

SYSTEMATIC REVIEW

Oxidative Stress as an Etiopathogenic Factor in Periodontal Disease

Estrés oxidativo como factor etiopatogénico en la enfermedad periodontal

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ABSTRACT

Periodontal disease is a chronic, multifactorial inflammatory condition characterized by the progressive destruction of the tooth-supporting tissues. In recent years, oxidative stress has been recognized as a relevant pathophysiological mechanism in its development and progression due to the imbalance between the production of reactive oxygen species and the body's antioxidant mechanisms. Objective: To analyze the role of oxidative stress as an etiopathogenic factor in periodontal disease through a review of recent literature. Methodology: A narrative review of scientific articles published between 2020 and 2025 was conducted. The search was carried out in PubMed and Scopus databases, selecting relevant studies related to oxidative stress and periodontal disease. Results: The reviewed evidence indicates that oxidative stress plays an active role in the periodontal inflammatory response, promoting tissue destruction and bone resorption. Additionally, several studies report the presence of oxidative biomarkers associated with the severity of the disease. Conclusion: Oxidative stress plays a significant role in the pathogenesis of periodontal disease by contributing to the amplification of the inflammatory process and damage to periodontal tissues; therefore, its study represents an important area of research for future diagnostic and therapeutic strategies.

Keywords: Periodontal Diseases. Oxidative Stress. Reactive Oxygen Species.

RESUMEN

La enfermedad periodontal es una patología inflamatoria crónica multifactorial caracterizada por la destrucción progresiva de los tejidos de soporte dental. En los últimos años, el estrés oxidativo ha sido reconocido como un mecanismo fisiopatológico relevante para su desarrollo y progresión, debido al desequilibrio entre la producción de especies reactivas de oxígeno y los mecanismos antioxidantes del organismo. Objetivo: analizar el papel del estrés oxidativo como factor etiopatogénico en la enfermedad periodontal mediante una revisión de la literatura reciente. Metodología: se realizó una revisión narrativa de artículos científicos publicados entre 2020 y 2025. La búsqueda se efectuó en las bases de datos PubMed y Scopus, seleccionando estudios relevantes relacionados con el estrés oxidativo y la enfermedad periodontal. Resultados: la evidencia revisada señala que el estrés oxidativo participa activamente en la respuesta inflamatoria periodontal, favoreciendo la destrucción del tejido y la reabsorción ósea. De la misma manera, diversos estudios reportan la presencia de biomarcadores oxidativos relacionados con la severidad de la patología. Conclusión: el estrés oxidativo desempeña un papel relevante en la etiopatogenia de la enfermedad periodontal, al contribuir a la amplificación del proceso inflamatorio y al daño de los tejidos periodontales, por lo que su estudio representa una línea importante para futuras estrategias diagnósticas y terapéuticas.

Palabras clave: Enfermedades Periodontales. Estrés Oxidativo. Especies Reactivas de Oxígeno.

INTRODUCTION

Periodontal disease (PD) is one of the most prevalent chronic inflammatory diseases and the leading cause of tooth loss in adults¹⁻³, significantly affecting quality of life and imposing a substantial burden on healthcare systems^{3,4}. Its etiopathogenesis is multifactorial: although a pathogenic biofilm is essential^{1,2,5}, the host's immunoinflammatory response, modulated by genetic, systemic, and environmental factors, plays a decisive role in the severity and progression of the disease^{1,6-8}.

Within this response, oxidative stress (OS) has emerged as a central pathophysiological mechanism^{1,2}. Excessive generation of reactive oxygen species (ROS) in the presence of insufficient antioxidant capacity results in redox imbalance, leading to molecular damage and amplifying the inflammatory response^{4,7,9}.

Several studies^{2,3,10} have demonstrated a significant association between oxidative stress and periodontal disease^{2,3,10}. Nevertheless, the available evidence is dispersed across experimental^{11,12} and clinical^{10,13} investigations, making it difficult to obtain a comprehensive understanding of its etiopathogenic role. Therefore, the general objective of the present study is to analyze the role of oxidative stress as an etiopathogenic factor in periodontal disease through a critical review of recent literature, in order to understand its mechanism of action, clinical implications, and relevance to the development and progression of this condition.

MATERIALS AND METHODS

The present study is a descriptive narrative literature review aimed at answering the following research question: How does oxidative stress influence the etiology and pathogenesis of periodontal disease?

