



African Journal of Biological Sciences



Research Paper

Open Access

Use and Applications of Resveratrol in Dentistry, Systematic Review

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Article Info

Volume 6, Issue 8, April 2024

Received: 13 Feb 2024

Accepted: 13 March 2024

Published: 04 April 2024

Abstract

Resveratrol is a compound with multiple beneficial properties for oral health, such as its ability to prevent dental caries, reduce gum inflammation and pain, and promote the regeneration of damaged dental tissues. The aim of this work is to describe the use and different clinical applications of resveratrol in dentistry through a systematic review using the PRISMA procedure, for which 19 original articles obtained from the electronic search of the following databases were analyzed: PudMed & Scopus. It is concluded that, the reviewed studies suggest that the use of dental products with resveratrol can be beneficial in several cases, such as the prevention of gingivitis and periodontitis, as well as in the promotion of wound healing, regeneration of dental tissues and improvement in the bonding strength in dental adhesive systems. In general, more research is needed to determine the possible side effects and contraindications of resveratrol use in dentistry.

Keywords: Resveratrol, Resveratrol, Polyphenols, Dentistry, Oral Health.
(Decs)

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Introduction

Resveratrol (RSV) is a naturally occurring derivative of polyphenols and stilbenes, it exists as a cis and trans isomer. The preferred steric form is trans-RSV, which is relatively stable when protected from high pH values and light. Its synthesis in plants can be induced by microbial infections, ultraviolet (UV) radiation, and ozone exposure (1). Izzo et al. (2) state that resveratrol is a non-flavonoid phenol produced by many plants in response to bacterial or fungal colonization. It is mainly found in the skin of grapes, blueberries, raspberries, blackberries and peanuts while its high concentration in red wine partly explains the relatively low incidence of cardiovascular disease in the French, despite the high fat content of this population. Many studies have shown that resveratrol can prevent or delay the development of various diseases, such as malignant tumors, neurodegenerative diseases, cardiovascular diseases, ischemic damage, and viral infections.

Trans-resveratrol has been reported to have numerous health benefits, such as anti-inflammatory, antidiabetic, antioxidant, and neuroprotective, and has been traditionally used in Eastern medicine, there is increasing evidence that resveratrol has antimicrobial properties against a number of bacterial species, viruses, and fungi. Resveratrol inhibits virulence factor expression and interferes with biofilm formation, where *P. gingivalis* is a key pathogen (4). Li et al. (1) mention that resveratrol has an inhibitory effect at the sub-MIC level on cariogenic virulence factors of *S. mutans*, including acid production, acid tolerance, synthesis of extracellular polysaccharides, biofilm formation and structure, and expression of virulence genes. Also, resveratrol may be beneficial in improving pulp damage during the acute phase of inflammation in vital pulp therapy (5). Therefore, the objective of this work is to describe the use and different clinical applications of resveratrol in Dentistry.

Materials and Methods

In this systematic review of the scientific literature, the PRISMA procedure was used, through which information from studies carried out and published during the period 2018-2023 was analyzed; A total of 19 scientific articles were analyzed, which were obtained from the electronic search of the databases: PudMed & Scopus and were selected through the following criteria.

Inclusion criteria:

- Articles in English or Spanish.
- Articles published within the period: 2018 – 2023.
- Articles published in high-impact scientific journals.
- Articles with extensive relevance to this research topic.

Exclusion Criteria:

- Articles that could not be accessed directly to their content.
- Articles that lacked usefulness for the topic of study.
- Articles published outside the period established as a research parameter.
- Duplicate items.

Table 1. Search strategy for articles used in research

E-Journals	Publication period	Search strategy	Articles found
PubMed	2018-2023	1. Resveratrol in Dentistry, cranberries, resveratrol applications. 2. Properties of cranberries, cranberries in Dentistry.	45
Scopus	2018-2023	1. Resveratrol in Dentistry, cranberries, resveratrol applications. 2. Cranberries in Dentistry, properties of cranberries.	15

Results and Discussion

The results are presented according to the inclusion and exclusion criteria proposed in the methodology, in accordance with the phases of the PRISMA procedure, which are described in Figure 1 and Table 2.

