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Resveratrol-based biomaterials and therapeutic strategies for dental implant osseointegration and peri-implant tissue healing: A systematic review

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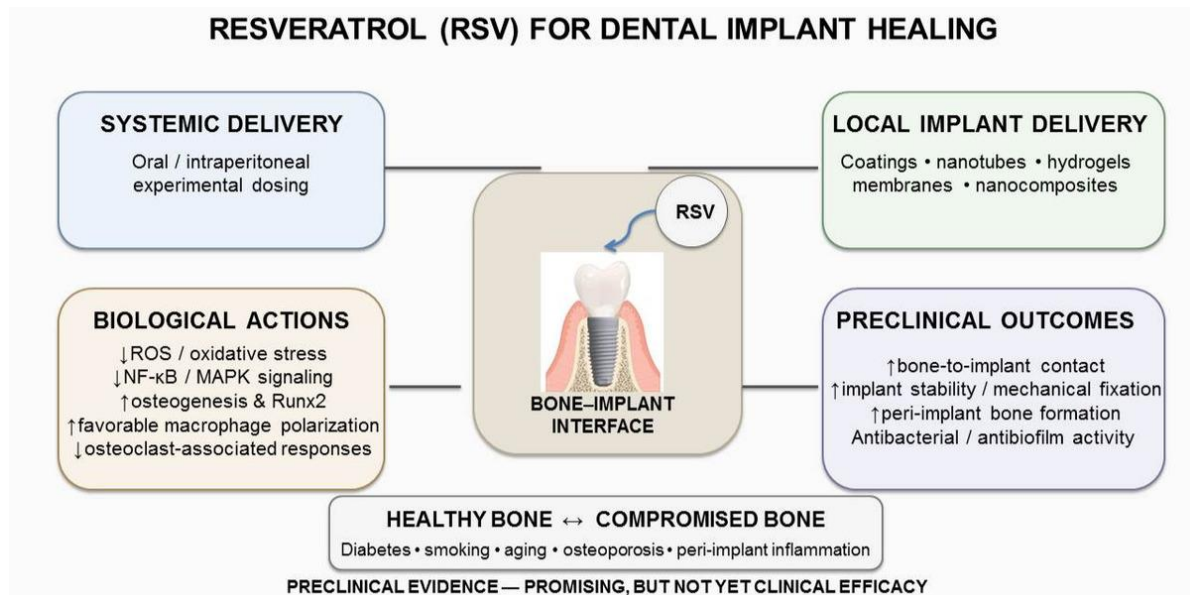
Abstract

Background. Resveratrol (RSV) is a polyphenolic compound with antioxidant, anti-inflammatory, osteomodulatory, and antimicrobial properties that may influence dental implant osseointegration and peri-implant tissue healing. However, preclinical findings remain inconsistent. This systematic review evaluated preclinical evidence on the effects of RSV on dental implant osseointegration and peri-implant tissue responses, with emphasis on pathological conditions, implant surface modifications, delivery systems, and biological mechanisms.

Methods. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched from inception to August 2026. In vivo and in vitro studies investigating RSV in dental implant, osseointegration, or implant-associated infection models were eligible. Outcomes included implant stability, bone-to-implant contact, peri-implant bone formation, osteogenic/osteoclast markers, inflammatory/oxidative responses, and antimicrobial activity. Risk of bias was assessed using SYRCLE for animal studies. Findings were synthesized narratively due to substantial heterogeneity.

Results. Twenty studies were included. Systemic RSV showed beneficial effects in several experimental models of diabetes, smoking exposure, and aging/alcohol-associated skeletal impairment. In contrast, findings were inconsistent across streptozotocin-induced diabetes, type 2 diabetes models, and osteoporosis models. RSV-functionalized surfaces, hydrogels, membranes, nanotube coatings, and nanocomposite systems showed osteogenic, antioxidant, anti-inflammatory, immunomodulatory, and/or antimicrobial effects in experimental models. Antibacterial and antibiofilm effects were also reported. Proposed mechanisms involved modulation of ROS, NF-κB/MAPK signaling, osteogenesis, osteoclast activity, and macrophage polarization.

Conclusions. RSV shows promise as a multifunctional adjunct for implant-associated bone healing and peri-implant tissue modulation. However, substantial heterogeneity and inconsistent findings limit definitive conclusions and warrant standardized, clinically relevant in vivo studies. These findings remain preclinical and should not be interpreted as evidence of clinical efficacy.



Key words: Biomaterials, dental implants, diabetes, implant stability, osseointegration, peri-implant bone, peri-implantitis, resveratrol, systematic review, titanium.

Introduction

Dental implant osseointegration is a dynamic biological process involving coordinated interactions among inflammatory, vascular, cellular, and extracellular matrix responses at the implant–bone interface.¹ Successful osseointegration establishes stable mechanical anchorage and represents a fundamental determinant of long-term implant function. Although advances in implant design, surface modification, and clinical protocols have substantially improved treatment predictability, impaired osseointegration remains a concern in patients with systemic or local conditions that adversely affect bone metabolism and peri-implant tissue homeostasis. Diabetes mellitus, cigarette smoking, a history of periodontitis, advanced age, and systemic conditions affecting bone metabolism may influence peri-implant tissue stability and the risk of biological complications.^{2–6}

The biological response to an implant is strongly influenced by the local redox and inflammatory microenvironment. Oxidative stress can impair osteoblast differentiation, alter osteoclast activity, promote inflammatory signaling, and interfere with the balance between bone formation and resorption. Similarly, persistent activation of inflammatory pathways, including nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling, may adversely affect peri-implant bone remodeling.⁶ These observations have stimulated interest in adjunctive biological strategies capable of simultaneously modulating oxidative stress, inflammation, osteogenesis, and bone remodeling rather than targeting a single component of the osseointegration process.

Resveratrol (RSV; 3,5,4'-trihydroxystilbene) is a naturally occurring polyphenolic compound that has attracted considerable interest because of its antioxidant, anti-inflammatory, and osteomodulatory properties.⁷ Experimental studies have reported that RSV can influence osteoblast differentiation and extracellular matrix mineralization,⁸ attenuate oxidative stress,⁹ modulate inflammatory signaling,¹⁰ and regulate osteoclast-mediated bone remodeling.¹¹ These pleiotropic biological effects provide a rationale for investigating RSV as a potential adjunctive strategy for improving the biological response to dental implants, particularly under pathological conditions characterized by oxidative stress, inflammation, or impaired bone turnover.

Early implant-related evidence suggested that systemic RSV may improve implant fixation in experimental models. Casarin et al.¹² reported increased implant counter-torque and upregulation of bone-related genes following systemic RSV administration in rats receiving titanium implants. Subsequent experimental studies extended this research to several adverse biological conditions relevant to impaired implant healing. In smoking-exposed animals, RSV was associated with improved peri-implant bone healing and modulation of osteogenic and osteoclast-associated pathways.¹³ In diabetic models, RSV has been investigated as a potential means of attenuating impaired peri-implant bone repair, with studies reporting improvements in bone-to-implant contact, mechanical fixation, trabecular parameters, and bone-related molecular markers.^{14,15} However, these effects have not been uniform. Studies performed in healthy animals, ovariectomy-induced osteoporosis, and some experimentally induced diabetic models have reported limited or absent improvements in peri-implant osseointegration.^{16–20} Such findings suggest that the biological effect of RSV may depend on the underlying metabolic environment, disease severity, treatment regimen, implant characteristics, and stage of bone healing.

Interest in RSV has subsequently expanded beyond systemic administration toward implant surface engineering and controlled local delivery. RSV has been incorporated into titanium-based coatings, titania nanotube systems, polymeric membranes, hydrogels, collagen-based materials, and nanocomposite surfaces.^{21–29} These approaches aim to overcome limitations associated with systemic delivery while providing localized antioxidant, anti-inflammatory, osteogenic, or antimicrobial activity at the implant–tissue interface. Experimental evidence suggests that RSV-functionalized surfaces may reduce reactive oxygen species and inflammatory mediators while promoting osteoblast activity, extracellular matrix mineralization, and osteogenic gene expression.^{23,25,28} Responsive delivery systems may additionally provide controlled RSV release under conditions associated with inflammation or infection.^{22,25}

However, the clinical translation of systemic RSV administration is complicated by its extensive intestinal and hepatic metabolism, including glucuronidation and sulfation, which results in very low systemic bioavailability of unchanged trans-resveratrol.³⁰ Therefore, systemic doses used in experimental animal models cannot be directly extrapolated to clinically applicable human doses.³⁰

The potential role of RSV may also extend to preventing or managing implant-associated inflammation and microbial contamination. Experimental models of peri-implant inflammation and bone loss in the included studies reported inflammatory changes accompanied by peri-implant bone loss and modulation of MAPK/NF- κ B- or MAPK/AKT/NF- κ B-related signaling following systemic RSV treatment.^{31,32} According to the 2017 World Workshop definition, peri-implantitis is a biofilm-associated inflammatory condition characterized by inflammation of the peri-implant tissues accompanied by progressive supporting bone loss; therefore, peri-implant bone resorption or inflammation alone should not automatically be considered equivalent to clinical peri-implantitis.⁴ Other investigations have demonstrated antibacterial and antibiofilm activity of RSV-containing membranes and RSV-based titanium surface decontamination strategies.^{22,26,29} These findings are particularly relevant because successful implant therapy depends not only on initial osseointegration but also on maintenance of a biologically stable peri-implant environment. Importantly, the available evidence shows substantial biological and methodological heterogeneity. Studies differ in animal species, metabolic status, implant design and surface topography, RSV dose and route of administration, treatment duration, local delivery platform, and outcome assessment. Moreover, some investigations focus directly on implant stability or bone-to-implant contact, whereas others primarily evaluate surrogate osteogenic, inflammatory, oxidative, antimicrobial, or cellular outcomes. Reports from the same

experimental research program may also address overlapping experimental models and time points, creating a potential risk of treating related reports as independent evidence.