A literature search was conducted in the PubMed and Scopus databases for articles published in English between 2020 and 2025. MeSH terms and keywords were combined using Boolean operators:

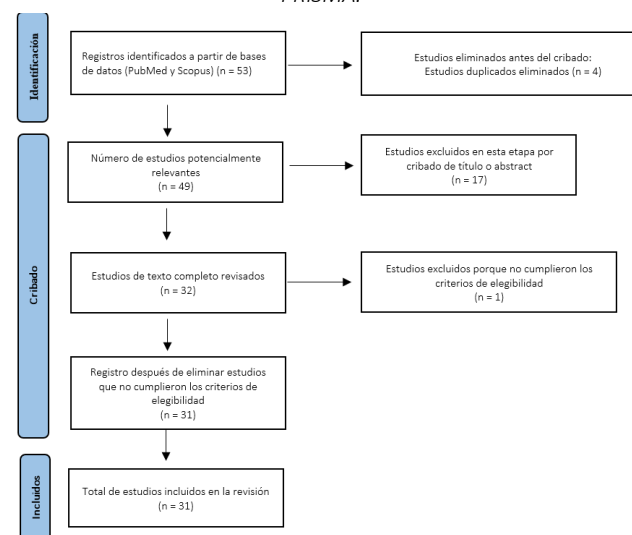
((("Periodontal Diseases"[MeSH Terms] OR "Periodontitis"[MeSH Terms] OR "Periodontal disease" OR "Gum disease" OR "Chronic periodontitis" OR "Aggressive periodontitis")) AND (("Oxidative Stress"[MeSH Terms] OR "Reactive Oxygen Species"[MeSH Terms] OR "ROS" OR "Free radicals" OR "Antioxidant status" OR "Oxidative damage")) AND (("Etiology"[Subheading] OR "Pathogenesis"[Subheading] OR "Etiopathogenesis" OR "Mechanism*" OR "Causal pathway*" OR "Disease development"))).

Reviews, clinical studies, and experimental studies addressing oxidative stress, biomarkers, and periodontal pathophysiology were included. Duplicate articles, incomplete or inconsistent studies, and studies involving animal models that were not applicable to humans were excluded. The selection and organization of the studies were performed using the Mendeley reference manager, supplemented by manual screening. A total of 53 articles were identified; following application of the eligibility criteria, 31 studies were selected for the final analysis

(Figure 1). The main characteristics of the included studies are presented in Table 1.

The information obtained was organized narratively and thematically, allowing the integration of the main findings related to oxidative stress, its involvement in the periodontal inflammatory response, and its impact on tissue damage and disease progression.

Figure 1. Flow diagram of the literature search according to PRISMA.



Source: Own elaboration based on the PRISMA model.