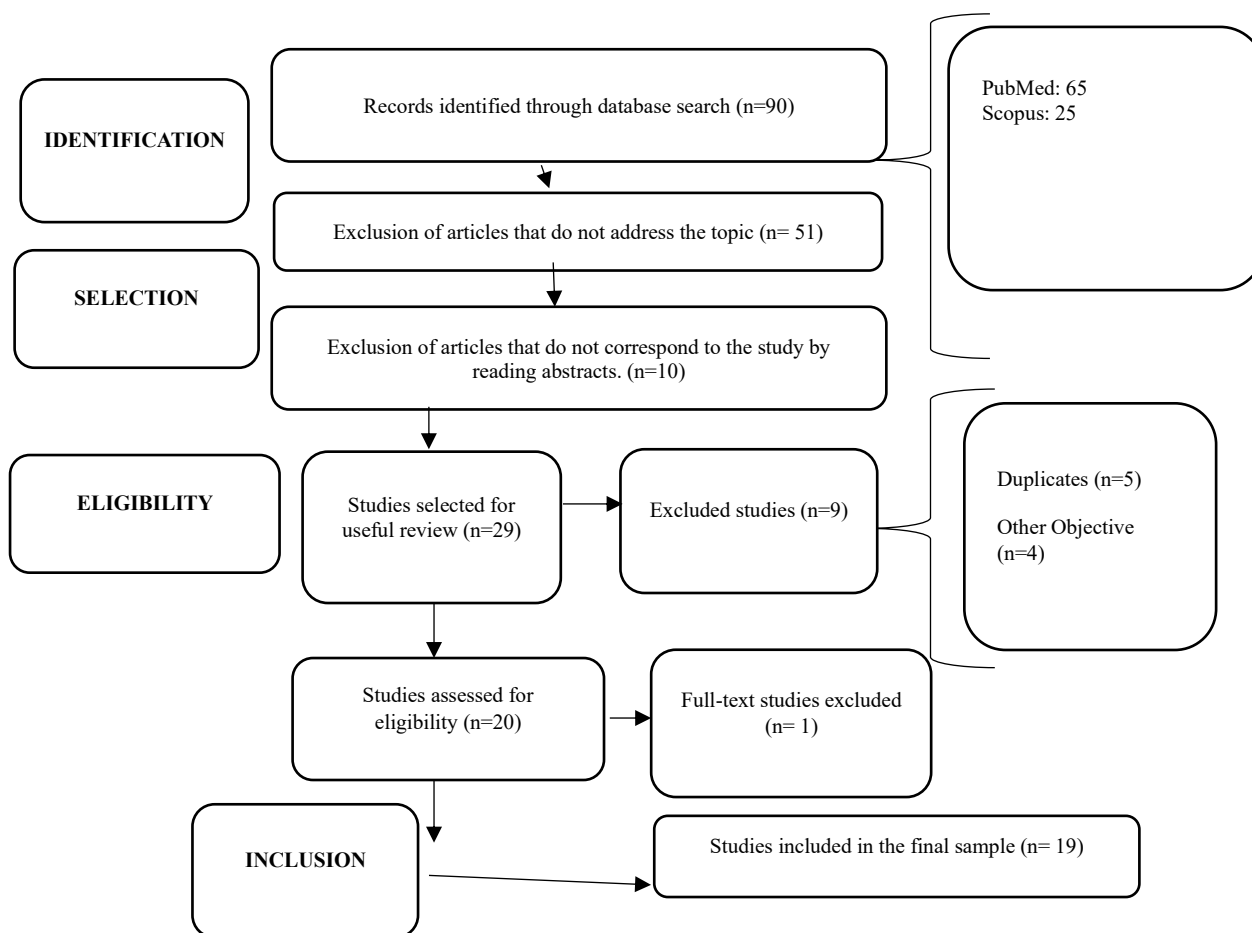


Figure 1. Article Search Flow Chart

Table 2. Description of the items used for the research.

Authors & Title	Data	Category
Murgia et al. (1). Advance on Resveratrol Application in Bone Regeneration: Progress and Perspectives for Use in Oral and Maxillofacial Surgery. Biomolecules.	Resveratrol, thanks to its immunomodulatory effects and ability to reduce the levels of certain pro-inflammatory cytokines, is considered one more element to improve the progression of alveolar bone regeneration. It could also represent a therapeutic approach within the processes of bone healing and rehabilitation of edentulous patients who have dental implants, and it also has great potential in the treatment of oral diseases that are related to oxidative stress and bisphosphonate-induced maxillary osteonecrosis.	Prevention and treatment of bone diseases
Izzo et al. (2). The Role of Resveratrol in Liver Disease: A Comprehensive Review from In Vitro to Clinical Trials. Nutrients	Resveratrol is widely used as a dietary supplement. Despite this, no specific dosages and dosing intervals are detailed for this compound. If there were a specific approach, the potential therapeutic indications for RSV would greatly benefit, including combination therapy with other drugs and compounds. RSV has been shown to possess several beneficial effects both in vitro, in vivo, and in clinical trials. An important limitation, in addition to the administration of RSV, is its bioavailability, this compound is safe; however, it does	Clinical Limitations of RSV