Therefore, this systematic review aimed to comprehensively synthesize available preclinical evidence on the effects of resveratrol on dental implant osseointegration and peri-implant tissue responses. Particular emphasis was placed on distinguishing direct implant-related outcomes from surrogate biological and mechanistic findings and on evaluating the influence of pathological conditions, implant surface characteristics, and RSV delivery strategies. The review also examined evidence regarding the potential osteogenic, antioxidant, anti-inflammatory, immunomodulatory, and antimicrobial mechanisms underlying the reported effects of RSV.

Methods

Protocol and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) on 26 August 2026 (CRD420261488782) prior to the literature search, which was conducted on 31 August 2026.

Research Question

The review was designed to address the following question:

What are the effects of resveratrol on dental implant osseointegration and peri-implant tissue responses in preclinical experimental models, and what biological or biomaterial-related mechanisms may underlie these effects?

The eligibility framework was structured according to the following components:

Population/Model: Experimental animal or in vitro models relevant to dental implants, titanium implants, implant surfaces, osseointegration, peri-implant tissues, or implant-associated infection.

Intervention: Resveratrol (RSV), including systemic administration, local delivery, surface immobilization, implant coating, hydrogel, membrane, or other implant-associated delivery systems.

Comparator: Untreated or vehicle controls, non-RSV materials, unmodified implant surfaces, alternative surface/material controls, or appropriate pathological/healthy controls.

Outcomes: Implant stability, osseointegration, bone formation, bone-to-implant contact, peri-implant bone loss, histomorphometric and micro-CT parameters, osteogenic and osteoclastic responses, inflammatory and oxidative-stress markers, macrophage responses, antimicrobial/antibiofilm activity, and relevant biomaterial properties.

Search Strategy

A comprehensive electronic search was conducted in PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Google Scholar from database inception to August 2026.

The search strategy combined three main conceptual domains:

1. Resveratrol-related terms
2. Dental implant/osseointegration-related terms
3. Peri-implant, implant surface, biomaterial, and implant-associated infection terms

The search strategy was designed to maintain a strong implant-related focus and avoid retrieving studies that investigated resveratrol solely in non-implant bone defects or general bone regeneration models.

No restriction based on publication year or language was applied during the electronic search. Reference lists of included studies and relevant reviews were also manually screened to

identify potentially eligible studies that might not have been retrieved by the electronic searches. The complete database-specific search strategies are provided in Supplementary File 1. Because Google Scholar uses relevance-based ranking and does not provide a reproducible exhaustive retrieval set, the first 200 records were screened according to relevance.

Eligibility Criteria

Studies were considered eligible when they met all of the following criteria:

1. Investigated resveratrol as the active experimental intervention or as a functional component of an implant-associated delivery/surface system
2. Evaluated a dental implant, titanium implant, implant-associated surface, implant coating, implant-related biomaterial, or peri-implant experimental model, or a biomaterial explicitly developed for implant-associated osseointegration, peri-implant tissue healing, or prevention of implant-associated infection
3. Reported at least one outcome directly or mechanistically relevant to implant osseointegration, peri-implant bone healing, peri-implant inflammation, implant-associated infection, or biological responses at the implant–tissue interface
4. Were original experimental studies conducted using animal or in vitro models
5. Included an appropriate comparator or control condition where applicable

Studies were excluded if they:

1. Investigated resveratrol only in non-implant bone defects or general bone regeneration models, without an implant-related component
2. Evaluated resveratrol solely for systemic bone health without an implant-related outcome
3. Did not investigate resveratrol as an intervention or functional component
4. Were clinical studies, observational human studies, case reports, case series, reviews, systematic reviews, meta-analyses, conference abstracts, editorials, letters, or dissertations without sufficient original experimental data for extraction
5. Were unrelated to osseointegration, peri-implant tissue responses, implant-associated infection, or implant surface biology

Types of Studies

Both in vivo animal studies and in vitro experimental studies were eligible. Animal studies included models of healthy or experimentally compromised implant healing, including streptozotocin-induced diabetes or hyperglycemia, type 2 diabetes models, cigarette smoke exposure, osteoporosis, aging, alcohol-associated bone impairment, experimental peri-implant inflammation and bone loss, and immediate implant placement.

In vitro studies were eligible when they directly investigated RSV-containing implant surfaces, titanium substrates, implant-associated membranes, coatings, hydrogels, or other biomaterials specifically intended for implant-related applications and reported outcomes relevant to osteogenesis, inflammatory modulation, oxidative stress, cytocompatibility, antimicrobial activity, antibiofilm activity, or RSV delivery.

Intervention and Comparators

Eligible RSV interventions included: systemic RSV administration; oral, intraperitoneal, or subcutaneous administration; local RSV delivery; RSV-immobilized implant-associated membranes; RSV-loaded titanium or titania nanotube surfaces; RSV-containing hydrogels; RSV-loaded polymeric or collagen-based systems; RSV-containing nanocomposite implant coatings; RSV-based responsive or controlled-release systems; RSV-based implant decontamination approaches.

Comparators included vehicle or untreated controls, non-RSV biomaterials, unmodified implant surfaces, carrier-only coatings, conventional decontamination agents, healthy controls, pathological controls, and other treatment groups.

Where multiple treatment arms were reported, each comparison was evaluated according to the study design and the prespecified outcomes.

Outcomes

The main implant-related outcomes were: implant removal torque or reverse torque, implant stability or mechanical anchorage, bone-to-implant contact (BIC), peri-implant bone formation, histomorphometric measures of osseointegration, and micro-CT measures directly reflecting peri-implant bone integration.

Secondary outcomes included: micro-CT parameters, including BV/TV, Tb.Th, Tb.N, Tb.Sp, and connectivity-related measures; osteogenic markers, including BMP-2, BMP-7, OPN, RUNX2, ALP, OCN, COL-I, β -catenin, and LRP-5; osteoclast-associated markers, including RANKL, OPG, RANKL/OPG, TRAP, and CTSK; inflammatory mediators, including TNF- α , IL-1 β , IL-6, and IL-10; oxidative-stress markers, including ROS, MDA, NO, and SOD; macrophage polarization and immunomodulatory markers; osteoblast proliferation and differentiation; ALP activity, collagen production, and extracellular matrix mineralization; bacterial viability, antibacterial activity, and antibiofilm activity; peri-implant inflammatory bone loss; RSV release kinetics and responsiveness; implant surface characteristics and cytocompatibility.

Study Selection

All records identified through the electronic searches were imported into Rayyan software, and duplicates were removed before screening. Two reviewers independently screened titles and abstracts according to the predefined eligibility criteria. Potentially eligible records were subsequently assessed by full-text review. Reasons for exclusion at the full-text stage were documented. Reports originating from the same experimental research program were examined for overlapping experimental populations, interventions, implant configurations, and outcomes. Related reports with substantial overlap were not counted as independent studies to avoid double-counting. Any disagreement between reviewers was resolved through discussion and, when necessary, consultation with a third reviewer. The study selection process was summarized using a PRISMA flow diagram.

Data Extraction

Two reviewers independently extracted the data using a predefined standardized data-extraction form. The following information was collected: first author and publication year, experimental model and species, sample size, implant type and implant material, implant surface/topography, pathological condition when applicable, RSV formulation, dose and route of administration; duration of treatment; control/comparator groups; follow-up duration, primary and secondary outcomes, molecular and cellular findings, antimicrobial findings, biomaterial characteristics, and major methodological limitations.

For studies from the same experimental program, experimental design, animal model, implant configuration, treatment protocol, and outcome overlap were carefully examined to determine whether the reports represented independent datasets.

Risk of Bias Assessment

The risk of bias of the included in vivo animal studies was assessed using the SYRCLE risk-of-bias tool. Two reviewers independently evaluated each study across the relevant domains, including sequence generation, baseline characteristics, allocation concealment, random

housing, blinding of caregivers or investigators, random outcome assessment, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting. Each domain was judged as having low, high, or unclear risk of bias according to the information reported in the original publication. When a methodological procedure was not sufficiently described, the corresponding domain was classified as unclear rather than inferred to be adequate. Disagreements between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer.

For the included in vitro studies, a predefined methodological appraisal framework was applied, focusing on the adequacy of experimental controls, characterization of the RSV intervention, outcome measurement, and completeness of reporting. Because the available in vitro studies differed substantially in experimental design and outcome assessment, these evaluations were interpreted descriptively rather than combined into a numerical overall quality score.

