

The Role and Significance of Oxidative Stress in Inflammatory Periodontal Disease and Contemporary Approaches to Antioxidant Therapy

Review began 09/19/2026

Review ended 10/13/2026

Published 10/20/2026

© Copyright 2026

Belenichev et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.118234

Igor Belenichev¹, Olena Popazova², Valeriy Salnykov³, Nina Bukhtiyarova⁴, Victor Ryzhenko⁵, Pavlo Petakh⁶, Oleksandr Kamyshnyi⁷, Sergiy Oliynyk⁸, Suyeon Lee⁹, Kyu-Ho Yi¹⁰

1. Department of Pharmacology and Medical Formulation With Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, UKR 2. Department of Histology, Cytology, and Embryology, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, UKR 3. Department of Surgical and Propaedeutic Dentistry, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, UKR 4. Department of Clinical Laboratory Diagnostics, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, UKR 5. Department of Medical and Pharmaceutical Informatics and Advanced Technologies, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, UKR 6. Department of Biochemistry and Pharmacology, Uzhhorod National University, Uzhhorod, UKR 7. Department of Microbiology, Virology, and Immunology, I. Horbachevsky Ternopil National Medical University, Ternopil, UKR 8. School of Medicine, Ewha Womans University, Seoul, KOR 9. Department of Medical Research, Medical Research Inc., Seoul, KOR 10. Department of Anatomy, Yonsei University, Seoul, KOR

Corresponding author: Kyu-Ho Yi, kyuhu90@daum.net

Abstract

Periodontitis is a chronic inflammatory disease driven by dysbiotic biofilms and an exaggerated host immune response, resulting in progressive destruction of periodontal tissues and tooth loss. Increasing evidence suggests that oxidative and nitrosative stress play central roles in disease progression by amplifying inflammation, promoting tissue damage, and impairing repair mechanisms.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) derived from immune cells, mitochondria, and enzymatic pathways contribute to lipid peroxidation, DNA damage, and alveolar bone resorption. These mechanisms help explain persistent inflammation and variable treatment response despite conventional periodontal therapy.

This narrative review summarizes current evidence on oxidative stress in periodontitis and evaluates the potential role of antioxidant therapy as an adjunct to standard treatment. Particular emphasis is placed on selenium-containing compounds due to their involvement in glutathione peroxidase activity, thioredoxin systems, and mitochondrial protection.

Although antioxidant strategies show promise in improving biochemical and clinical outcomes, current evidence remains heterogeneous. Further well-designed clinical studies are needed to clarify their role in routine periodontal care.

Categories: Pharmacology, Oral Medicine, Dentistry

Keywords: antioxidant therapy, oxidative stress, periodontitis, reactive oxygen species, selenium

Introduction And Background

Periodontitis is a chronic inflammatory disease initiated by dysbiotic plaque biofilms and shaped by interactions among microbial virulence, host immune responses, environmental exposures, and patient-specific susceptibility [1-7]. Rather than representing a localized gingival infection, periodontitis involves progressive destruction of tooth-supporting tissues and can substantially affect oral function and quality of life [1-7]. Despite advances in classification and treatment, its clinical burden remains substantial, and contemporary guidelines emphasize stepwise treatment and long-term supportive periodontal care [8,9].

Periodontal tissue destruction is driven not only by microbial challenge but also by a dysregulated host inflammatory response. An important component of this response is oxidative stress, which occurs when the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the capacity of endogenous antioxidant defenses [10-14]. Excessive ROS and RNS can promote lipid, protein, and DNA damage while amplifying inflammatory signaling and contributing to collagen degradation, alveolar bone resorption, and impaired tissue repair [10-15]. Oxidative stress is therefore increasingly regarded as a pathogenic amplifier of periodontal inflammation rather than merely a secondary consequence of tissue injury.

Recent research has expanded this redox framework beyond conventional descriptions of inflammatory

How to cite this article

Belenichev I, Popazova O, Salnykov V, et al. (October 20, 2026) The Role and Significance of Oxidative Stress in Inflammatory Periodontal Disease and Contemporary Approaches to Antioxidant Therapy. Cureus 18(10): e118234. DOI 10.7759/cureus.118234

oxidant production. Mitochondrial dysfunction, defective mitophagy, altered nitric oxide signaling, and ferroptosis have emerged as potentially relevant mechanisms linking persistent inflammation to cellular injury and impaired periodontal homeostasis [16–24]. At the same time, disturbances in endogenous antioxidant systems have stimulated interest in antioxidant and host-modulating strategies as possible adjuncts to conventional periodontal therapy [10,11,24].

Accordingly, this narrative review critically examines the role of oxidative and nitrosative stress in periodontitis, with particular attention to mitochondrial dysfunction, ferroptosis, endogenous antioxidant defenses, and redox-related biomarkers. It also evaluates current evidence for antioxidant adjunctive therapies, including selenium-based approaches, while distinguishing mechanistic and preclinical findings from observational and clinical evidence. Particular emphasis is placed on the strength and limitations of the available evidence and on the translational requirements that must be addressed before antioxidant strategies can be incorporated into routine periodontal care.

Review

Review methodology

This narrative review was developed through a focused evaluation of the literature relevant to oxidative and nitrosative stress in periodontitis and to antioxidant-based adjunctive therapy. The literature considered encompassed periodontal pathogenesis, reactive oxygen and nitrogen species, mitochondrial dysfunction and mitophagy, ferroptosis, endogenous antioxidant systems, oxidative and nitrosative biomarkers, host modulation, antioxidant interventions, selenium biology, selenium nanoparticles, and Selenase. Periodontal-specific evidence was prioritized when available, while broader mechanistic literature was used to provide biological context for pathways not yet extensively studied in periodontal tissues.

Evidence was considered according to study design and relevance to the review question. Systematic reviews and meta-analyses were used preferentially when available for established periodontal outcomes or biomarker associations, followed by randomized or other clinical studies and observational human studies. Experimental studies in periodontal cells, tissues, animal models, or disease models were included when they provided mechanistic or translational information not established in human studies. General redox, mitochondrial, antioxidant, or nanotechnology literature was used selectively to explain biological mechanisms or delivery concepts and was not treated as direct evidence of clinical efficacy in periodontitis.

The evidence was synthesized narratively because the included literature was heterogeneous in study design, populations, experimental models, interventions, formulations, routes of administration, biomarkers, and clinical outcomes. Findings were therefore interpreted according to their level of evidence rather than quantitatively pooled within this review. Particular attention was given to distinguishing biological plausibility from demonstrated clinical benefit. For selenium-based approaches, mechanistic, observational, and preclinical findings were evaluated separately from evidence of therapeutic efficacy in humans because the current periodontal literature spans substantially different levels of translational development.