	not have optimal pharmacokinetic and pharmacodynamic properties.	
Bahar et al. (3). An evaluation of the molecular mode of action of trans-resveratrol in the <i>Porphyromonas gingivalis</i> lipopolysaccharide challenged neuronal cell model.	In this study, it was shown that, through gene expression analysis, trans-resveratrol possesses multiple quite effective bioactivities that work by modulating the interconnected mechanisms of cellular oxidative stress, nutrient metabolism, and inflammatory response. Therefore, it is concluded that the therapeutic use of trans-resveratrol in the pathophysiology of the disease caused by <i>P. gingivalis</i> can be explored and investigated in depth.	Bioactivity of RSV
Li et al. (4). Effects of resveratrol on cariogenic virulence properties of <i>Streptococcus mutans</i> .	RSV at sub-MIC levels greatly minimized acid production and acid tolerance, compromised biofilm formation, and inhibited the synthesis of both water-soluble and water-insoluble polysaccharides. Gene expression of related virulence (<i>ldh</i> , <i>relA</i> , <i>gtfC</i> , <i>comDE</i>) was decreased when RSV concentrations were increased. It is concluded that resveratrol has an effect that inhibits the cariogenic virulence properties of <i>S. mutans</i> and represents an anticariogenic agent with a promising future.	Anticariogenic property
Wang et al (5). Resveratrol represses tumor necrosis factor α /c-Jun N-terminal kinase signaling via autophagy in human dental pulp stem cells.	The results of this research suggest that resveratrol inhibits TNF α -induced inflammatory cytokines expressed by dental pulp stem cells by regulating the autophagy-JNK inhibitory signaling cascade. Therefore, it is considered that resveratrol could be effective and beneficial in improving damage to the dental pulp during the acute inflammatory phase in vital pulp therapy.	Treating Pulp Damage as an Anti-Inflammatory
Yuan et al. (6). Resveratrol rescues TNF- α -induced inhibition of osteogenesis in human periodontal ligament stem cells via the ERK1/2 pathway.	This study is the first to demonstrate that resveratrol, in addition to improving the osteogenesis of human periodontal ligament stem cells by activating the ERK1/2 pathway, also has anti-inflammatory effects by activating this pathway. As another instance, resveratrol minimizes TNF- α -mediated inflammatory cytokine secretion. Therefore, resveratrol is a good candidate as an anti-inflammatory agent to induce bone remodeling in response to an inflammatory microenvironment. Despite this, more in vivo research is needed to study efficacy and safety as a treatment for periodontitis.	Treatment of periodontitis
Shi et al. (7). Remodeling immune microenvironment in periodontitis using resveratrol liposomes as an antibiotic-free therapeutic strategy.	A Lipo-RSV system was developed to treat periodontitis through modulation of p-STAT1 and p-STAT3 antibodies to reprogram macrophages from M1 to M2 phenotype. It is described that the treatment can effectively suppress inflammation, evidenced by the reduced secretion of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α and IL-12) and the increase of the anti-inflammatory factor IL-10 by inhibiting the NF- κ B/NLRP3 signaling pathways. In this way, Lipo-RSV provides a promising antibiotic-free treatment method for periodontitis, as well as translational potential.	Treatment of periodontitis