Management of Related Reports and Overlapping Datasets

The reports by Guo,¹⁷ Staibano,¹⁸ and Liddell et al.¹⁹ were identified as related reports from the same experimental research program. Liddell et al.¹⁹ was retained as the primary peer-reviewed report for study-level synthesis, whereas the Guo¹⁷ and Staibano¹⁸ theses were treated as related companion reports rather than independent studies.

Data Synthesis

Because of substantial heterogeneity in experimental models, implant systems, RSV doses and routes, delivery systems, outcome definitions, follow-up periods, and experimental conditions, a quantitative meta-analysis was not considered appropriate.

Therefore, the findings were synthesized narratively and organized according to systemic RSV administration, pathological implant healing conditions, implant surface and biomaterial engineering, peri-implant inflammatory disease, antimicrobial and decontamination applications, and cellular and molecular mechanisms.

Particular emphasis was placed on distinguishing direct implant-related outcomes from surrogate biological outcomes and mechanistic in vitro findings.

Results

Study Characteristics

Figure 1 illustrates the study selection process. After searching databases, removing duplicates, and screening titles/abstracts and full texts, 20 preclinical studies met the eligibility criteria and were included in the qualitative synthesis. The included evidence comprised animal studies and in vitro investigations evaluating systemic or locally delivered resveratrol (RSV), RSV-functionalized implant surfaces and biomaterials, and RSV-based approaches targeting peri-implant inflammation or implant-associated infection.

The studies were broadly classified into four evidence domains: (1) systemic RSV administration in implant-bearing animal models; (2) RSV-mediated modulation of peri-implant healing under pathological conditions, including diabetes, hyperglycemia, smoking, osteoporosis, aging, and alcohol exposure; (3) RSV-functionalized implant surfaces, coatings, membranes, and hydrogels; and (4) anti-inflammatory, antimicrobial, and mechanistic applications related to peri-implant tissue healing. Table 1 summarizes the characteristics and principal findings of the included preclinical studies.

Nine studies evaluated systemic RSV administration in animal models with implants,^{12–16,19,20,33,34} whereas several additional studies investigated RSV-containing implant-associated biomaterials or surface modifications.^{21–29} Two studies specifically investigated experimental

peri-implant inflammation and bone loss models,^{31,32} and other studies evaluated antimicrobial decontamination or implant-associated infection prevention.^{22,26,29}

Risk of Bias

Risk of bias was assessed for the 13 independent in vivo animal studies using SYRCLE's risk-of-bias tool (Supplementary File 2). Overall, reporting of methodological safeguards varied. Sequence generation was judged as low risk in 9 studies and unclear in 4 studies. Baseline characteristics were judged as low risk in all 13 studies. Allocation concealment and random housing were unclear across all studies because they did not report sufficient methodological details. Blinding of caregivers and investigators was unclear in 11 studies and high risk in one study, while one study was judged low risk. Random outcome assessment was unclear across all studies. Outcome assessor blinding was judged as low risk in 4 studies and unclear in 9 studies. Incomplete outcome data were judged as low risk in 6 studies and unclear in 7 studies. Selective reporting and other sources of bias were predominantly unclear because of insufficient methodological reporting. Overall, the assessment raised concerns about reporting and methodological transparency, particularly for allocation concealment, housing, and blinding domains.

Risk of bias was assessed for the seven included in vitro studies using predefined methodological criteria (Supplementary File 3). Overall, the seven in vitro studies were assessed as having low overall methodological concern according to the predefined appraisal domains; however, several studies provided limited information regarding aspects such as biological versus technical replication, donor or passage independence, and blinding of outcome assessment. Therefore, these judgments should be interpreted in the context of the available reporting, rather than as evidence that all aspects of experimental rigor were fully established.

It is important to emphasize that the predominantly 'unclear' judgments, particularly for allocation concealment, random housing, and blinding domains, primarily reflect incomplete reporting in the primary literature rather than confirmed methodological flaws. This distinction is critical because it highlights the need for improved adherence to reporting guidelines such as ARRIVE in future preclinical studies, rather than implying that the underlying experiments were necessarily biased.

Systemic Resveratrol in Implant-bearing Animal Models

Healthy and euglycemic conditions: Casarin et al.¹² were among the first to directly investigate systemic RSV in an implant-bearing animal model. Healthy Wistar rats receiving 10 mg/kg RSV by oral gavage for 30 days showed significantly higher implant counter-torque than untreated controls (5.67 ± 2.15 N/cm vs. 4.11 ± 0.88 N/cm; $P=0.031$), a 37.8% increase. RSV was also associated with reduced residual calvarial defect size and increased expression of BMP-2 ($P=0.011$), BMP-7 ($P=0.049$), and OPN ($P=0.002$). BSP, OPG, and RANKL expression showed no significant changes.

In contrast, Liddell et al.¹⁹ found no statistically significant improvement in the parameters describing early implant integration in euglycemic animals. Thus, the available evidence under physiological conditions was inconsistent.

Systemic Resveratrol under Metabolic and Skeletal Stress

Diabetes and hyperglycemia: Several studies investigated RSV in diabetic or hyperglycemic implant models. Hua et al.¹⁴ reported that STZ-induced diabetic rats treated with 25 mg/kg RSV intraperitoneally for 8 weeks showed significantly greater BIC, BV/TV, and push-out force than untreated diabetic controls, with approximately 3.3-fold, 3.5-fold, and 1.8-fold increases, respectively. However, the osseointegration parameters did not completely reach

those of normoglycemic controls. Corrêa et al.¹⁵ evaluated RSV alone, insulin alone, and combined RSV plus insulin treatment in diabetic rats. RSV treatment increased counter-torque, BIC, and trabecular thickness relative to diabetic controls ($P<0.05$), while reducing RANKL expression. The RSV + insulin combination was associated with increased Runx2 expression ($P<0.05$).

Liddell et al.¹⁹ provided a time-dependent assessment of RSV under hyperglycemia. RSV had little measurable effect during early osseointegration but was associated with improved late implant anchorage at 84 days in hyperglycemic animals. Nonlinear modeling distinguished early osseointegration from the later remodeling phase and indicated that the principal RSV-associated difference occurred during the later phase.

Wajima et al.¹⁶ evaluated 100 mg/kg systemic RSV in type 2 diabetic rats. Although RSV improved long bone biomechanics and metabolic status, it did not significantly improve peri-implant osseointegration. These findings therefore did not demonstrate a uniform benefit of systemic RSV across all diabetic models. The diabetic models included in these studies should be interpreted as experimental representations of selected aspects of metabolic impairment rather than direct equivalents of human diabetes mellitus. In particular, streptozotocin-induced diabetes primarily reproduces chemically induced pancreatic β -cell dysfunction and sustained hyperglycemia and may differ substantially from the multifactorial, chronic metabolic and vascular pathology of human type 2 diabetes mellitus. Therefore, findings from these experimental models should not be directly extrapolated to clinical outcomes in patients with type 2 diabetes. Rather, they provide preclinical evidence that RSV may modulate selected mechanisms associated with impaired peri-implant healing under experimentally induced metabolic conditions.

Pitol-Palin et al.³⁴ investigated systemic resveratrol (100 mg/kg) combined with antimicrobial photodynamic therapy (aPDT) in a type 2 diabetes model with immediate implant placement. Systemic resveratrol improved glycemic control and body weight, while aPDT significantly increased implant removal torque in diabetic animals. The combination of resveratrol and aPDT was associated with reduced expression of bone resorption-related markers, increased expression of bone mineralization-related genes, and higher mineral apposition rates, supporting enhanced peri-implant bone repair under diabetic conditions.

Smoke exposure: Ribeiro et al.¹³ evaluated systemic RSV in rats exposed to cigarette smoke. RSV at 10 mg/kg for 30 days increased counter-torque and BIC compared with smoking-exposed controls. The CSI+RSV group did not differ significantly from nonsmoking controls in counter-torque measurements ($P=0.171$), while the smoking-placebo group showed significantly lower values. RSV was also associated with a reduced RANKL/OPG ratio ($P=0.0342$), reduced Lrp-5 expression ($P=0.0189$), and increased β -catenin expression ($P=0.0362$).

Osteoporosis, aging, and alcohol exposure: Zamai et al.²⁰ found that systemic RSV at 10 mg/kg did not improve peri-implant bone repair in ovariectomized osteoporotic rats. Compared with sham controls, RSV-treated osteoporotic animals showed unfavorable changes in BIC, BV/TV, trabecular number, porosity, and trabecular spacing, whereas zoledronate-containing regimens improved several trabecular parameters. RSV did not significantly modify BMP-2, OPG, RANKL, or Runx2 expression.

Tao et al.³³ investigated senile female rats exposed to alcohol and found that RSV at 40 mg/kg increased BV/TV, Tb.N, Tb.Th, and connectivity density and decreased trabecular spacing compared with alcohol-exposed controls ($P<0.05$). Push-out force increased approximately 1.45-fold, while Runx2, osteocalcin, and OPG expression increased and RANKL expression decreased. Fan et al.²⁴ developed a resveratrol-containing responsive coating for titanium implants in a senile osteoporosis model. The RSV-based coating enhanced peri-implant bone formation and osseointegration and was associated with reduced

oxidative stress and senescence-associated secretory phenotype markers, together with increased osteogenic differentiation.