Mitochondrial dysfunction and redox imbalance in periodontitis

Mitochondrial dysfunction has emerged as a potentially important component of periodontal inflammatory injury. Periodontal-specific experimental evidence indicates that *Porphyromonas gingivalis* and its virulence-associated effects can promote mitochondrial fission, alter mitochondrial membrane potential and respiratory function, and disrupt mitochondrial quality control pathways [16–19]. PINK1-mediated mitophagy has also been implicated in the regulation of inflammatory responses to *P. gingivalis* in macrophages [17]. Collectively, these findings support a mechanistic relationship between periodontal microbial challenge, mitochondrial dysfunction, and persistent inflammatory signaling, while broader evidence from infection and immunity provides additional biological context for the role of mitochondrial reactive oxygen species [20].

Mitochondrial injury may amplify periodontal inflammation through several interconnected mechanisms. Dysfunctional mitochondria can increase intracellular ROS generation, while mitochondrial damage-associated signals can activate innate immune and inflammatory pathways [18–20]. Impaired mitophagy may further sustain this process by limiting the removal of damaged mitochondria [17–20]. Because mitochondria also regulate apoptosis, calcium homeostasis, and cellular energy metabolism, persistent mitochondrial dysfunction provides a biologically plausible link between microbial-inflammatory stress and impaired periodontal tissue homeostasis [18–20]. These observations remain primarily mechanistic and should not be interpreted as evidence that mitochondria-targeted treatment has established clinical efficacy in periodontitis.

Ferroptosis, iron, and emerging redox-dependent cell death pathways

Ferroptosis is an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and failure of protective systems that include glutathione peroxidase 4 (GPx4). Periodontal literature has increasingly examined ferroptosis in relation to altered iron metabolism, oxidative stress, impaired

GSH/GPx4 defense, and lipid peroxidation-mediated injury [22]. A 2026 periodontitis-specific review further synthesized evidence from cellular experiments, animal models, and human clinical associations and highlighted the potential involvement of ferroptosis across multiple periodontal cell types [25]. These findings strengthen the mechanistic rationale for investigating ferroptosis in periodontal tissue destruction, but they do not establish ferroptosis-targeted therapy as clinically effective in patients with periodontitis.

The periodontal relevance of ferroptosis remains an emerging area of investigation. Its principal value at present is mechanistic: it provides a more specific framework for understanding how iron availability, glutathione metabolism, lipid peroxidation, and antioxidant defense may interact during oxidative tissue injury [22,24]. At present, however, these mechanistic observations should not be interpreted as evidence that targeting ferroptosis improves clinical periodontal outcomes.

Endogenous antioxidant defense in periodontal tissues

Antioxidant defense in periodontal tissues involves complementary enzymatic and non-enzymatic systems. Superoxide dismutases (SODs) convert superoxide to hydrogen peroxide, whereas catalase and glutathione peroxidases participate in peroxide detoxification; glutathione-related pathways and low-molecular-weight antioxidants provide additional redox buffering [24]. In periodontitis, studies have reported disturbances in oxidative stress markers and endogenous antioxidant capacity, although individual findings vary according to disease status, biological sample, and analytical method [10-14]. Antioxidant defense in periodontitis should therefore be viewed as a dynamic system rather than as a uniformly depleted state.

Superoxide dismutases constitute an important first-line enzymatic defense against superoxide. Broader biochemical and immunological evidence indicates that SOD enzymes participate in radical detoxification and redox-sensitive immune regulation [26,27]. These sources provide mechanistic background rather than direct evidence of periodontal treatment effects. Glutathione-related defenses have more direct periodontal evidence: a systematic review and meta-analysis reported alterations in glutathione, glutathione peroxidase, glutathione reductase, and oxidized glutathione parameters in patients with periodontitis [28]. These findings support disruption of glutathione-dependent redox homeostasis in periodontal disease while also illustrating the need to distinguish periodontal-specific evidence from broader antioxidant biology.

Selenium-dependent proteins provide a mechanistic link between micronutrient biology and antioxidant defense. Several glutathione peroxidases and thioredoxin reductases are selenoproteins involved in peroxide detoxification, thiol redox regulation, and cellular stress responses [29]. GPx4 is particularly relevant to ferroptosis because it limits phospholipid peroxidation, providing a biological rationale for examining selenium-dependent pathways in redox-mediated periodontal injury [22,29]. This mechanistic rationale, however, should not be interpreted as evidence that selenium supplementation or selenium-based treatment improves clinical periodontal outcomes.

Other antioxidant pathways may also be influenced by interindividual biological variation. In a case-control study, polymorphisms in glutathione S-transferase genes were investigated in relation to periodontitis, further illustrating that redox-related host factors extend beyond selenium-dependent pathways [30].

Biomarkers of oxidative and nitrosative damage

Biomarker research provides a potential bridge between redox mechanisms and clinical periodontal assessment. Saliva, gingival crevicular fluid, and blood have been investigated as sources of redox-related biological information in periodontitis [12,13]. An updated 2026 systematic review and meta-analysis reported consistent evidence of altered oxidative stress and antioxidant biomarkers in periodontitis across multiple biological sample types, while also identifying substantial between-study heterogeneity [31]. These findings strengthen the evidence for measurable redox disturbance in periodontitis but also emphasize that individual biomarkers should not be interpreted as interchangeable or as stand-alone indicators of disease activity.

Among individual redox-related biomarkers, 8-hydroxydeoxyguanosine (8-OHdG) reflects oxidative DNA damage and has been investigated in relation to periodontal inflammation [12,14]. The updated meta-analysis also identified significant elevations of 8-OHdG in local periodontal biofluids and demonstrated that biomarker patterns vary according to analyte and sample type [31]. Protein carbonyl formation provides an index of oxidative protein modification, whereas nitrotyrosine reflects protein modification associated with reactive nitrogen species [21,32]. Glutathione-related measures provide a complementary view of endogenous antioxidant status [28]. Collectively, these findings support redox disturbance as an associated biological feature of periodontitis but do not establish any single oxidative stress biomarker as a stand-alone diagnostic or prognostic test.

The clinical interpretation of redox biomarkers remains limited by substantial methodological heterogeneity. Saliva is non-invasive and readily repeatable, whereas gingival crevicular fluid more directly samples the periodontal microenvironment but is technically more demanding; circulating markers may capture systemic redox or inflammatory influences but are less specific to periodontal tissues [12,13]. Comparisons across studies are further complicated by differences in sampling procedures, analytical

methods, periodontal case definitions, and potential confounding by factors such as smoking, diabetes, obesity, and diet [12-14,21]. Consequently, redox biomarkers are currently better regarded as research and adjunctive assessment tools than as replacements for established clinical and radiographic periodontal evaluation. Standardized sampling protocols, validated thresholds, and evidence that biomarker measurement meaningfully improves clinical decision-making are still required before routine implementation [12-14,21,32,33].

Standard periodontal therapy and the rationale for adjunctive host modulation

Contemporary periodontal treatment remains centered on control of supragingival biofilm and modifiable risk factors, subgingival instrumentation, management of residual periodontal pockets or complex defects when indicated, and long-term supportive periodontal care [8,9]. This stepwise framework remains the foundation against which any adjunctive intervention should be evaluated. Antioxidant, anti-inflammatory, and antimicrobial natural products have been investigated within this broader adjunctive context, but the strength of evidence varies substantially among individual agents and formulations [34].