Borsani et al. (8). Beneficial Effects of Concentrated Growth Factors and Resveratrol on Human Osteoblasts In Vitro Treated with Bisphosphonates	Resveratrol promotes bone formation by boosting osteoblast activity and stimulating their proliferation and differentiation. Daily intake of resveratrol had a beneficial effect on bone turnover in ovariectomized rats, preventing bone loss and suggesting a positive effect of this compound in the prevention of postmenopausal osteoporosis. Similarly, there is a beneficial effect of resveratrol against osteoporosis.	Prevention and treatment of bone diseases
Inchingolo et al. (9). Benefits and Implications of Resveratrol Supplementation on Microbiota Modulations: A Systematic Review of the Literature.	In the oral cavity, RSV has properties that inhibit the caryogenic virulence of <i>Streptococcus mutans</i> , reducing acid production and biofilm formation. At the level of bone metabolism, the study shows that RSV, by activating SIRT-1, favors osteogenic proliferation by the differentiation of mesenchymal stem cells and angiogenic proliferation because it stimulates the proliferation and migration of HUVEC. RSV associated with SrRn inhibits osteoclastogenesis by reducing bone resorption and promoting bone synthesis. RSV associated with concentrated growth factors enhances its protective effects against osteonecrosis of the jaws, induced by the intake of bisphosphonates, by promoting osteoinductive processes and angiogenesis.	Anticariogenic property and treatment in bone resorption of RSV.
Inchingolo et al. (10). Effects of Resveratrol, Curcumin and Quercetin Supplementation on Bone Metabolism-A Systematic Review.	Phenolic compounds are naturally occurring phytochemicals that have recently reported numerous health benefits. Among these molecules, resveratrol, curcumin, and quercetin are currently the most important for their documented antioxidant effects. The studies reported on the positive effects of the phenolic compounds investigated on bone metabolism and their potential application as adjuvant treatments for osteoporosis, bone tumours and periodontitis. In addition, its use on the titanium surfaces of orthopaedic prostheses could represent a possible application to improve osteogenic processes and osseointegration. Resveratrol, curcumin, and quercetin have a wide variety of beneficial effects as therapeutic supplements.	Inhibition of bone resorption and treatment of periodontitis.
Fukuda et al. (11). Resveratrol Inhibits Proliferation and Induces Autophagy by Blocking SREBP1 Expression in Oral Cancer Cells.	Resveratrol reduced cell viability and induced autophagic cell death in oral cancer cells, but not in normal cells. This selective effect was accompanied by a significant reduction in lipogenesis, which is caused by downregulation of the gene's element-binding protein 1 (SREBP1) regulatory sterol transcription factor, followed by downregulation of epidermal fatty acid-binding protein (E-FABP). In conclusion, resveratrol induces autophagy in oral cancer cells by suppressing lipid metabolism through regulation of SREBP1 expression, which highlights a novel mechanism of resveratrol's anti-cancer effect.	RSV in the treatment of oral cancer
Ikeda et al. (12). Healing effects of monomer and dimer resveratrol in a	It was shown that the effect of resveratrol dimer and monomer on the cure of periodontitis was experimentally induced in mice and that the healing inducing effects were likely related to oxidative stress	Treatment of periodontitis

mouse periodontitis model.	and mediated through that antioxidant Nrf2 pathway. In addition, resveratrol dimer induced greater periodontal bone healing compared to that related to resveratrol monomer use. Treatment with MSE (a mixture of resveratrol monomer, dimer, and related complexes) promoted healing of periodontal bone loss in mice, even when the agents used to induce periodontitis were not removed.	
D'Amico et al. (13). Emerging Effects of Resveratrol Derivatives in Cells Involved in Oral Wound Healing: A Preliminary Study	There are two sulfonamide derivatives of RSV capable of promoting the proliferation of key cells involved in oral wound healing, better than the parent compound, at low doses. Compounds 1d and 1h, selected from a first screening, showed pro-proliferative effects at the lowest concentration. In addition, the increase in eNOS in endothelial cells, COL1 in gingival fibroblasts, and ALP in osteoblasts, at the lowest concentration, makes 1d and 1h a possible choice for wound healing, paving the way for new applications in tissue engineering. The selected compounds showed similar pharmacokinetic properties and stability. Although the LogP of the studied compounds and RSV is similar, their stability in plasma at different pHs is an additional advantage demonstrated by these novel RSV derivatives, suggesting that they could be useful as potential drug candidates to promote oral tissue repair.	RSV for Oral Wound Healing
Nikniaz S, et al. (14). Impact of resveratrol supplementation on clinical parameters and inflammatory markers in patients with chronic periodontitis: a randomized clinical trail.	Resveratrol supplementation in combination with non-surgical periodontal treatment is suggested to have a significant effect on reducing plaque index (PI) over 4 weeks. Taken together, it appears that the use of resveratrol in conjunction with non-surgical periodontal treatment may be beneficial in improving clinical parameters and inflammatory condition in patients with periodontitis.	Treatment of periodontitis
Wenan et al. (15). Effects of resveratrol/ethanol pretreatment on dentin bonding durability	Resveratrol/ethanol improves the durability of the adhesive in vitro and thus extends the life of the restoration. It also has anti-enzyme and antibacterial properties. The control group of this study demonstrated a greater inhibitory effect of matrix metalloproteinases and activity of <i>S. mutans</i> with acceptable cytotoxicity. On the other hand, a gradual decrease in cohesive failure in dentin was observed with increasing resveratrol concentration. Therefore, resveratrol/ethanol solution can effectively improve the durability of dentin junction and prevent secondary caries.	RSV in adhesive systems
Chia-Cheng et al. (16). Resveratrol antagonizes thyroid hormone-induced expression of checkpoint and	Thyroxine induces gene expression of checkpoints that can promote proliferation in cancer cells. Alternatively, resveratrol reverses the stimulatory effects of thyroid hormone to induce antiproliferation.	RSV in Oral Cancer