Interaction between Resveratrol and Implant Surface Topography

Liddell et al.¹⁹ provided the most detailed evaluation of the interaction between RSV and implant surface topography. Nanotopographic implants demonstrated greater mechanical anchorage than microtopographic implants across experimental conditions. The advantage of nanotopography was particularly evident during early osseointegration, whereas the RSV-associated effect was more apparent at later stages under hyperglycemic conditions. Liddell et al.¹⁹ reported that RSV did not substantially alter the early topography-related differences but was associated with improved late anchorage in hyperglycemic animals. Thus, surface topography and RSV treatment were evaluated as potentially distinct contributors to the temporal pattern of implant integration.

RSV-Functionalized Implant Surfaces and Biomaterials

Hydrogel and responsive coatings: Wang et al.²⁵ developed a resveratrol-releasing GelMA hydrogel coating for micro/nanostructured titanium. The coating provided sustained RSV release and increased osteoblast proliferation, ALP activity, collagen production, mineralization, and expression of RUNX2, ALP, COL-I, OPG, and OCN in experimental conditions. It also reduced osteoclast-associated responses and promoted M2 macrophage polarization, accompanied by reduced IL-1 β and TNF- α and increased IL-10. In the corresponding diabetic rat implant model, the RSV-containing coating increased new bone formation and bone-implant integration. However, the in vivo improvement was not significantly greater than that observed with the GelMA-modified titanium control, indicating that the contribution of RSV itself could not be completely separated from that of the carrier.

Fan et al.²⁴ similarly used an RSV-loaded GelMA-chitosan hydrogel coating on titanium implants in senile osteoporotic rats. The coating reduced oxidative stress and senescence-associated markers and enhanced osteogenic differentiation and peri-implant bone formation.

Titania nanotube and nanocomposite surfaces: Yang et al.²³ developed RSV-loaded titania nanotube coatings on titanium surfaces. RSV release from the nanotube system reduced ROS production in macrophages and bone marrow stromal cells, with reported inhibition of up to 45.75% ($P < 0.01$). TNF- α , IL-1 β , and NO production were reduced, while ALP activity, extracellular matrix mineralization, and expression of OCN, OPN, Runx2, and COL-I increased. These effects were associated with modulation of NF- κ B signaling.

Kan et al.²⁹ developed a graphene oxide coating incorporating a resveratrol-gold nanocomposite and evaluated its antibacterial activity and osteogenic bioactivity. The coating enhanced antibacterial performance, including under X-ray activation, while maintaining favorable osteogenic responses. This study extended RSV-based surface engineering toward combined antimicrobial and osteogenic functionality.

Polymeric, cellulose acetate, and collagen-based systems: Pande et al.²¹ covalently immobilized RSV onto cellulose acetate membranes applied to magnesium-based alloys. RSV-functionalized membranes maintained osteoblast viability and significantly increased ALP activity and extracellular matrix mineralization compared with unmodified controls.

Bonadies et al.²² developed RSV-loaded electrospun PLA membranes with pH-responsive release. RSV release increased under acidic conditions designed to mimic an infection-associated environment. The membranes demonstrated antibacterial and antibiofilm activity against *Pseudomonas aeruginosa* PAO1 and *Streptococcus mutans*.

Wang et al.²⁷ investigated collagen films containing RSV and celastrol. RSV-containing films promoted periodontal ligament fibroblast proliferation, while the system also demonstrated effects on osteoclastogenic responses in bone marrow-derived macrophages. The findings

supported the biological compatibility of RSV-containing collagen-based dental biomaterials. Hang et al.²⁸ further investigated RSV-mediated responses in senescent macrophages. RSV at 0.1–1 μ M increased autophagy, cell viability, and proliferation, reduced intracellular ROS, and promoted M2 polarization, reflected by increased CD206 and decreased iNOS expression. The altered macrophage phenotype was accompanied by enhanced osteogenic and angiogenic responses. The study also demonstrated the feasibility of incorporating RSV into silk fibroin coatings for titanium surfaces.

Antimicrobial and Implant Decontamination Applications

Zhou et al.²⁶ evaluated RSV and naringin as chemical decontaminants for SLA titanium surfaces. RSV treatment reduced mature bacterial biofilms, including *Staphylococcus aureus* and *Porphyromonas gingivalis*, while maintaining favorable surface characteristics and cytocompatibility. RSV-treated surfaces demonstrated increased cell adhesion, proliferation, and osteogenic differentiation compared with conventional decontamination approaches. Bonadies et al.²² likewise demonstrated antimicrobial and antibiofilm activity from RSV-loaded PLA membranes against *P. aeruginosa* and *S. mutans*. Kan et al.²⁹ extended this concept by combining RSV with a gold nanocomposite and graphene oxide coating, providing antibacterial activity while preserving osteogenic bioactivity.

Experimental Peri-implant Inflammation and Bone Loss

Liu et al.³¹ established a murine model of experimental peri-implant inflammation and bone loss and administered RSV at 20 or 40 mg/kg for 6 weeks. RSV reduced inflammatory cell infiltration, tissue edema, and peri-implant bone resorption. Micro-CT demonstrated reduced bone loss at proximal, distal, buccal, and palatal sites ($P < 0.05$). TNF- α and IL-6 concentrations were also reduced, while phosphorylation of ERK, JNK, p38 MAPK, I κ B α , and NF- κ B was inhibited.

Zhang et al.³² reported similar anti-inflammatory effects in a murine model of experimental peri-implant inflammation. RSV at 200–600 mg/kg for 2 weeks reduced peri-implant bone loss and cellular apoptosis and decreased oxidative stress markers, including MDA and NO, while increasing SOD activity. These effects were accompanied by modulation of the MAPK/AKT/NF- κ B signaling pathway.

Mechanistic Evidence: Osteoimmunology and Cellular Responses

The included experimental studies provided mechanistic evidence supporting several biological pathways potentially relevant to implant healing. Across different experimental platforms, RSV was associated with reduced oxidative stress, attenuation of inflammatory signaling, enhanced osteogenic differentiation, and modulation of macrophage phenotype.^{23,25,28}

Hang et al.²⁸ specifically demonstrated that RSV promoted autophagy and M2 polarization in senescent macrophages and subsequently enhanced osteogenic and angiogenic responses. Yang et al.²³ linked RSV-loaded titania nanotube coatings to reduced ROS production and NF- κ B signaling, whereas the GelMA-based system evaluated by Wang et al.²⁵ combined osteogenic and immunomodulatory effects.

These mechanistic findings were generally consistent with the animal evidence showing modulation of inflammatory, oxidative, osteogenic, and osteoclast-associated pathways, although the experimental concentrations and biological models differed substantially among studies.

Negative and Context-dependent Findings

Not all studies demonstrated a beneficial effect of RSV on implant-related outcomes. Liddell

et al.¹⁹ found no significant RSV-related improvement in healthy euglycemic animals, particularly during early osseointegration. Zamai et al.²⁰ reported no beneficial effect of RSV alone in ovariectomized osteoporotic rats. Wajima et al.¹⁶ similarly found that systemic RSV improved long-bone biomechanics without significantly improving peri-implant osseointegration in type 2 diabetic rats.¹⁶

The 2026 GelMA study also demonstrated the importance of the carrier control: although the RSV-containing coating improved several biological parameters, its *in vivo* bone-formation advantage over GelMA-modified titanium was not statistically significant.²⁵

Overall, the included studies demonstrated substantial heterogeneity in animal models, metabolic conditions, RSV dose and route, implant characteristics, delivery systems, outcome measures, and follow-up periods. Accordingly, the evidence was synthesized qualitatively rather than pooled quantitatively.

Discussion

This review synthesized the available preclinical evidence on the effects of RSV on dental implant osseointegration and peri-implant tissue responses. Across 20 eligible studies, RSV demonstrated a potentially beneficial but clearly context-dependent profile. More consistent beneficial findings were observed in experimental conditions characterized by metabolic dysfunction, oxidative stress, inflammation, or impaired bone remodeling, whereas effects were less reproducible in physiologically healthy or severely compromised bone. In parallel, RSV-based implant coatings and delivery systems demonstrated osteogenic, anti-inflammatory, antioxidant, immunomodulatory, and antimicrobial properties. Taken together, the evidence does not support viewing RSV simply as a conventional osteogenic agent; its potential value may instead reflect simultaneous effects on several biological processes involved in implant integration. Importantly, the absence of a statistically significant difference between the RSV-containing hydrogel and the corresponding carrier-only control in selected outcomes indicates that RSV's independent contribution may be outcome- and formulation-dependent. This finding should be distinguished from methodological risk of bias and underscores the importance of appropriate carrier-only controls in future biomaterial studies.

The earliest implant-specific evidence came from Casarin et al.,¹² who reported enhanced reverse torque and increased expression of BMP-2, BMP-7, and OPN following systemic RSV administration in healthy rats.¹² These findings provided an initial biological rationale for RSV supplementation during implant healing. However, subsequent investigations indicate that the response to RSV is strongly dependent on the biological environment.

