr. An In t. Rev. J. 2016, 7, 706–718.
7. Marchesan, J.; Girnary, M.S.; Jing, L.; Miao, M.Z.; Zhang, S.; Sun, L.; Morelli, T.; Schoenfisch, M.H.; Inohara, N.; Offen bacher, S.; et al. An experimental murine model to study periodontitis. Nat. Protoc. 2018, 13, 2247–2267.
8. Chin, Y.-T.; Cheng, G.-Y.; Shih, Y.-J.; Lin, C.-Y.; Lin, S.-J.; Lai, H.-Y.; Whang-Peng, J.; Chiu, H.-C.; Lee, S.-Y.; Fu, E.; et al. Therapeutic applications of resveratrol and its derivatives on periodontitis. Ann. N. Y. Acad. Sci. 2017, 1403, 101–10 8.
9. Cekici, A.; Kantarci, A.; Hasturk, H.; Van Dyke, T.E. Inflammatory and immune pathways in the pathogenesis of periodo ntal disease. Periodontol. 2000 2014, 64, 57–80.
10. Casanova, L.; Hughes, F.J.; Preshaw, P.M. Diabetes and periodontal disease: A two-way relationship. Br. Dent. J. 2014, 217, 433–437.
11. Winning, L.; Linden, G.J. Periodontitis and systemic disease. BDJ Team 2015, 2, 15163. [Green Version]
12. Borgnakke, W.S.; Ylöstalo, P.V.; Taylor, G.W.; Genco, R.J. Effect of periodontal disease on diabetes: Systematic review of epidemiologic observational evidence. J. Periodontol. 2013, 84, S135–S152.
13. Eke, P.I.; Lu, H.; Zhang, X.; Thornton-Evans, G.; Borgnakke, W.S.; Holt, J.B.; Croft, J.B. Geospatial distribution of perio dontists and US adults with severe periodontitis. J. Am. Dent. Assoc. 2019, 150, 103–110.
14. Kassebaum, N.J.; Smith, A.G.C.; Bernabé, E.; Fleming, T.D.; Reynolds, A.E.; Vos, T.; Murray, C.J.L.; Marcenes, W.; GB D 2015 Oral Health Collaborators. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Y ears for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuri es, and Risk Factors. J. Dent. Res. 2017, 96, 380–387. [Green Version]
15. Dumitrescu, A.L. Editorial: Periodontal Disease—A Public Health Problem. Front. Public. Heal. 2015, 3, e278.
16. Genco, R.J.; Borgnakke, W.S. Risk factors for periodontal disease. Periodontol. 2000 2013, 62, 59–94.
17. Jiang, H.; Xiong, X.; Su, Y.; Zhang, Y.; Wu, H.; Jiang, Z.; Qian, X. A randomized controlled trial of pre-conception treatm ent for periodontal disease to improve periodontal status during pregnancy and birth outcomes. BMC Pregnancy Childb irth 2013, 13, 1–7.
18. Al-Zahrani, M.S.; Borawski, E.A.; Bissada, N.F. Periodontitis and three health-enhancing behaviors: maintaining normal weight, engaging in recommended level of exercise, and consuming a high-quality diet. J. Periodontol. 2005, 76, 1362–

1366.