The biological rationale for antioxidant adjuncts arises from evidence linking oxidative stress to periodontal inflammatory injury [10,11,34]. Nevertheless, biological plausibility alone is insufficient to establish therapeutic benefit. Any antioxidant strategy must demonstrate added clinical value when used alongside effective plaque control and conventional periodontal therapy, and its effects should be interpreted according to the level and quality of intervention-specific evidence.

Drug delivery research provides a separate translational consideration. Local delivery systems may improve retention, concentration, or controlled release of therapeutic agents within periodontal sites, and nanotechnology-based platforms are being investigated for periodontal applications [35,36]. These studies support the feasibility and rationale of local delivery technologies, but they should not be interpreted as evidence that locally delivered antioxidants themselves improve clinical periodontal outcomes. The therapeutic value of an antioxidant formulation must therefore be established independently of the delivery platform used.

Evidence from non-antioxidant periodontal interventions illustrates how adjunctive approaches must be interpreted according to their specific therapeutic purpose. Local minocycline and doxycycline have been evaluated clinically in periodontal abscess management [37]. Experimental drug delivery research has also examined biodegradable nanocomposite hydrogels capable of releasing antiseptic and antibiotic agents [38], while metronidazole has been shown experimentally to enhance neutrophil-mediated killing of *Porphyromonas gingivalis* [39]. These findings provide context for local antimicrobial and delivery strategies but do not constitute evidence that antioxidant agents delivered through similar platforms will produce equivalent clinical benefits.

Host modulation research provides a broader conceptual framework for adjunctive redox therapy. Experimental periodontal evidence indicates that immune pathways such as the type I interferon-IL-17-neutrophil axis can influence inflammatory bone loss [40], while broader reviews describe a range of immunomodulatory approaches under investigation in dentistry and periodontics [41]. These findings support continued investigation of host-directed strategies but do not establish antioxidant therapy as an equivalent or clinically validated form of periodontal host modulation. Accordingly, antioxidant interventions should be evaluated as potential adjuncts to, rather than substitutes for, established periodontal treatment.

Evidence for synthetic and natural antioxidant adjuncts

Clinical evidence for antioxidant adjuncts has recently been synthesized at the comparative level. A 2026 systematic review and network meta-analysis of 19 randomized controlled trials involving 810 patients evaluated seven antioxidant interventions used adjunctively with conventional periodontal therapy [42]. The analysis identified favorable signals for selected clinical outcomes with melatonin, resveratrol, green tea, and curcumin, but the certainty of evidence for several comparisons was low or very low. These findings support the possibility that some antioxidant adjuncts may improve selected periodontal outcomes while also reinforcing the need for cautious interpretation because efficacy and evidence certainty differ among individual agents.

Vitamin E and related lipophilic antioxidants

Vitamin E is a lipid-soluble antioxidant that can limit lipid peroxidation within cellular membranes. Periodontal evidence has progressed beyond mechanistic plausibility: a systematic review and meta-analysis evaluated tocopherol supplementation and reported favorable changes in some clinical periodontal parameters [43]. However, the available studies were limited in number and heterogeneous in intervention protocols and outcome assessment. Vitamin E should therefore be regarded as a potential adjunctive intervention with preliminary clinical support rather than as an established component of routine periodontal therapy.

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10) has antioxidant and bioenergetic functions that provide a biological rationale for its investigation in a disease associated with oxidative stress. A systematic review and meta-analysis of clinical trials evaluated CoQ10 as an adjunct in periodontitis and reported improvements in some periodontal outcomes [44]. Nevertheless, interpretation is constrained by differences among studies in formulation, route of administration, treatment protocols, and sample size. The available evidence therefore supports continued clinical investigation of CoQ10 but does not establish a basis for routine universal use.

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is mechanistically relevant to redox regulation because of its relationship to thiol availability and glutathione metabolism. Periodontal evidence cited in this review is primarily preclinical: in human periodontal ligament fibroblasts, NAC reduced pyroptosis-related signaling and attenuated impairment of osteogenic differentiation through a SIRT1/NF- κ B/Caspase-1-associated pathway [45]. This study supports biological plausibility at the cellular level but does not demonstrate clinical efficacy in patients with periodontitis. Clinical periodontal trials are therefore needed before NAC can be considered an evidence-based therapeutic adjunct.

Melatonin

Melatonin has antioxidant and anti-inflammatory properties that have prompted investigation as an adjunct in periodontal treatment. The literature cited here includes a review of systemic melatonin in periodontal disease [46] and a systematic review evaluating melatonin in the non-surgical treatment of periodontitis [47]. Collectively, these reports suggest potential improvements in selected periodontal outcomes when melatonin is used adjunctively, but heterogeneity in study design and intervention protocols limits definitive conclusions. The evidence is therefore more clinically developed than that available for some experimental antioxidants, although optimal dose, formulation, route, and patient selection remain insufficiently established. A recent network meta-analysis likewise identified favorable signals for melatonin in probing depth and clinical attachment outcomes, although certainty limitations require cautious interpretation [42].

Polyphenols: resveratrol, quercetin, and related agents

Among plant-derived polyphenols, resveratrol has both clinical and mechanistic periodontal literature. A randomized clinical trial evaluated resveratrol supplementation in patients with chronic periodontitis and reported effects on clinical periodontal parameters and inflammatory markers [48]. Broader literature has discussed potential mechanisms and applications of resveratrol and related analogs in periodontal disease management [49]. Although these findings provide a clinical signal supported by biological plausibility, evidence from an individual clinical trial and broader mechanistic literature is not sufficient to establish consistent efficacy across patient populations, formulations, and treatment protocols. Comparative network meta-analytic evidence has also identified a favorable signal for probing depth reduction with adjunctive resveratrol, although the certainty and breadth of evidence remain limited [42].

Evidence for quercetin is less clinically mature. A systematic review and meta-analysis of animal models reported protective effects of quercetin in experimentally induced periodontal disease [50], while additional experimental work has examined its effects on oral inflammation and microbial dysbiosis [51]. These findings support preclinical plausibility but should not be interpreted as evidence of clinical efficacy in human periodontitis. Other natural bioactive compounds, including additional polyphenolic agents, have been reviewed in the periodontal literature [52], but their evidence bases differ substantially in study design, formulation, dose, and clinical validation.

A further translational issue is formulation and delivery. Differences in solubility, metabolism, local retention, and route of administration may contribute to heterogeneity among antioxidant studies. Periodontal drug delivery and nanotechnology literature demonstrates that local carriers and controlled-release platforms can alter how therapeutic agents are delivered to periodontal sites [35,36]. However, the feasibility of a delivery platform does not establish the efficacy of the antioxidant compound it carries. Future antioxidant studies should therefore evaluate both pharmacologic activity and clinically relevant delivery characteristics.