proliferative genes in oral cancer cells		
Ehsan et al. (17). Current natural bioactive materials in bone and tooth regeneration in dentistry: a comprehensive overview	RSV is a natural compound capable of inhibiting alveolar bone resorption and periodontal deterioration in periodontitis-induced rat models thanks to its antioxidant effects. An animal study showed that intraperitoneal injection of resveratrol (10 µmol/kg) greatly improved the bone regeneration process following an extractions. Many preclinical studies have evaluated the bone and cartilaginous regenerative capacity of tissue scaffolds such as collagen, chitosan, poly-ε-caprolactone, and polycaprolactone after enriching them with resveratrol with most of the promising results.	Inhibition of alveolar bone resorption by RSV
Osamudiamen et al. (18). Trans-resveratrol, piceatannol and gallic acid: Potent polyphenols isolated from <i>Mezoneuron benthamianum</i> effective as anticaries, antioxidant and cytotoxic agents	This is the first report of the anticaries activities of resveratrol and piceatannol, which are polyphenols isolated from the root of <i>Mezoneuron benthamianum</i> . All three polyphenols demonstrated marked inhibitory activity against bacterial organisms, in addition to antioxidant and cytotoxic activities. The effectiveness of using <i>M. benthamianum</i> traditionally in oral hygiene could be attributed to the presence of these bioactive compounds, which have proven to be very potent. This result further justifies the ethno-medicinal use of <i>M. benthamianum</i> as a therapeutic agent in the prevention and treatment of dental caries and the maintenance of oral hygiene.	Anticariogenic property of RSV
Celerino et al. (19), Polyphenols and Brazilian red propolis incorporated into a total-etching adhesive system help in maintaining bonding durability	Quercetin and RSV showed high antioxidant activity. The degree of conversion (DC) of the adhesives studied remained adequate for this material category. Dentin bonding agents with quercetin and RSV possess the potential to increase the longevity of composite restorations.	RSV in adhesive systems

Among the properties of resveratrol in dentistry, Murgia et al. (1) highlight its immunomodulatory effects and the ability to improve the progression of alveolar bone regeneration, representing a therapeutic approach within bone healing processes and has great potential in the treatment of oral diseases that are related to oxidative stress and bisphosphonate-induced maxillary osteonecrosis. Thus, Borsani et al. (8), Inchingolo et al. (9) and Ehsan et al. (17) detail that RSV promotes bone formation by potentiating the activity of osteoblasts in their differentiation and proliferation, inhibits osteoclastogenesis, adding that it has a positive effect against osteoporosis. In another study, Inchingolo et al. (10) support the positive effects of these phenolic compounds on bone metabolism and their possible application as adjuvant treatments for osteoporosis, bone tumors, and periodontitis. Regarding its applications in oral rehabilitation, it is mentioned that its use on the titanium surfaces of orthopedic prostheses could represent a possible application to improve osteogenic processes and osseointegration, in which Murgia et al. also agree (1).

Yuan et al. (6) describe that they conducted the first study in which it is demonstrated that RSV, in addition to improving the osteogenesis of human periodontal ligament stem cells by

activating the ERK1/2 pathway, also has anti-inflammatory effects during such activation. As another instance, resveratrol minimizes TNF- α -mediated inflammatory cytokine secretion. Therefore, resveratrol is a good candidate as an anti-inflammatory agent to induce bone remodeling in response to an inflammatory microenvironment. This information is supported by the study by Shi et al. (7), in which they developed a Lipo-RSV system to treat periodontitis through the modulation of p-STAT1 and p-STAT3 antibodies to reprogram macrophages from M1 to M2 phenotypes. This treatment can suppress inflammation by reducing the secretion of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α and IL-12) and increasing the anti-inflammatory factor IL-10, proving to be a promising antibiotic-free treatment for periodontitis.