19. Zhen, L.; Fan, D.; Zhang, Y.; Cao, X.; Wang, L. Resveratrol ameliorates experimental periodontitis in diabetic mice thro ugh negative regulation of TLR4 signaling. Acta Pharmacol. Sin. 2015, 36, 221–228.
20. Corrêa, M.G.; Absy, S.; Tenenbaum, H.; Ribeiro, F.V.; Cirano, F.R.; Casati, M.Z.; Pimentel, S.P. Resveratrol attenuates oxidative stress during experimental periodontitis in rats exposed to cigarette smoke inhalation. J. Periodontal Res. 201 8.
21. Bhattarai, G.; Poudel, S.B.; Kook, S.-H.; Lee, J.-C. Resveratrol prevents alveolar bone loss in an experimental rat mod el of periodontitis. Acta Biomater. 2016, 29, 398–408.
22. Casati, M.Z.; Algayer, C.; Cardoso da Cruz, G.; Ribeiro, F.V.; Casarin, R.C.V.; Pimentel, S.P.; Cirano, F.R. Resveratrol Decreases Periodontal Breakdown and Modulates Local Levels of Cytokines During Periodontitis in Rats. J. Periodonto l. 2013, 84, e58–e64.
23. Tamaki, N.; Cristina Orihuela-Campos, R.; Inagaki, Y.; Fukui, M.; Nagata, T.; Ito, H.-O. Resveratrol improves oxidative s tress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defens e pathways in a rat periodontitis model. Free Radic. Biol. Med. 2014, 75, 222–229.
24. Ribeiro, F.V.; Pino, D.S.; Franck, F.C.; Benatti, B.B.; Tenenbaum, H.; Davies, J.E.; Pimentel, S.P.; Casarin, R.C.; Ciran o, F.R.; Casati, M.Z. Resveratrol Inhibits Periodontitis-Related Bone Loss in Rats Subjected to Cigarette Smoke Inhalati on. J. Periodontol. 2017, 88, 788–798.
25. Corrêa, M.G.; Pires, P.R.; Ribeiro, F.V.; Pimentel, S.Z.; Casarin, R.C.V.; Cirano, F.R.; Tenenbaum, H.T.; Casati, M.Z. Sy stemic treatment with resveratrol and/or curcumin reduces the progression of experimental periodontitis in rats. J. Perio dontal Res. 2017, 52, 201–209.
26. Corrêa, M.G.; Pires, P.R.; Ribeiro, F.V.; Pimentel, S.P.; Cirano, F.R.; Napimoga, M.H.; Casati, M.Z.; Casarin, R.C.V. Sys temic treatment with resveratrol reduces the progression of experimental periodontitis and arthritis in rats. PLoS One 2 018, 13, e0204414.
27. Ikeda, E.; Ikeda, Y.; Wang, Y.; Fine, N.; Sheikh, Z.; Viniegra, A.; Barzilay, O.; Ganss, B.; Tenenbaum, H.C.; Glogauer, M. Resveratrol derivative-rich melinjo seed extract induces healing in a murine model of established periodontitis. J. Perio dontol. 2018, 89, 586–595.
28. Mokni, M.; Elkahoui, S.; Limam, F.; Amri, M.; Aouani, E. Effect of Resveratrol on Antioxidant Enzyme Activities in the Br ain of Healthy Rat. Neurochem. Res. 2007, 32, 981–987.
29. Cochran, D.L. Inflammation and Bone Loss in Periodontal Disease. J. Periodontol. 2008, 79, 1569–1576. [Green Versi on]
30. Liu, C.; Mo, L.; Niu, Y.; Li, X.; Zhou, X.; Xu, X. The Role of Reactive Oxygen Species and Autophagy in Periodontitis an d Their Potential Linkage. Front. Physiol. 2017, 8, 1–13.
31. Chin, Y.-T.; Hsieh, M.-T.; Lin, C.-Y.; Kuo, P.-J.; Yang, Y.-C.S.H.; Shih, Y.-J.; Lai, H.-Y.; Cheng, G.-Y.; Tang, H.-Y.; Lee, C.- C.; et al. 2,3,5,4'-Tetrahydroxystilbene-2-O-β-glucoside Isolated from Polygoni Multiflori Ameliorates the Development o f Periodontitis. Mediators Inflamm. 2016, 2016, 6953459.
32. Walle, T.; Hsieh, F.; DeLegge, M.H.; Oatis, J.E.; Walle, U.K. High absorption but very low bioavailability of oral resveratr ol in humans. Drug Metab Dispos. 2004, 32, 1377–1382.
33. Ilango, P.; Mahalingam, A.; Parthasarathy, H.; Katamreddy, V.; Subbareddy, V. Evaluation of TLR2 and 4 in Chronic Per iodontitis. J. Clin. Diagn. Res. 2016, 10, 86–89.
34. Dessaune Neto, N.; Porpino, M.T.M.; Antunes, H.d.S.; Rodrigues, R.C.V.; Perez, A.R.; Pires, F.R.; Siqueira, J.F., Jr.; Ar mada, L.; Dessaune Neto, N.; Porpino, M.T.M.; et al. Pro-inflammatory and anti-inflammatory cytokine expression in po st-treatment apical periodontitis. J. Appl. Oral Sci. 2018, 26, e20170455.
35. Oz, H.S.; Puleo, D.A. Animal Models for Periodontal Disease. J. Biomed. Biotechnol. 2011, 2011, 1–8. [Green Version]
36. Cirano, F.R.; Casarin, R.C.V.; Ribeiro, F.V.; Casati, M.Z.; Pimentel, S.P.; Taiete, T.; Bernardi, M.M. Effect of Resveratrol on periodontal pathogens during experimental periodontitis in rats. Braz. Oral Res. 2016, 30, e128.
37. Theodoro, L.H.; Pires, J.R.; Fernandes, L.A.; Gualberto Júnior, E.C.; Longo, M.; de Almeida, J.M.; Garcia, V.G. Effect of antimicrobial photodynamic therapy on periodontally infected tooth sockets in rats. Lasers Med. Sci. 2015, 30, 677–68 3.
38. Rovin, S.; Costich, E.R.; Gordon, H.A. The influence of bacteria and irritation in the initiation of periodontal disease in g ermfree and conventional rats. J. Periodontal Res. 1966, 1, 193–204.
39. Arora, H.; Ivanovski, S. Melatonin as a pro-osteogenic agent in oral implantology: a systematic review of histomorphom etric outcomes in animals and quality evaluation using ARRIVE guidelines. J. Periodontal Res. 2017, 52, 151–161.

40. Dereka, X.; Calciolari, E.; Donos, N.; Mardas, N. Osseointegration in osteoporotic-like condition: A systematic review of preclinical studies. J. Periodontal Res. 2018, 53, 933–940.
41. Osorio Parra, M.M.; Elangovan, S.; Lee, C.-T. Specialized pro-resolving lipid mediators in experimental periodontitis: A systematic review. Oral Dis. 2018.
42. Hooijmans, C.R.; Rovers, M.M.; de Vries, R.B.; Leenaars, M.; Ritskes-Hoitinga, M.; Langendam, M.W. SYRCLE’s risk of bias tool for animal studies. BMC Med. Res. Methodol. 2014, 14, e43.
43. Ma, B.; Xu, J.; Wu, W.; Liu, H.; Kou, C.; Liu, N.; Zhao, L. Survey of basic medical researchers on the awareness of animal experimental designs and reporting standards in China. PLoS One 2017, 12, e0174530.
44. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, T.P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009, 6, e1000097.
45. de Vries, R.B.M.; Hooijmans, C.R.; Langendam, M.W.; van Luijk, J.; Leenaars, M.; Ritskes-Hoitinga, M.; Wever, K.E. A protocol format for the preparation, registration and publication of systematic reviews of animal intervention studies. Evidence-based Preclin. Med. 2015, 2, e00007.