Comparative interpretation of antioxidant adjuncts

Antioxidants comprise mechanistically diverse compounds rather than a single therapeutic class. Broad antioxidant literature distinguishes compounds according to their chemical properties, biological targets, sources, and mechanisms of redox activity [53,54]. Within the periodontal literature reviewed here, the level of evidence also differs substantially among agents: vitamin E and CoQ10 have been evaluated in meta-analytic clinical literature [43,44]; NAC is supported here primarily by cellular experimental evidence [45]; melatonin has been evaluated in reviews, including a systematic review of non-surgical periodontal treatment [46,47]; resveratrol has clinical trial evidence [48]; and quercetin remains predominantly supported by preclinical evidence [50,51]. These differences preclude treating all antioxidant adjuncts as

clinically equivalent. A consolidated comparison of the evidence levels, principal findings, and limitations of antioxidant and selenium-based approaches is provided in the subsequent section.

These differences have implications for future trial design. Studies should specify the biological rationale for the selected antioxidant, formulation and route of administration, background periodontal therapy, relevant redox or inflammatory outcomes, and clinically meaningful periodontal endpoints. Biomarker-guided or phenotype-based selection may be worth investigating, but evidence is currently insufficient to recommend matching individual patients to antioxidant agents on the basis of a defined oxidative phenotype. Comparative trials with standardized outcome reporting will be necessary to determine whether any antioxidant strategy provides reproducible benefit beyond conventional periodontal therapy.

Selenium-based approaches in periodontitis

Biological Rationale and Current Periodontal Evidence

Selenium is an essential component of multiple selenoproteins involved in redox regulation, including glutathione peroxidases and thioredoxin reductases [29]. This provides a mechanistic rationale for investigating selenium-related pathways in periodontitis, particularly in relation to peroxide detoxification, thiol homeostasis, lipid peroxidation, and ferroptosis [22,29]. Periodontal and dental literature has discussed potential applications of selenium-containing compounds in the context of oxidative stress and inflammatory disease [55]. A recent 2026 review specifically examining selenium in periodontal health and disease further synthesized evidence relating to selenium and selenoproteins, antioxidant defense, periodontal biomarkers, supplementation, and selenium nanoparticles [56]. However, this biological rationale should be distinguished from evidence that selenium supplementation or selenium-based therapy improves clinical periodontal outcomes.

Broader mechanistic literature also supports the capacity of selenium compounds to influence inflammatory signaling. For example, selenium compounds have been investigated for their effects on cytokine-related pathways outside the specific setting of periodontal clinical therapy [57]. Such findings provide biological context for selenium-mediated immunomodulation but should not be treated as direct evidence of therapeutic efficacy in periodontitis. At present, the periodontal relevance of selenium must therefore be evaluated separately at mechanistic, observational, and experimental intervention levels.

Selenium Nanoparticles

Selenium nanoparticles represent a distinct preclinical approach rather than an established periodontal therapy. Experimental work has evaluated selenium nanoparticles against *Streptococcus mutans* biofilms and proposed their potential relevance to periodontal applications [58]. This finding provides antimicrobial and platform-level rationale, but activity against a model oral biofilm does not demonstrate efficacy against periodontitis in humans. Furthermore, nanoparticle characteristics such as size, surface chemistry, concentration, and formulation can substantially influence biological activity. The available evidence should therefore be interpreted as exploratory and preclinical.

Human evidence currently includes observational data on selenium status rather than evidence of therapeutic efficacy. In patients with stage III-IV periodontitis, a recent study reported lower serum selenium concentrations together with an altered systemic oxidant-antioxidant profile compared with periodontally healthy controls [59]. This association supports investigation of selenium status as a potential correlate of periodontal and redox disturbance, but it does not establish causality, demonstrate that selenium deficiency initiates or worsens periodontitis, or show that selenium supplementation improves periodontal outcomes.

Selenase: Periodontal Preclinical Evidence

Selenase has been evaluated in experimental chronic generalized periodontitis. One experimental study reported changes in inflammatory and cytoprotective markers following Selenase administration, including effects on parameters related to inflammatory signaling and cellular stress responses [60]. These findings provide periodontal-specific experimental evidence for biological activity, but the study design remains preclinical and does not establish efficacy or safety in patients with periodontitis.

A subsequent experimental study specifically examined antioxidant mechanisms associated with Selenase in chronic generalized periodontitis and reported effects consistent with modulation of oxidative stress pathways [61]. Considered together, the two Selenase studies [60,61] provide periodontal-specific preclinical support for anti-inflammatory, antioxidant, and cytoprotective mechanisms. However, they represent experimental evidence from related disease models rather than independent confirmation in controlled human periodontal trials.

The Selenase findings are biologically compatible with the broader role of selenium-dependent redox systems, including glutathione peroxidase-related antioxidant defense [29]. Their translational significance

nevertheless remains uncertain. Mechanistic coherence does not substitute for demonstration of clinically meaningful improvements in probing depth, clinical attachment, bleeding outcomes, disease progression, or other validated periodontal endpoints in humans. Controlled human studies would be required to determine dose, route of administration, safety, added benefit beyond standard periodontal therapy, and the patient populations in whom a selenium-based intervention might be appropriate.

Safety and translational limitations of selenium-based approaches

Safety is a central consideration in the translation of selenium-based interventions. Selenium is an essential micronutrient, but biological effects depend on dose, chemical form, route of administration, and baseline selenium status. Selenium nanoparticles have been investigated in broader biomedical settings for antioxidant and anti-inflammatory properties [62], but such evidence is not specific to periodontal treatment. Consequently, the potential advantages of selenium-based formulations cannot be extrapolated directly to periodontal clinical efficacy or safety.

Nanoparticle-specific safety also requires separate consideration. Reviews of selenium nanoparticles describe antimicrobial potential together with toxicological concerns, indicating that biological effects may vary according to physicochemical characteristics and exposure conditions [63]. For periodontal applications, relevant uncertainties include local tissue compatibility, concentration-dependent effects, formulation characteristics, and the consequences of repeated exposure. These issues require direct periodontal evaluation rather than inference from antimicrobial activity or studies conducted in other biological settings.

A separate translational question is whether selenium status and selenium-based treatment should be considered equivalent concepts. The reported association between lower serum selenium concentrations and stage III-IV periodontitis [59] does not demonstrate that selenium supplementation will improve periodontal outcomes. Correction of a documented nutritional deficiency and pharmacologic use of a selenium-containing agent represent different clinical questions and should be evaluated separately. At present, the evidence reviewed here does not establish whether selenium-based periodontal interventions should be targeted according to baseline selenium status, oxidative stress profile, disease severity, or other patient characteristics.

Overall, the selenium literature reviewed here, including the recent periodontal-focused review [56], supports biological plausibility, human observational associations, and periodontal-specific preclinical investigation, but it does not yet establish therapeutic efficacy in human periodontitis. No inference of routine clinical benefit should therefore be made from the current mechanistic, nanoparticle, observational, or experimental Selenase findings. Translation will require appropriately controlled human studies that define the selenium formulation, dose and route, baseline selenium status, concomitant periodontal therapy, safety outcomes, and clinically meaningful periodontal endpoints. The evidence levels, principal findings, major limitations, and current interpretations of the antioxidant and selenium-based approaches discussed in this review are summarized in Table 1. This comparison highlights the distinction between interventions supported by clinical studies and those supported predominantly by observational, mechanistic, or preclinical evidence.