More consistent experimental signals were observed in metabolically compromised models. In diabetic rats, Hua et al.¹⁴ reported improvements in BIC, BV/TV, and push-out force after RSV treatment, while Corrêa et al.¹⁵ observed improved mechanical fixation and trabecular characteristics, accompanied by reduced RANKL expression. These findings are biologically plausible because diabetes is associated with oxidative stress, impaired osteoblast function, altered osteoclast activity, and chronic low-grade inflammation. RSV may therefore modulate selected biological pathways involved in impaired peri-implant healing under experimentally induced metabolic stress. However, these findings represent responses observed in specific animal models and should not be interpreted as evidence of clinical efficacy in patients with diabetes. In particular, BIC, BV/TV, mechanical fixation, and related micro-CT or biomechanical outcomes are experimental measures of osseointegration rather than direct evidence of clinically meaningful benefit in patients with diabetes.

Evidence from smoking-associated models provides a similar interpretation. Ribeiro et al.¹³ reported that RSV substantially attenuated the adverse effect of cigarette smoke on peri-implant repair and improved both mechanical and micro-CT outcomes. Modulation of the

RANKL/OPG axis and β -catenin-related signaling suggested that RSV may influence the balance between bone formation and resorption under smoke-induced stress. However, these findings remain model-specific and should not be interpreted as evidence that RSV can overcome the clinical effects of smoking in human implant therapy. Rather, they provide preclinical evidence that RSV may modulate selected biological responses associated with experimentally induced smoking-related impairment.

Importantly, the evidence does not support a universal osteogenic effect of RSV. Liddell et al.¹⁹ found little or no improvement in healthy euglycemic animals, particularly during early osseointegration. Similarly, Zamai et al.²⁰ found that RSV alone did not improve peri-implant bone repair in ovariectomy-induced osteoporosis, and Wajima et al.¹⁶ reported improved long-bone biomechanics without significant improvement in peri-implant osseointegration in rats with type 2 diabetes. These findings indicate that systemic RSV may not overcome all forms or degrees of impaired bone healing and further support interpreting the observed effects as model-specific preclinical signals rather than demonstrated therapeutic benefit in clinically compromised patients.

A key contribution of Liddell et al.¹⁹ was distinguishing early osseointegration from later bone remodeling. RSV did not substantially improve early implant integration in hyperglycemic conditions but enhanced mechanical anchorage at the later 84-day stage. This temporal pattern challenges the assumption that RSV acts primarily by directly accelerating early bone formation. The findings suggest that RSV's effects may become more apparent during later remodeling, although the biological basis of this temporal pattern remains uncertain.¹⁹ This interpretation may also explain some apparent inconsistencies among studies with different observation periods. Studies terminating after only a few weeks may underestimate effects that become evident during later remodeling.

The interaction with implant surface topography adds another layer of complexity. Nanotopographic implants exhibited greater mechanical anchorage than microtopographic implants, particularly during early osseointegration.¹⁹ However, RSV did not substantially modify the topographic advantage, suggesting that surface nanotopography and RSV may influence implant integration through partially distinct biological mechanisms. This finding supports combining optimized physical surface properties with biologically active agents rather than expecting RSV to replace established surface-engineering strategies.

Recent studies have increasingly examined localized RSV delivery rather than systemic administration. RSV-functionalized titanium surfaces, titania nanotubes, hydrogels, polymeric membranes, collagen-based materials, and nanocomposite coatings have been investigated as strategies to provide biological activity directly at the implant–tissue interface.^{21–29}

Local delivery is particularly compelling because systemic RSV exposure may be limited by pharmacokinetic constraints, while excessive local concentrations may adversely affect cellular responses. Yang et al.²³ demonstrated that RSV-loaded titania nanotube coatings reduced ROS production and inflammatory mediator release while enhancing osteogenic differentiation. Similarly, the RSV-releasing GelMA coating investigated by Wang et al.²⁵ promoted osteogenic and immunomodulatory responses under diabetic conditions. Fan et al.²⁴ further demonstrated the potential of an RSV-loaded GelMA-chitosan hydrogel coating on titanium implants to counter oxidative and senescence-related mechanisms in an aging-associated osteoporotic model.

However, interpreting these findings requires caution. In surface-engineering studies, the carrier or surface modification itself may contribute substantially to the observed biological effect. Notably, Wang et al.²⁵ reported that the improvement in *in vivo* bone formation with the RSV-containing coating was not significantly greater than that observed with the GelMA-modified titanium control. This underscores the importance of carrier-only controls and

factorial experimental designs that can separate the effect of RSV from that of the delivery platform.

Oxidative stress represents a plausible mechanistic link between systemic disease and impaired implant integration. Several included studies demonstrated that RSV reduced ROS or oxidative stress markers while improving osteogenic or inflammatory outcomes.^{23–25,28,32} This may be particularly relevant in diabetes, aging, and peri-implant inflammatory disease, where excessive oxidative stress can impair osteoblast differentiation and alter immune cell behavior.

RSV has also consistently shown anti-inflammatory effects. In a mouse model of experimental peri-implant inflammation and bone loss, RSV reduced inflammatory bone loss and suppressed MAPK/NF- κ B signaling.³¹ Zhang et al.³² similarly reported reductions in inflammatory and oxidative stress markers together with modulation of MAPK/AKT/NF- κ B signaling. These findings support a potential role for RSV in controlling the inflammatory microenvironment around implants rather than acting exclusively through direct stimulation of osteoblasts.

Nevertheless, pathway-level findings should be interpreted as mechanistic evidence rather than proof of causality. Most included studies used pharmacological or molecular endpoints without genetic pathway manipulation. Consequently, whether these signaling pathways are necessary mediators of the observed clinically relevant effects remains uncertain.

The interaction between immune responses and bone regeneration has emerged as an important component of implant osseointegration. Hang et al.²⁸ demonstrated that RSV influenced senescent macrophage behavior, reduced intracellular oxidative stress, promoted M2 polarization, and generated an environment favorable for osteogenesis and angiogenesis. Similarly, Wang et al.²⁵ reported M2 polarization in association with RSV-releasing hydrogel coatings under diabetic conditions.

These findings are particularly relevant because macrophages are among the earliest cells to interact with an implant surface and can influence subsequent osteoblast and osteoclast activity. RSV may therefore act indirectly by modifying the immune microenvironment rather than directly stimulating osteoblasts.

However, the evidence remains predominantly experimental. The optimal balance between inflammatory activation required for normal tissue repair and excessive inflammation that compromises osseointegration has not been established for RSV treatment. Moreover, macrophage phenotype cannot be reduced to a simple M1/M2 dichotomy in vivo. Future studies should therefore investigate broader immune cell states and temporal changes in the peri-implant immune microenvironment.

Importantly, several outcomes reported in the included studies should be considered surrogate or mechanistic endpoints rather than direct measures of clinically meaningful implant success. For example, changes in M1/M2 macrophage-associated markers, inflammatory or oxidative stress mediators, and osteogenic gene expression provide insights into potential biological mechanisms but do not establish that RSV improves tissue healing in clinically compromised patients. Similarly, changes in bone volume, micro-CT parameters, and other experimental measures of osseointegration in rodent models should not be interpreted as direct evidence of clinical benefit in patients with diabetes, smoking exposure, osteoporosis, or other systemic conditions. These findings are therefore best regarded as hypothesis-generating evidence that may inform subsequent translational research rather than as demonstrated therapeutic solutions for compromised human implant beds.

An additional potential advantage of RSV is its antimicrobial activity. Bonadies et al.²² demonstrated pH-responsive RSV release from electrospun membranes and antibacterial/antibiofilm activity against relevant microorganisms. Zhou et al.²⁶ further reported that RSV-based decontamination of SLA titanium surfaces reduced mature biofilms

while maintaining favorable cytocompatibility and osteogenic responses. These findings suggest that RSV could simultaneously address microbial contamination and biological healing. However, these findings demonstrate antibacterial and antibiofilm activity rather than complete eradication of mature polymicrobial peri-implant biofilms, and their clinical relevance remains to be established.

The studies modeling experimental peri-implant inflammation and bone loss provide complementary *in vivo* evidence. RSV reduced inflammatory bone loss and altered MAPK/NF- κ B-associated signaling in experimental models of peri-implant inflammation and bone loss.^{31,32} Nevertheless, antimicrobial and anti-inflammatory effects should not be interpreted as evidence that RSV can replace established peri-implantitis prevention or treatment approaches. Most evidence remains preclinical, and the microbial spectrum, biofilm complexity, delivery kinetics, and safety profile under clinically relevant conditions remain insufficiently characterized. In interpreting these findings, experimental models of peri-implant inflammation and bone loss should not be considered complete equivalents of human peri-implantitis. In accordance with contemporary clinical definitions, peri-implantitis is characterized by inflammation of the peri-implant mucosa accompanied by progressive loss of supporting bone; therefore, experimental findings describing peri-implant bone loss or inflammation are interpreted according to the specific phenotype modeled rather than assumed to represent the full clinical disease entity.⁴

A major challenge identified across the literature is the substantial variation in RSV dose, route, formulation, and exposure period. Systemic doses varied widely across animal studies, while *in vitro* studies used concentrations spanning several orders of magnitude. Hang et al.²⁸ showed that concentration was biologically important, with lower concentrations producing favorable effects whereas higher exposure was less effective or potentially detrimental. The included studies used RSV doses ranging from 10 to 600 mg/kg, with systemic administration typically employing 10–100 mg/kg in rats and higher doses (200–600 mg/kg) in mouse models of experimental peri-implant inflammation and bone loss. *In vitro* concentrations ranged from 0.1 to 1 μ M for cellular studies, with higher concentrations (10 μ M) sometimes showing reduced efficacy. This wide dose range complicates direct comparisons and highlights the need for dose–response studies in future investigations.