The mouse experiment by Ikeda et al. (12) showed that treatment with MSE (a mixture of resveratrol monomer, dimer, and related complexes) promoted healing of periodontal bone loss, even when the agents used to induce periodontitis were not removed. On the other hand, Nikniaz S, et al. (14) point out that resveratrol supplementation in combination with non-surgical periodontal treatment generates a significant effect on reducing plaque index for 4 weeks and improving inflammatory condition in patients with periodontitis.

Osamudiamen et al. (18), who are the first to report the anticaries activities of resveratrol and piceatannol, demonstrated marked inhibitory activity against bacterial organisms, in addition to antioxidant and cytotoxic activities. This result further justifies the ethno-medicinal use of *M. benthamianum* as a therapeutic agent in the prevention and treatment of dental caries and the maintenance of oral hygiene. Li et al. (4) add that RSV at sub-CMI levels significantly minimized acid production and acid tolerance, compromised biofilm generation, and inhibited the synthesis of both water-soluble and water-insoluble polysaccharides. Resveratrol has an effect that inhibits the cariogenic virulence properties of *S. mutans* and represents an anticariogenic agent with a promising future. Inchingolo et al. (9) agree with the latter, as they point out that, in the oral cavity, RSV has properties that inhibit the cariogenic virulence of *Streptococcus mutans*, reducing acid production and biofilm formation.

In Endodontics, Wang et al (5) demonstrated that resveratrol inhibits TNF α -induced inflammatory cytokines expressed by dental pulp stem cells by regulating the autophagy inhibitory-JNK signaling cascade. Therefore, it is considered that resveratrol could be effective and beneficial in improving damage to the dental pulp during the acute inflammatory phase in vital pulp therapy. In oral cancer, thyroxine was found to induce gene expression of checkpoints that can promote proliferation in cancer cells. Alternatively, resveratrol reverses the stimulatory effects of thyroid hormone to induce antiproliferation, as noted by Chia-Cheng et al. (16).

Finally, the effects of RSV in conjunction with adhesive systems are detailed; resveratrol/ethanol improves the durability of the adhesive in vitro and thus prolongs the shelf life of the restoration. A gradual decrease in cohesive failure in dentin was observed with increasing resveratrol concentration. Therefore, resveratrol/ethanol solution can effectively improve the durability of dentin junction and prevent secondary caries. Quercetin and RSV showed high antioxidant activity. The degree of conversion (DC) of the adhesives studied remained adequate for this material category. Dentin bonding agents with quercetin and RSV possess the potential to increase the longevity of composite restorations; Celerino et al. (19) and Wenan et al. (15) agree and detail this.

Conclusion

To conclude this article, it was found that resveratrol is a natural compound found in various plants and foods, and that it has demonstrated multiple beneficial properties for oral health. These include its ability to prevent tooth decay, reduce inflammation and pain in the gums, and promote the regeneration of damaged dental tissues. These effects are due to its antioxidant, anti-inflammatory and antimicrobial action, which make it an important ally for the prevention and treatment of various dental diseases. In particular, it has been shown to have an inhibitory

effect on the expression of virulence factors and the formation of biofilms of key pathogens such as *P. gingivalis* and *S. mutans*.

In addition to its inhibitory effect on oral pathogens, resveratrol is also a useful compound for vital pulp therapy and the prevention of periodontal disease. Resveratrol has a variety of clinical uses in dentistry, including its use in dental products such as mouthwashes, toothpastes, and filling materials. However, more clinical studies are required to determine the efficacy and safety of resveratrol in these applications. They suggest that the use of dental products with resveratrol may be beneficial in a variety of cases, such as the prevention of tooth decay, gingivitis, and periodontitis, as well as in promoting wound healing and tooth tissue regeneration. In addition, it has been shown that it can improve the effectiveness of other dental treatments, such as periodontal therapy and endodontics. However, more research is required to determine the optimal dosage and manner of administration of this compound in dentistry.

Resveratrol has been studied in relation to adhesive systems in dentistry and has been shown to improve the durability of the adhesive in vitro and extend the life of the restoration. In addition, a gradual decrease in cohesive failure in dentin has been observed with increasing dentin concentration. Dentin bonding agents with quercetin and resveratrol have also been shown to have the potential to increase the longevity of composite restorations. Overall, these findings suggest that resveratrol has great potential in restorative dentistry and may improve patients' quality of life by preventing secondary caries and improving the durability of restorations.

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