Approach	Evidence represented in this review	Principal findings	Major limitations	Current interpretation
Vitamin E	Systematic review and meta-analysis of periodontal clinical studies [43]	Tocopherol supplementation was associated with favorable changes in selected clinical periodontal parameters [43]	Limited number of studies and heterogeneity in intervention protocols and outcome assessment [43]	Potential adjunct with preliminary clinical support; routine use is not established [43]
CoQ10	Systematic review and meta-analysis of clinical trials [44]	Adjunctive CoQ10 was associated with improvements in selected periodontal outcomes [44]	Variation in formulation, administration route, treatment protocols, and sample size [44]	Clinical evidence supports further investigation, but not routine universal use [44]
NAC	Cellular experimental study in human periodontal ligament fibroblasts [45]	NAC attenuated pyroptosis-related signaling and impairment of osteogenic differentiation through a SIRT1/NF-κB/Caspase-1-associated pathway [45]	Evidence represented here is primarily preclinical and does not demonstrate efficacy in patients [45]	Mechanistically plausible but clinically unproven [45]
Melatonin	Review, systematic review, and comparative network meta-analysis [42,46,47]	Evidence suggests potential improvement in selected periodontal outcomes; comparative analysis identified favorable signals for probing depth and clinical attachment outcomes [42,46,47]	Heterogeneous study designs and intervention protocols; optimal dose, formulation, route, and patient selection remain uncertain [42,46,47]	One of the more clinically developed antioxidant adjuncts, but evidence is insufficient for definitive routine recommendations [42,46,47]
Resveratrol	Randomized clinical trial, mechanistic literature, and network meta-analysis [42,48,49]	Clinical and comparative evidence provides favorable signals for selected periodontal and inflammatory outcomes [42,48,49]	Limited breadth of clinical evidence and uncertainty across populations, formulations, and protocols [42,48,49]	Promising clinical signal requiring further confirmatory trials [42,48,49]
Quercetin	Systematic review and meta-analysis of animal models and experimental evidence [50,51]	Preclinical studies support protective effects in experimental periodontal disease and effects on inflammation and microbial dysbiosis [50,51]	Predominantly preclinical evidence; human clinical efficacy has not been established [50,51]	Preclinical candidate requiring human clinical validation [50,51]
Selenium status	Human observational study [59]	Lower serum selenium concentrations and altered systemic oxidant-antioxidant profiles were reported in patients with stage III-IV periodontitis [59]	Observational association does not establish causality or benefit from supplementation [59]	Supports investigation of selenium status as a correlate of periodontal redox disturbance, not therapeutic efficacy [59]
Selenium nanoparticles	Experimental antimicrobial/preclinical literature and broader biomedical reviews [58,62,63]	Selenium nanoparticles show antimicrobial, antioxidant, and anti-inflammatory potential in experimental settings [58,62,63]	Evidence is not equivalent to human periodontal efficacy; physicochemical characteristics and toxicological issues require consideration [58,62,63]	Exploratory/preclinical approach requiring periodontal-specific efficacy and safety studies [58,62,63]
Selenase	Periodontal-specific experimental studies [60,61]	Experimental studies reported modulation of inflammatory, cytoprotective, and oxidative stress-related pathways [60,61]	Preclinical disease models; no controlled human periodontal efficacy or safety evidence [60,61]	Periodontal-specific mechanistic/preclinical support exists, but clinical use remains investigational [60,61]

TABLE 1: Summary of Evidence for Antioxidant and Selenium-Based Approaches in Periodontitis

CoQ10: coenzyme Q10, NAC: N-acetylcysteine

Current limitations of antioxidant therapy

Although antioxidant adjuncts have substantial biological rationale, the clinical evidence remains heterogeneous. Studies differ in periodontal case definitions, intervention type and duration, route of

administration, background periodontal therapy, sampling methods, biomarkers, and clinical outcomes [10-14,34,43-52]. In addition, several intervention-specific evidence bases remain limited by small or heterogeneous studies, and preclinical findings cannot be assumed to translate into sustained clinical benefit. Systemic antioxidant exposure may also be influenced by diet, smoking, metabolic conditions, baseline nutritional status, and other patient-level factors. These sources of heterogeneity complicate comparisons among studies and currently limit broad treatment recommendations.

A further conceptual limitation is that ROS are not exclusively harmful by-products. Redox signaling participates in normal cellular regulation and immune defense, whereas excessive or dysregulated oxidant production can contribute to tissue injury [18-20,53]. This distinction argues against viewing antioxidant therapy simply as maximal suppression of ROS. Instead, periodontal redox interventions would need to reduce pathologic oxidative injury without disrupting physiologic signaling or antimicrobial defense. General literature on mitochondrial oxidative stress further illustrates the importance of maintaining this balance across biological systems [64], but such evidence does not establish mitochondria-targeted treatment efficacy in periodontitis.

Oral-systemic implications of periodontal oxidative stress

Periodontitis has been studied in relation to multiple systemic inflammatory and metabolic conditions, and oxidative stress has been proposed as one of several biological pathways that may contribute to oral-systemic interactions [2,7,10]. Shared inflammatory and redox mechanisms provide a plausible framework for investigating these associations. However, the evidence reviewed here does not establish periodontal oxidative stress as an independent cause of systemic disease, nor does it demonstrate that antioxidant periodontal therapy improves systemic clinical outcomes. The oral-systemic relevance of redox biology should therefore be interpreted as an area of mechanistic and translational interest rather than as an established indication for antioxidant treatment.

Patient-level factors may nevertheless be important sources of biological and clinical heterogeneity. Nutritional status, smoking exposure, metabolic disease, medication use, and other host characteristics can influence inflammatory or redox biology and may also affect responses observed in antioxidant studies [10-14]. Future trials should determine whether such variables identify reproducible treatment response subgroups. Until such evidence is available, antioxidant selection based on an individual patient's presumed oxidative phenotype should be considered investigational rather than an established precision periodontology strategy.

These considerations reinforce the role of antioxidant approaches as potential adjuncts rather than alternatives to established periodontal care. Biofilm control, management of modifiable risk factors, appropriate periodontal instrumentation, and supportive periodontal care remain the therapeutic foundation [8,9]. Any antioxidant intervention should therefore be evaluated according to the additional clinical benefit it provides beyond this standard framework, rather than on mechanistic plausibility alone.

Translational priorities and ideal trial design

Future clinical studies of antioxidant adjuncts should be designed to determine whether biological effects translate into clinically meaningful periodontal benefit. Trials should clearly define periodontal diagnosis and stage, relevant patient characteristics and risk factors, background periodontal treatment, antioxidant formulation and dose, route of administration, and duration of follow-up. Both mechanistic outcomes and validated clinical periodontal endpoints should be reported. Short-term changes in biomarkers or inflammatory indices may provide evidence of biological activity, but sustained effects on probing depth, clinical attachment, bleeding outcomes, disease recurrence, and treatment response are necessary to establish clinical relevance.