This wide variation in dose and concentration has important translational implications. A biologically effective concentration in an *in vitro* culture system cannot be directly extrapolated to a clinically applicable systemic or local dose. Future investigations should therefore characterize pharmacokinetics, local tissue concentrations, release kinetics, and dose–response relationships using standardized models. Another important translational consideration is the concentration-dependent and potentially biphasic nature of RSV activity. The available preclinical evidence suggests that relatively low concentrations may support favorable cellular responses, whereas higher concentrations may produce less favorable effects depending on cell type, exposure duration, and experimental conditions. Thus, a single therapeutic concentration cannot be assumed to be universally applicable across different biomaterials or biological systems. For localized implant delivery, the loading amount and release profile should therefore be optimized to maintain therapeutically relevant local concentrations while minimizing excessive initial burst release. Future studies should systematically evaluate dose–response relationships, release kinetics, local tissue exposure, and long-term cellular responses using standardized experimental protocols.

Despite promising preclinical findings, translating systemic RSV administration to clinical implant therapy is constrained by its pharmacokinetic characteristics. Following oral administration, RSV undergoes extensive intestinal and hepatic metabolism, including glucuronidation and sulfation, resulting in limited systemic exposure to unmetabolized trans-resveratrol. Moreover, the doses used in several animal studies are substantially higher on a

body weight basis than those typically considered for routine human supplementation or therapeutic use. For example, a 100 mg/kg dose in rats corresponds to approximately 16.2 mg/kg when converted using standard body surface-area scaling, equivalent to approximately 1.1 g for a 70-kg adult. Such comparisons do not establish clinical efficacy or safety, but they illustrate the translational challenge associated with reproducing experimental exposure systemically. Therefore, systemic oral administration should currently be regarded as a promising experimental strategy rather than an established clinical approach. Localized delivery systems, including implant surface coatings, titania nanotubes, hydrogels, membranes, and other controlled-release biomaterials, may provide a more feasible strategy by concentrating RSV at the implant–tissue interface while reducing reliance on high systemic exposure. However, these approaches also require rigorous evaluation of release kinetics, local tissue concentrations, stability, long-term safety, sterilization compatibility, and reproducibility before clinical translation.

To facilitate future quantitative synthesis, primary studies should adopt standardized outcome definitions and measurement protocols. For micro-CT, consensus-based thresholds for bone volume fraction and standardized region-of-interest definitions would improve comparability across studies. Similarly, consistent reporting of BIC measurement methods (histomorphometry versus micro-CT) and implant surface characterization would enable more reliable meta-analyses. The lack of such standardization currently represents a major obstacle to quantitative evidence synthesis in this field.

Methodological Considerations

Interpreting the preclinical evidence should account for the methodological limitations identified across the included studies. In particular, incomplete reporting of randomization procedures, allocation concealment, housing allocation, and blinding limited our ability to determine risk of bias in several domains. The frequent ‘Unclear’ judgments in the SYRCLE assessment should primarily be interpreted as reporting limitations rather than definitive evidence of methodological failure. Nevertheless, incomplete reporting of random sequence generation, allocation concealment, random housing, and blinded outcome assessment limits confidence in the internal validity and magnitude of the reported effects. Accordingly, the apparently beneficial effects of RSV should be interpreted as promising preclinical signals rather than precise estimates of treatment efficacy. Future animal studies should transparently describe randomization, allocation procedures, blinding, sample size calculation, attrition, and prespecified outcome assessment in accordance with established reporting standards.

Although the included in vitro studies were generally considered to have low overall methodological concern, incomplete reporting of biological replication, donor or passage independence, and blinding may limit the certainty of mechanistic and cytocompatibility findings.

These studies should therefore be interpreted primarily as supportive mechanistic or biomaterial evidence rather than as evidence free of methodological limitations.

Strengths and limitations of the evidence

This review has several strengths. It integrates evidence from systemic administration, implant surface engineering, local delivery, experimental peri-implant inflammation and bone loss, antimicrobial applications, and osteoimmunological mechanisms. It also explicitly distinguishes direct implant-related outcomes from surrogate cellular and molecular findings and considers related reports from the same experimental research program to reduce the risk of double-counting.

The review also has several methodological limitations. First, the number of studies within individual intervention categories was small, limiting the strength and generalizability of

category-specific conclusions. Second, substantial heterogeneity was observed in animal models, systemic conditions, implant characteristics, RSV dose and formulation, delivery route, follow-up duration, and outcome definitions, preventing meaningful quantitative pooling. Third, incomplete reporting of several methodological procedures resulted in unclear risk-of-bias judgments across multiple domains. Finally, because no human clinical studies were identified, the findings cannot be directly extrapolated to clinical implant therapy.

Clinical and Translational Implications

The available evidence supports resveratrol as a promising preclinical adjunct for modulating implant-related tissue healing, particularly in compromised biological conditions. However, the current evidence does not justify clinical use of RSV at this stage because all identified evidence was preclinical, and human clinical evidence is currently lacking. The substantial variation in RSV dose, administration route, formulation, biomaterial carrier, implant surface characteristics, experimental model, and outcome assessment limits direct translation to human implant therapy. Localized RSV delivery through implant coatings, hydrogels, membranes, or other biomaterial-based systems may represent a particularly relevant translational strategy because it could concentrate the compound at the implant–tissue interface while reducing systemic exposure. Well-designed animal studies followed by controlled human clinical trials are required to establish the optimal formulation, dose, delivery strategy, safety, and clinical effectiveness of RSV-based implant interventions.

Implications for future research

Future preclinical studies should prioritize standardized implant models and reporting protocols, clinically relevant RSV doses, well-defined control groups, and longer observation periods encompassing both early osseointegration and late remodeling. Factorial designs comparing RSV, carrier, surface topography, and their combinations would be particularly valuable for determining whether these interventions exert additive or synergistic effects.

Studies should also report both mechanical and biological endpoints, including implant stability, BIC, three-dimensional bone parameters, inflammatory and oxidative markers, and histological outcomes. For local delivery systems, release kinetics, coating stability, degradation behavior, and tissue-level RSV concentrations should be systematically characterized.

Finally, translational studies should establish the safety profile and therapeutic window of RSV before clinical evaluation. Current evidence supports continued investigation but does not justify clinical use of RSV at this stage, as human clinical evidence is lacking.

Conclusion

The available preclinical evidence indicates that resveratrol has a potentially beneficial but context-dependent role in dental implant biology. Its effects appear to extend beyond direct osteogenic stimulation and include modulation of oxidative stress, inflammatory signaling, osteoclast activity, macrophage responses, and microbial activity. Benefits were observed in several adverse biological environments, including diabetes, smoking-associated impairment, aging-related dysfunction, and peri-implant inflammation, although findings were not consistent across all pathological models.

RSV-functionalized implant surfaces and localized delivery systems are particularly promising because they may concentrate biological activity at the implant–tissue interface while simultaneously addressing oxidative, inflammatory, osteogenic, and antimicrobial pathways. However, substantial heterogeneity in experimental design, dosing, delivery systems, and outcome assessment currently limits definitive conclusions regarding efficacy.

Overall, RSV should be regarded as a promising multifunctional preclinical strategy rather

than an established osseointegration-enhancing therapy. Well-controlled studies using standardized implant models, clinically relevant dosing, appropriate carrier and surface controls, and long-term follow-up are needed to determine whether the favorable biological effects observed experimentally translate into clinically meaningful improvements in implant outcomes.

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Competing Interests

The authors declare no competing interests regarding authorship and/or publication of this paper.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Not applicable.

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Supplementary Files

Supplementary File 1: Search strategy.

Supplementary File 2: Risk of bias assessment of the included animal studies.

Supplementary File 3: Methodological appraisal of the included in vitro studies.