Biomarkers may also have a role in future translational studies. Measures of lipid peroxidation, oxidative DNA or protein damage, nitrosative stress, glutathione-related defense, and selenium status could be evaluated alongside conventional periodontal outcomes to determine whether treatment-associated biological changes correspond to clinical improvement [12-14,21,28,59]. However, current evidence does not establish validated biomarker thresholds for selecting a specific antioxidant intervention or predicting treatment response. Biomarker-guided antioxidant selection should therefore be tested prospectively rather than assumed from mechanistic associations.

Formulation and delivery represent a separate translational priority. Periodontal drug delivery literature has investigated local and controlled-release systems, including nanoparticle and hydrogel-based approaches [35,36,38]. Such technologies may provide useful platforms for studying local therapeutic exposure, but evidence supporting a delivery system should not be conflated with evidence supporting the efficacy of the antioxidant agent being delivered. Future studies should therefore characterize formulation, local retention, release behavior, tissue compatibility, and safety together with clinically relevant periodontal outcomes.

Evidence should also be interpreted according to the developmental stage of each intervention. The literature reviewed here ranges from cellular and animal studies to observational human research,

randomized clinical studies, and systematic reviews. Consequently, favorable findings for one antioxidant or formulation cannot be generalized to the antioxidant class as a whole. Progress toward clinical implementation requires demonstration of added benefit beyond optimized periodontal care, clinically meaningful effect sizes, acceptable safety, reproducibility, and practical feasibility.

Several priorities emerge from the current evidence gaps. First, prospective studies should determine whether standardized redox biomarkers can identify reproducible periodontal phenotypes or predict response to adjunctive treatment [12–14,21,32,33]. Second, mechanistic investigation of mitochondrial dysfunction, mitophagy, ferroptosis, and related redox pathways should continue using periodontal-specific models and, where feasible, human periodontal evidence [17–20,22]. Third, antioxidant formulations and delivery systems should undergo staged evaluation from physicochemical characterization and preclinical safety to controlled clinical testing [35,36,38]. Finally, selenium-based approaches require particularly careful translational development because the current evidence spans mechanistic literature, human observational associations, nanoparticle studies, and experimental Selenase models without established therapeutic efficacy in human periodontitis [29,55,58–63].

Conclusions

Oxidative and nitrosative stress are closely linked to the inflammatory and tissue-destructive processes associated with periodontitis, with mitochondrial dysfunction, altered antioxidant defenses, and emerging ferroptosis-related mechanisms providing additional biological context. However, the evidence reviewed here spans substantially different levels of investigation, from mechanistic and preclinical studies to observational human research, clinical trials, and systematic reviews. Conventional periodontal treatment based on biofilm control, management of modifiable risk factors, periodontal instrumentation, and supportive care therefore remains the therapeutic foundation. Antioxidant interventions should be evaluated as potential adjuncts, and their clinical relevance must be determined individually according to the quality and level of evidence available for each agent.

Current evidence for antioxidant adjuncts is heterogeneous. Some agents, including vitamin E, CoQ10, melatonin, and resveratrol, have been evaluated in clinical literature, whereas evidence for other approaches remains predominantly preclinical or mechanistic. Selenium-based strategies are biologically relevant because selenium-dependent pathways participate in redox regulation, but the periodontal evidence currently consists of mechanistic literature, observational associations, nanoparticle studies, and experimental Selenase models rather than established therapeutic efficacy in humans. Accordingly, selenium-based interventions should remain investigational until controlled clinical studies establish their safety, dosing, patient selection, and added benefit beyond standard periodontal therapy. Future research should prioritize standardized clinical endpoints, transparent evidence-level interpretation, and rigorous evaluation of whether redox-targeted interventions provide reproducible clinical benefit.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Kyu-Ho Yi, Igor Belenichev, Oleksandr Kamyshnyi

Critical review of the manuscript for important intellectual content: Kyu-Ho Yi, Igor Belenichev, Olena Popazova, Valeriy Salnykov, Nina Bukhtiyarova, Victor Ryzhenko, Pavlo Petakh, Oleksandr Kamyshnyi, Sergiy Oliynyk, Suyeon Lee

Supervision: Kyu-Ho Yi, Igor Belenichev

Drafting of the manuscript: Igor Belenichev, Oleksandr Kamyshnyi

Acquisition, analysis, or interpretation of data: Olena Popazova, Valeriy Salnykov, Nina Bukhtiyarova, Victor Ryzhenko, Pavlo Petakh, Sergiy Oliynyk, Suyeon Lee