References

1. Davies JE. Understanding peri-implant endosseous healing. *J Dent Educ.* 2003;67(8):932-49. doi:10.1002/j.0022-0337.2003.67.8.tb03681.x
2. Chrcanovic BR, Albrektsson T, Wennerberg A. Diabetes and oral implant failure: a systematic review. *J Dent Res.* 2014;93(9):859-67. doi: 10.1177/0022034514538820
3. Mustapha AD, Salame Z, Chrcanovic BR. Smoking and Dental Implants: A Systematic Review and Meta-Analysis. *Medicina (Kaunas).* 2021;58(1):39. doi:

10.3390/medicina58010039

4. 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. *J Clin Periodontol.* 2018;45 Suppl 20:S286-S291. doi: 10.1111/jcpe.12957
5. Heitz-Mayfield LJ, Aaboe M, Araujo M, Carrión JB, Cavalcanti R, Cionca N, et al. Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry. *Clin Oral Implants Res.* 2018;29 Suppl 16:351-358. doi: 10.1111/clr.13307
6. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Clin Periodontol.* 2018;45 Suppl 20:S246-S266. doi: 10.1111/jcpe.12954
7. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov.* 2006;5(6):493-506. doi: 10.1038/nrd2060
8. Tseng PC, Hou SM, Chen RJ, Peng HW, Hsieh CF, Kuo ML, et al. Resveratrol promotes osteogenesis of human mesenchymal stem cells by upregulating RUNX2 gene expression via the SIRT1/FOXO3A axis. *J Bone Miner Res.* 2011;26(10):2552-63. doi: 10.1002/jbmr.460
9. Shakibaei M, Buhrmann C, Mobasheri A. Resveratrol-mediated SIRT-1 interactions with p300 modulate receptor activator of NF-kappaB ligand (RANKL) activation of NF-kappaB signaling and inhibit osteoclastogenesis in bone-derived cells. *J Biol Chem.* 2011;286(13):11492-505. doi: 10.1074/jbc.M110.198713
10. Casati MZ, Algayer C, Cardoso da Cruz G, Ribeiro FV, Casarin RC, Pimentel SP, et al. Resveratrol decreases periodontal breakdown and modulates local levels of cytokines during periodontitis in rats. *J Periodontol.* 2013;84(10):e58-64. doi: 10.1902/jop.2013.120746
11. Boissy P, Andersen TL, Abdallah BM, Kassem M, Plesner T, Delaissé JM. Resveratrol inhibits myeloma cell growth, prevents osteoclast formation, and promotes osteoblast differentiation. *Cancer Res.* 2005;65(21):9943-52. doi: 10.1158/0008-5472.CAN-05-0651
12. Casarin RC, Casati MZ, Pimentel SP, Cirano FR, Algayer M, Pires PR, et al. Resveratrol improves bone repair by modulation of bone morphogenetic proteins and osteopontin gene expression in rats. *Int J Oral Maxillofac Surg.* 2014;43(7):900-6. doi: 10.1016/j.ijom.2014.01.009
13. Ribeiro FV, Pimentel SP, Corrêa MG, Bortoli JP, Messori MR, Casati MZ. Resveratrol reverses the negative effect of smoking on peri-implant repair in the tibia of rats. *Clin Oral Implants Res.* 2019;30(1):1-10. doi: 10.1111/clr.13384
14. Hua Y, Bi R, Li Z, Li Y. Resveratrol treatment promotes titanium implant osseointegration in diabetes mellitus rats. *J Orthop Res.* 2020;38(10):2113-2119. doi: 10.1002/jor.24651
15. Corrêa MG, Ribeiro FV, Pimentel SP, Benatti BB, Felix Silva PH, Casati MZ, et al. Impact of resveratrol in the reduction of the harmful effect of diabetes on peri-implant bone repair: bone-related gene expression, counter-torque and micro-CT analysis in rats. *Acta Odontol Scand.* 2021;79(3):174-181. doi: 10.1080/00016357.2020.1797159
16. Wajima CS, Pitol-Palin L, de Souza Batista FR, Dos Santos PH, Matsushita DH, Okamoto R. Morphological and biomechanical characterization of long bones and peri-implant bone repair in type 2 diabetic rats treated with resveratrol. *Sci Rep.* 2024;14(1):2860. doi: 10.1038/s41598-024-53260-4
17. Guo SH. Effects of Resveratrol on Peri-Implant Bone Healing [Master's thesis]. University of Toronto (Canada); 2019. Available from: <https://utoronto.scholaris.ca/server/api/core/bitstreams/160af5b2-5c8c-4fc6-846e-21494404be2f/content>
18. Staibano AJ. Effect of Resveratrol and Implant Surface Topography on Osseointegration under Hyperglycemic Conditions [Master's thesis]. University of Toronto (Canada); 2021. Available from: <https://utoronto.scholaris.ca/server/api/core/bitstreams/912197c2-3346-47fc->

19. Liddell RS, Guo S, Staibano A, Davies JE. Effects of hyperglycemia and resveratrol on the processes of implant osseointegration and peri-implant bone remodeling: revealed by non-linear analysis. *Materialia*. 2025;39:102371. doi: 10.1016/j.mtla.2025.102371
20. Zamai RS, Corrêa MG, Ribeiro FV, Cirano FR, Casati MZ, Messoria MR, et al. Does resveratrol favor peri-implant bone repair in rats with ovariectomy-induced osteoporosis? Gene expression, counter-torque and micro-CT analysis. *Braz Oral Res*. 2023;37:e003. doi: 10.1590/1807-3107bor-2023.vol37.0003
21. Pandele AM, Neacsu P, Cimpean A, Staras AI, Miculescu F, Iordache A, et al. Cellulose acetate membranes functionalized with resveratrol by covalent immobilization for improved osseointegration. *Appl Surf Sci*. 2018;438:2-13. doi: 10.1016/j.apsusc.2017.11.102
22. Bonadies I, Di Cristo F, Valentino A, Peluso G, Calarco A, Di Salle A. pH-Responsive Resveratrol-Loaded Electrospun Membranes for the Prevention of Implant-Associated Infections. *Nanomaterials (Basel)*. 2020;10(6):1175. doi: 10.3390/nano10061175
23. 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- κ B signaling pathway. *Mater Sci Eng C Mater Biol Appl*. 2021;131:112513. doi: 10.1016/j.msec.2021.112513
24. Fan W, Zheng T, Mao M, Gao P, Yang Y, Wang R, et al. A Study of Skeletal Stem Cell Dynamics and Its Potential Applications in the Design of a Titanium Implant for Senile Osteoporosis. *Adv Sci (Weinh)*. 2025;12(34):e06982. doi: 10.1002/advs.202506982
25. Wang W, Chen J, Li J, He M, Wang H, Shen Y, et al. Resveratrol-releasing hydrogel coating on titanium surface with osteogenic and anti-inflammatory properties enhanced osseointegration in diabetes mellitus. *Mater Today Chem*. 2026;52:103425. doi: 10.1016/j.mtchem.2026.103425
26. Zhou Y, Shen Z, Xu Y, Qian X-n, Chen W, Qiu J. Antimicrobial efficiency and cytocompatibility of resveratrol and naringin as chemical decontaminants on SLA surface. *Microbiol Spectr*. 2024;12(10):e0367923. doi: 10.1128/spectrum.03679-23
27. Wang R, Bao B, Bao C, Wang S, Ur Rahman S, Hou C, et al. Resveratrol and Celastrol Loaded Collagen Dental Implants Regulate Periodontal Ligament Fibroblast Growth and Osteoclastogenesis of Bone Marrow Macrophages. *Chem Biodivers*. 2020;17(9):e2000295. doi: 10.1002/cbdv.202000295
28. Hang R, Wang J, Tian X, Wu R, Hang R, Zhao Y, et al. Resveratrol promotes osteogenesis and angiogenesis through mediating immunology of senescent macrophages. *Biomed Mater*. 2022;17(5). doi: 10.1088/1748-605X/ac80e3
29. Kan SA, Fang SW, Lin YT, Lai CW, Tung FI, Wang YC, et al. Enhancing antibacterial performance of graphene oxide coatings by a resveratrol-gold nanocomposite with X-ray activation and preserved osteogenic bioactivity. *Appl Surf Sci*. 2026;730:166397. doi:10.1016/j.apsusc.2026.166397
30. Walle T, Hsieh F, DeLegge MH, Oatis JE Jr, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos*. 2004;32(12):1377-82. doi: 10.1124/dmd.104.000885
31. Liu SQ, Zhang H, Chen YY, He HP, Huang JM, Yuan JY, et al. Resveratrol treats peri-implantitis in mice via inhibiting the MAPKs/NF- κ B signaling pathway. *J Prev Treat Stomatol Dis*. 2024;32(11):845-852. doi: 10.12016/j.issn.2096-1456.202440228
32. Zhang C, Jiao B, Qian D. Protective Effect of Resveratrol Against Peri-Implant Inflammation and Oxidative Stress: An in vivo Study. *Discov Med*. 2025;37(196):862-870. doi: 10.24976/Discov.Med.202537196.76
33. Tao ZS, Zhou WS, Yang M, Xu H. Resveratrol reverses the negative effect of alcohol on hydroxyapatite-coated implant osseointegration in senile female rats. *Z Gerontol Geriatr*.