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- Loos BG, Van Dyke TE: The role of inflammation and genetics in periodontal disease . *Periodontol* 2000. 2020, 83:26-39. [10.1111/prd.12297](#)
- Bhuyan R, Bhuyan SK, Mohanty JN, Das S, Juliana N, Juliana IF: Periodontitis and its inflammatory changes linked to various systemic diseases: a review of its underlying mechanisms. *Biomedicines*. 2022, [10:10.3390/biomedicines10102659](#)
- Santacroce L, Passarelli PC, Azzolino D, et al.: Oral microbiota in human health and disease: a perspective . *Exp Biol Med* (Maywood). 2023, 248:1288-301. [10.1177/15353702231187645](#)
- Basic A, Dahlén G: Microbial metabolites in the pathogenesis of periodontal diseases: a narrative review . *Front Oral Health*. 2023, 4:1210200. [10.3389/froh.2023.1210200](#)
- Łasica A, Golec P, Laskus A, Zalewska M, Gędaj M, Popowska M: Periodontitis: etiology, conventional treatments, and emerging bacteriophage and predatory bacteria therapies. *Front Microbiol*. 2024, 15:1469414. [10.3389/fmicb.2024.1469414](#)
- Abe FC, Kodaira K, Motta CC, et al.: Antimicrobial resistance of microorganisms present in periodontal diseases: a systematic review and meta-analysis. *Front Microbiol*. 2022, 13:961986. [10.3389/fmicb.2022.961986](#)
- Martínez-García M, Hernández-Lemus E: Periodontal inflammation and systemic diseases: an overview . *Front Physiol*. 2021, 12:709438. [10.3389/fphys.2021.709438](#)
- Sanz M, Herrera D, Kebschull M, et al.: Treatment of stage I-III periodontitis-the EFP S3 level clinical practice guideline. *J Clin Periodontol*. 2020, 47 Suppl 22:4-60. [10.1111/jcpe.13290](#)
- Herrera D, Sanz M, Kebschull M, et al.: Treatment of stage IV periodontitis: the EFP S3 level clinical practice guideline. *J Clin Periodontol*. 2022, 49 Suppl 24:4-71. [10.1111/jcpe.13639](#)
- Liu W, Guo D: Oxidative stress in periodontitis and the application of antioxidants in treatment: a narrative review. *Front Physiol*. 2025, 16:1485367. [10.3389/fphys.2025.1485367](#)
- Patil RT, Dhadse PV, Salian SS, Punse SD: Role of oxidative stress in periodontal diseases . *Cureus*. 2024, 16:e60779. [10.7759/cureus.60779](#)
- Viglianisi G, Tartaglia GM, Santonocito S, Amato M, Polizzi A, Mascitti M, Isola G: The emerging role of salivary oxidative stress biomarkers as prognostic markers of periodontitis: new insights for a personalized approach in dentistry. *J Pers Med*. 2023, 13: [10.3390/jpm13020166](#)
- Zhang Y, Kang N, Xue F, Qiao J, Duan J, Chen F, Cai Y: Evaluation of salivary biomarkers for the diagnosis of periodontitis. *BMC Oral Health*. 2021, 21:266. [10.1186/s12903-021-01600-5](#)
- Goriuc A, Cojocar KA, Luchian I, Ursu RG, Butnaru O, Foia L: Using 8-hydroxy-2'-deoxyguanosine (8-OHdG) as a reliable biomarker for assessing periodontal disease associated with diabetes. *Int J Mol Sci*. 2024, 25: [10.3390/ijms25031425](#)
- Neurath N, Kesting M: Cytokines in gingivitis and periodontitis: from pathogenesis to therapeutic targets . *Front Immunol*. 2024, 15:1435054. [10.3389/fimmu.2024.1435054](#)
- Xu T, Dong Q, Luo Y, Liu Y, Gao L, Pan Y, Zhang D: Porphyromonas gingivalis infection promotes mitochondrial dysfunction through Drp1-dependent mitochondrial fission in endothelial cells. *Int J Oral Sci*. 2021, 13:28. [10.1038/s41368-021-00134-4](#)
- Jiang K, Li J, Jiang L, Li H, Lei L: PINK1-mediated mitophagy reduced inflammatory responses to Porphyromonas gingivalis in macrophages. *Oral Dis*. 2023, 29:3665-76. [10.1111/odi.14286](#)
- Luo S, Xu T, Zheng Q, et al.: Mitochondria: an emerging unavoidable link in the pathogenesis of periodontitis caused by Porphyromonas gingivalis. *Int J Mol Sci*. 2024, 25: [10.3390/ijms25020737](#)
- Jia Y, Li Z, Huang P, Wang Y, Yang B: Mechanisms and therapeutic perspectives of mitochondrial dysfunction of macrophages in periodontitis. *Front Cell Infect Microbiol*. 2025, 15:1634909. [10.3389/fcimb.2025.1634909](#)
- Mukherjee A, Ghosh KK, Chakraborty S, Gulyás B, Padmanabhan P, Ball WB: Mitochondrial reactive oxygen species in infection and immunity. *Biomolecules*. 2024, 14: [10.3390/biom14060670](#)
- Toczewska J, Konopka T, Zalewska A, Maciejczyk M: Nitrosative stress biomarkers in the non-stimulated and stimulated saliva, as well as gingival crevicular fluid of patients with periodontitis: review and clinical study. *Antioxidants* (Basel). 2020, 9: [10.3390/antiox9030259](#)
- Guan P, Ruan Q, Li J, Xi M, Qi W, Ko KI, Ni J: Ferroptosis in periodontitis: mechanisms, impacts, and systemic connections. *Cell Death Discov*. 2025, 11:283. [10.1038/s41420-025-02550-5](#)
- Wu J, Zheng Z, Wang J, Xiao W, Shi L, Fan L: Iron status and risk of periodontitis and dental caries: a Mendelian randomization study. *Int Dent J*. 2025, 75:1441-9. [10.1016/j.identj.2024.11.018](#)
- Chaudhary P, Janmeda P, Docea AO, et al.: Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. *Front Chem*. 2023, 11:1158198. [10.3389/fchem.2023.1158198](#)
- Tan Y, Lin M, Gao X: Ferroptosis in periodontitis: mechanism, role, and therapeutic potential. *Pathol Res Pract*. 2026, 281:156401. [10.1016/j.prp.2026.156401](#)
- Liu T, Shang J, Chen Q: Superoxide dismutases in immune regulation and infectious diseases . *Antioxidants* (Basel). 2025, 14: [10.3390/antiox14070809](#)
- Frye KA, Sendra KM, Waldron KJ, Kehl-Fie TE: Old dogs, new tricks: new insights into the iron/manganese superoxide dismutase family. *J Inorg Biochem*. 2022, 230:111748. [10.1016/j.jinorgbio.2022.111748](#)
- Mohideen K, Krithika C, Jeyanthikumari T, Vani NV, Dhungel S, Ghosh S: The assessment of glutathione, glutathione peroxidase, glutathione reductase, and oxidized glutathione in patients with periodontitis-a systematic review and meta-analysis. *Clin Exp Dent Res*. 2024, 10:e907. [10.1002/cre2.907](#)
- Shahidin, Wang Y, Wu Y, et al.: Selenium and selenoproteins: mechanisms, health functions, and emerging applications. *Molecules*. 2025, 30: [10.3390/molecules30030437](#)
- Izakovicova P, Fassmann A, Dusek L, Izakovicova Holla L: Glutathione S-transferase M1, T1, and P1 polymorphisms and periodontitis in a Caucasian population: a case-control study. *BMC Oral Health*. 2024, 24:288. [10.1186/s12903-024-04034-x](#)
- Chen W, Ling X, Li W, et al.: Systemic and local oxidative stress biomarkers in periodontitis: an updated

- systematic review and meta-analysis. *BMC Oral Health*. 2026, [10.1186/s12903-026-09434-9](#)
32. Kehm R, Baldensperger T, Raupbach J, Höhn A: Protein oxidation - formation mechanisms, detection and relevance as biomarkers in human diseases. *Redox Biol*. 2021, 42:101901. [10.1016/j.redox.2021.101901](#)
33. Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E: The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. *Int J Mol Sci*. 2021, 22: [10.3390/ijms22094642](#)
34. López-Valverde N, López-Valverde A, Montero J, Rodríguez C, Macedo de Sousa B, Aragonese JM: Antioxidant, anti-inflammatory and antimicrobial activity of natural products in periodontal disease: a comprehensive review. *Front Bioeng Biotechnol*. 2023, 11:1226907. [10.3389/fbioe.2023.1226907](#)
35. Lima de Sousa T, Dourado D, Rodrigues JS, de Souza Rebouças J, Montes MA, Formiga FR: Treatment of periodontal disease: does drug delivery matter?. *Front Bioeng Biotechnol*. 2024, 12:1427758. [10.3389/fbioe.2024.1427758](#)
36. Nasiri K, Masoumi SM, Amini S, et al.: Recent advances in metal nanoparticles to treat periodontitis . *J Nanobiotechnology*. 2023, 21:283. [10.1186/s12951-023-02042-7](#)
37. Jung D, Cha JK, Kim YT, Kim CS: Comparing the clinical effects of local administration of minocycline ointment and doxycycline solution in the treatment of acute periodontal abscesses: a retrospective clinical study. *J Periodontal Implant Sci*. 2024, 54:149-60. [10.5051/jpis.2300800040](#)
38. Bako J, Toth F, Gall J, et al.: Combined release of antiseptic and antibiotic drugs from visible light polymerized biodegradable nanocomposite hydrogels for periodontitis treatment. *Pharmaceutics*. 2022, 14:[10.3390/pharmaceutics14050957](#)
39. Serbanescu MA, Oveisi M, Sun C, Fine N, Bosy A, Glogauer M: Metronidazole enhances killing of *Porphyromonas gingivalis* by human PMNs. *Front Oral Health*. 2022, 3:935997. [10.3389/froh.2022.935997](#)
40. Zhang J, Ding Q, Wang AX, et al.: Type I interferon protects against bone loss in periodontitis by mitigating an interleukin (IL)-17-neutrophil axis. *Life Sci*. 2025, 371:123559. [10.1016/j.lfs.2025.123559](#)
41. Pahade A, Bajaj P, Reche A, Shirbhate U: Immunomodulators and their applications in dentistry and periodontics: a comprehensive review. *Cureus*. 2023, 15:e46653. [10.7759/cureus.46653](#)
42. Jiang T, Jiang H, Wu J, et al.: Adjunctive antioxidant benefits in periodontal therapy: a systematic review and network meta-analysis. *Oral Dis*. 2026, 1-13. [10.1111/odi.70302](#)
43. Bumbu BA, Luca MM, Buzatu R: Impact of tocopherol supplementation on clinical parameters of periodontal disease: a systematic review and meta-analysis. *J Pers Med*. 2024, 14: [10.3390/jpm14101039](#)
44. Rasoolzadeh EA, Shidfar F, Rasoolzadeh RA, Hezaveh ZS: The effect of coenzyme Q10 on periodontitis: a systematic review and meta-analysis of clinical trials. *J Evid Based Dent Pract*. 2022, 22:101710. [10.1016/j.jebdp.2022.101710](#)
45. Chu Y, Xu Y, Yang W, Chu K, Li S, Guo L: N-acetylcysteine protects human periodontal ligament fibroblasts from pyroptosis and osteogenic differentiation dysfunction through the SIRT1/NF- κ B/Caspase-1 signaling pathway. *Arch Oral Biol*. 2023, 148:105642. [10.1016/j.archoralbio.2023.105642](#)
46. Pawane IR, Malaipappan S: Review on the effect of systemic melatonin in periodontal disease . *Bioinformation*. 2023, 19:692-7. [10.6026/97320630019692](#)
47. Purpura S, Fernandes GV, Oliveira FP, de Castro FC: Effects of melatonin in the non-surgical treatment of periodontitis: a systematic review. *Appl Sci*. 2022, 12:11698. [10.3390/app122211698](#)
48. Nikniaz S, Vaziri F, Mansouri R: Impact of resveratrol supplementation on clinical parameters and inflammatory markers in patients with chronic periodontitis: a randomized clinical trial. *BMC Oral Health*. 2023, 23:177. [10.1186/s12903-023-02877-4](#)
49. Lim YR, Preshaw PM, Lin H, Tan KS: Resveratrol and its analogs as functional foods in periodontal disease management. *Front Dent Med*. 2021, 2:636423. [10.3389/fdmed.2021.636423](#)
50. Laky M, Arslan M, Zhu X, et al.: Quercetin in the prevention of induced periodontal disease in animal models: a systematic review and meta-analysis. *Nutrients*. 2024, 16:[10.3390/nu16050735](#)
51. Mooney EC, Holden SE, Xia XJ, et al.: Quercetin preserves oral cavity health by mitigating inflammation and microbial dysbiosis. *Front Immunol*. 2021, 12:774273. [10.3389/fimmu.2021.774273](#)
52. Hashim NT, Babiker R, Rahman MM, et al.: Natural bioactive compounds in the management of periodontal diseases: a comprehensive review. *Molecules*. 2024, 29: [10.3390/molecules29133044](#)
53. Gulcin I: Antioxidants: a comprehensive review. *Arch Toxicol*. 2025, 99:1893-997. [10.1007/s00204-025-03997-2](#)
54. Flieger J, Flieger W, Baj J, Maciejewski R: Antioxidants: classification, natural sources, activity/capacity measurements, and usefulness for the synthesis of nanoparticles. *Materials (Basel)*. 2021, 14:[10.3390/ma14154135](#)
55. Ismikhonov AG, Dadaeva GT, Dzhabrailov SM, Maysigova JB, Semenov MR, Dzagurova LA: The role of selenium-containing compounds in periodontal and dental disease management. *Ann Orthod Periodontics Spec*. 2024, 4:32-8. [10.51847/pB7YqtH50J](#)
56. Rua RM, Nogales F, Carreras O, Ojeda ML: Selenium in periodontal health and disease: a narrative review . *J Trace Elem Med Biol*. 2026, 96:127917. [10.1016/j.jtemb.2026.127917](#)
57. Sinha I, Zhu J, Sinha R: Selective impact of selenium compounds on two cytokine storm players . *J Pers Med*. 2023, 13:[10.3390/jpm13101455](#)
58. Hamman N, Ramburrun P, Dube A: Selenium nanoparticle activity against *S. mutans* biofilms as a potential treatment alternative for periodontitis. *Pharmaceutics*. 2024, 16:[10.3390/pharmaceutics16040450](#)
59. Uytun M, Orbak R, Kızıltunç A: Potential relationship between decreased serum selenium levels and oxidative stress in periodontitis stage III-IV. *Biol Trace Elem Res*. 2025, 203:6415-25. [10.1007/s12011-025-04649-3](#)
60. Salnykov V, Belenichev I, Samura IB: The effect of Selenase on inflammatory and cytoprotective markers in experimental chronic generalized periodontitis. *Biomed Pharmacol J*. 2024, 17:1911-9. [10.13005/bpj/2993](#)
61. Salnykov V, Belenichev I, Makyeyeva L, Skoryna D, Oksenysh V, Kamysheyn O: Antioxidant mechanisms of the protective action of Selenase in experimental chronic generalized periodontitis. *Curr Issues Mol Biol*. 2025, 47:[10.3390/cimb47030186](#)
62. Andrés CMC, Pérez de la Lastra JM, Munguira EB, Juan CA, Pérez-Lebeña E: Selenium nanoparticles in

- critical illness-anti-inflammatory and antioxidant effects. *Dietetics*. 2025, 4:6. [10.3390/dietetics4010006](https://doi.org/10.3390/dietetics4010006)
63. Oliveira TP, Lima AK, Muehlmann LA: An updated review of the antimicrobial potential of selenium nanoparticles and selenium-related toxicological issues. *Future Pharmacol*. 2025, 5:3. [10.3390/futurepharmacol5010003](https://doi.org/10.3390/futurepharmacol5010003)
64. Kowalczyk P, Sulejczak D, Kleczkowska P, et al.: Mitochondrial oxidative stress-a causative factor and therapeutic target in many diseases. *Int J Mol Sci*. 2021, 22: [10.3390/ijms222413384](https://doi.org/10.3390/ijms222413384)