2020;53(6):538-545. doi: 10.1007/s00391-019-01595-3

34. Pitol-Palin L, Wajima CS, de Souza Batista FR, Monteiro NG, Sousa IC, Garcia VG, et al. Role of antimicrobial photodynamic therapy (aPDT) and systemic resveratrol on immediate implant placement in type 2 diabetic rats. Photochem Photobiol. 2026;102(4):934-948. doi:10.1111/php.70046

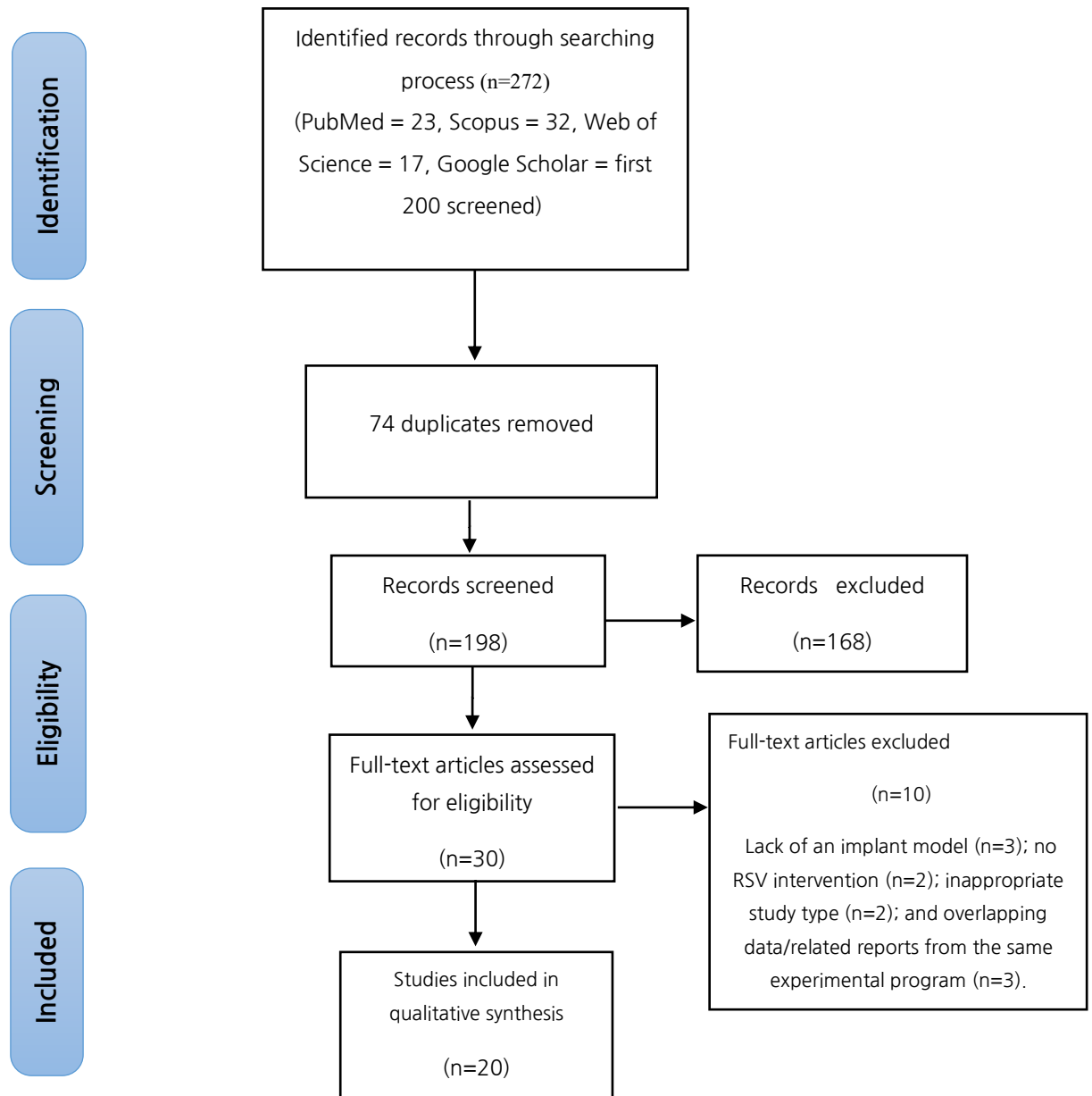


Figure 1. Study selection process (PRISMA 2020 flowchart).

Table 1. Characteristics and principal findings of the included preclinical studies

Study	Experimental model	RSV intervention	Main outcomes
Casarin et al. ¹² (2014)	Healthy Wistar rats with titanium implants	10 mg/kg, oral gavage, 30 days	Increased counter-torque by 37.8%; increased BMP-2, BMP-7, and OPN expression

Ribeiro et al. ¹³ (2019)	Cigarette-smoke-exposed rats with implants	10 mg/kg, oral gavage, 30 days	Increased counter-torque and BIC; reduced RANKL/OPG and Lrp-5; increased β -catenin
Wang et al. ²⁷ (2020)	Collagen-based dental implant-related biomaterial	0.5% RSV in collagen films	Increased periodontal ligament fibroblast proliferation; reduced osteoclastogenic responses
Pandele et al. ²¹ (2018)	Mg alloy with RSV-functionalized cellulose acetate membrane	Covalent RSV immobilization	Increased ALP activity and mineralization; maintained osteoblast viability
Corrêa et al. ¹⁵ (2021)	STZ-induced diabetic rats with implants	10 mg/kg, oral gavage, 30 days	Increased counter-torque, BIC, and trabecular thickness; reduced RANKL
Yang et al. ²³ (2021)	Titanium implants with RSV-loaded titania nanotube coating	RSV-loaded titania nanotubes	Reduced ROS production and inflammatory mediators and enhanced osteogenic activity, including ALP activity, mineralization, and expression of OCN, OPN, RUNX2, and COL-1, with modulation of NF- κ B signaling.
Bonadies et al. ²² (2020)	RSV-loaded electrospun PLA membrane	RSV-containing PLA membrane	pH-responsive release; antibacterial and antibiofilm activity
Hang et al. ²⁸ (2022)	Senescent macrophage model and Ti-associated coating	0.1–1 μ M RSV	Increased autophagy and M2 polarization; reduced ROS; enhanced osteogenic and angiogenic responses
Fan et al. ²⁴ (2025)	Senile osteoporosis rats with titanium implants	RSV-containing responsive coating	Enhanced osseointegration; reduced ROS and senescence-associated factors; increased osteogenic differentiation
Kan et al. ²⁹ (2026)	Implant-associated graphene oxide/resveratrol–gold coating	RSV–gold nanocomposite with X-ray activation	Enhanced antibacterial activity while preserving osteogenic bioactivity
Wang et al. ²⁵ (2026)	STZ-diabetic rats with modified titanium implants	RSV-releasing GelMA hydrogel coating	Enhanced osteogenic responses and M2 polarization; reduced osteoclast-associated responses
Hua et al. ¹⁴ (2020)	STZ-diabetic rats with titanium implants	25 mg/kg, intraperitoneal, 8 weeks	Increased BIC, BV/TV, and push-out force
Wajima et al. ¹⁶ (2024)	Type 2 diabetic rats with implants	100 mg/kg, oral gavage, 45 days	Improved long-bone biomechanics but no significant improvement in peri-implant osseointegration
Zamai et al. ²⁰ (2023)	Ovariectomized osteoporotic rats with implants	10 mg/kg, oral gavage, 18 weeks	No significant improvement in peri-implant bone repair
Tao et al. ³³ (2020)	Senile female rats with alcohol exposure and implants	40 mg/kg, oral gavage, 12 weeks	Increased BV/TV, Tb.N, Tb.Th, and push-out force; increased Runx2, OC, and OPG; reduced RANKL
Pitol-Palín et al. ³⁴ (2026)	Type 2 diabetic rats undergoing immediate implant placement	Systemic RSV (100 mg/kg) $\pm$ aPDT	RSV improved glycemic control and body weight; combined RSV + aPDT reduced bone-resorption-related markers, increased mineralization-related gene expression, and increased mineral apposition, supporting improved peri-implant bone repair.
Liddell et al. ¹⁹ (2025)	Hyperglycemic rats with micro- and nanotopographic implants	10 mg/kg, weekly subcutaneous injection, 84 days	Restoration of late implant anchorage; surface topography influenced early osseointegration
Liu et al. ³¹ (2024)	C57BL/6 mice with experimental peri-implant inflammation and peri-implant bone loss	20 or 40 mg/kg, oral gavage, 6 weeks	Reduced bone resorption, TNF- α and IL-6; inhibited MAPK/NF- κ B signaling
Zhang et al. ³² (2025)	C57BL/6 mice with experimental peri-implant inflammation	200–600 mg/kg, oral gavage, 2 weeks	Reduced bone loss, apoptosis, ROS, and MDA; increased SOD; modulated MAPK/AKT/NF- κ B
Zhou et al. ²⁶ (2024)	SLA titanium surfaces	0.1% RSV solution	Reduced bacterial biofilm; increased cell adhesion, proliferation, and osteogenic differentiation

AKT, AK strain of thymoma (also known as protein kinase B, PKB); ALP, alkaline phosphatase; aPDT, antimicrobial photodynamic therapy; BIC, bone-to-implant contact; BMP, bone morphogenetic protein; BV/TV, bone volume/total volume; C57BL/6, C57 Black 6 mouse strain; COL-I, collagen type I; GelMA, gelatin methacryloyl; IL, interleukin; Lrp-5, low-density lipoprotein receptor-related protein 5; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; micro-CT, micro-computed tomography; NF- κ B, nuclear factor kappa-B; NO, nitric oxide; OC, osteocalcin; OCN, osteocalcin; OPG, osteoprotegerin; OPN, osteopontin; PLA, polylactic acid; RANKL, receptor activator of nuclear factor kappa-B ligand; ROS, reactive oxygen species; RSV, resveratrol; RUNX2, runt-related transcription factor 2; SLA, sandblasted, large-grit, acid-etched; SOD, superoxide dismutase; STZ, streptozotocin; Tb.N, trabecular number; Tb.Th, trabecular thickness; Ti, titanium; TNF- α , tumor necrosis factor-alpha.