Table 1. Characteristics and Main Findings of the Included Studies

No.	Title	Authors and Year	Country	Study Type	Population/Model	Oxidative Stress (OS) Biomarkers or Mechanism Evaluated	Main Findings	Periodontal Implications
1	Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way.	Sczepanik et al., 2020	Brazil	Review	General adult population	Oxidative damage to proteins and DNA; respiratory burst of PMNs.	OS underlies the pathogenesis of several chronic diseases associated with periodontal disease (PD), such as smoking and diabetes.	PD should be treated as an OS-related disease, involving the use of natural antioxidants.
2	Role of Oxidative Stress in Periodontal Diseases.	Patil RT et al., 2024	India	Review	Global periodontal health burden	Mechanisms of reactive oxygen species (ROS) generation; DNA damage.	OS triggers harmful reactions, exacerbating inflammation and bone resorption.	OS weakens antioxidant defenses and increases periodontal destruction.
3	Heme oxygenase-1: potential therapeutic targets for periodontitis.	Lv et al., 2024	China	Review	Global population with PD	Heme oxygenase-1 (HO-1), CO, Fe ²⁺ .	HO-1 exerts antioxidant and anti-inflammatory activities through heme degradation.	HO-1 induction reduces periodontal tissue destruction.
4	Mechanisms and therapeutic perspectives of mitochondrial dysfunction of macrophages in periodontitis.	Jia et al., 2025	China	Review	Macrophages in periodontitis	Mitochondrial ROS (mtROS), mitochondrial fission.	Increased mitochondrial fission produces excessive mtROS formation in macrophages.	Mitochondrial dysfunction in macrophages contributes to bone and tissue destruction.
5	Interactions Between Neutrophils and Periodontal Pathogens in Late-Onset Periodontitis.	Jiang et al., 2021	China	Review	Neutrophils in PD	Respiratory burst in neutrophils.	Hyperactive neutrophils release massive amounts of ROS in response to bacteria.	ROS have a dual effect, as they may aggravate periodontal inflammation through OS.
6	Effects of Hypoxic Environment on Periodontal Tissue through the ROS/TXNIP/NLRP3 Inflammasome Pathway.	Zhu et al., 2022	China	Experimental (in vivo and in vitro)	Rats and periodontal ligament cells	ROS/TXNIP/NLRP3 inflammasome signaling pathway.	Hypoxia induces excessive ROS production, activating the NLRP3 inflammasome and increasing IL-1 β .	Hypoxia-induced OS is a key mechanism linking a hypoxic environment to PD.
7	Diabetes mellitus promotes susceptibility to periodontitis—novel insight into the molecular mechanisms.	Zhao et al., 2023	China	Review	Diabetes mellitus models	AGE/RAGE, ROS, DNA damage.	Hyperglycemia amplifies OS by stimulating ROS production through advanced glycation end products (AGEs).	Prolonged OS damages telomeres in periodontal stem cells, impairing tissue repair.
8	Pathogenic Mechanisms That May Link Periodontal Disease and Type 2 Diabetes Mellitus—The Role of Oxidative Stress.	Mirnic et al., 2024	Serbia	Literature review	Patients with PD and T2DM	OS–inflammation interaction, 8-OHdG.	A synergistic interaction exists in which periodontal infection impairs glycemic control through OS.	Periodontal treatment reduces systemic OS markers, improving the metabolic status of diabetic patients.
9	The Role of Oxidative Stress in the Relationship Between Periodontitis and Alzheimer's Disease: A Review of the Literature.	Papadakis et al., 2025	Greece	Review	Animal and human models	Cerebral oxidative damage (MDA, 8-OHdG), systemic advanced oxidation protein products (AOPPs).	PD exacerbates cerebral oxidative damage and neuroinflammation, contributing to cognitive decline in Alzheimer's disease.	Improving periodontal health reduces systemic oxidative burden and the risk of neurodegeneration.
10	Meta-Analysis of Assessment of Total Oxidative Stress and Total Antioxidant	Mohideen et al., 2023	India	Systematic review and meta-analysis	Patients with PD and healthy controls	Total oxidative status (TOS) and total antioxidant capacity (TAC).	Patients with PD show significantly elevated TOS levels and reduced TAC levels in serum,	Redox imbalance is a useful biomarker for assessing PD progression and

No.	Title	Authors and Year	Country	Study Type	Population/Model	Oxidative Stress (OS) Biomarkers or Mechanism Evaluated	Main Findings	Periodontal Implications
	Capacity in Patients with Periodontitis.						saliva, and gingival crevicular fluid (GCF).	therapeutic efficacy.
11	Hyperglycemia Aggravates Periodontitis via Autophagy Impairment and ROS-Inflammasome-Mediated Macrophage Pyroptosis.	Zhao et al., 2023	China	Experimental (in vivo and in vitro)	Rats and macrophages	Macrophages, ROS, inflammasome-mediated pyroptosis.	Hyperglycemia impairs macrophage autophagy, exacerbating ROS production and pyroptosis.	Systemic OS caused by diabetes accelerates inflammatory aging in periodontal tissues.
12	The Effect of Melatonin on Periodontitis.	Konečná et al., 2021	Slovakia	Experimental (animal and clinical)	Rats and patients with PD	AGEs, advanced oxidation protein products (AOPPs), TAC.	Melatonin reduces bone loss and improves OS levels in saliva in animal models.	In humans, melatonin treatment did not show significant short-term clinical changes (2 weeks), suggesting the need for longer studies.
13	Oxidative Stress and FOXO-1 Relationship in Stage III Periodontitis.	Gurbuz et al., 2024	Turkey	Cross-sectional observational	Patients with Stage III periodontitis, Grades B and C	8-OHdG (DNA damage), transcription factor FOXO1.	8-OHdG levels are elevated and FOXO1 levels are reduced in the saliva of patients with advanced periodontitis.	Low FOXO1 expression, which is important for antioxidant enzymes, promotes tissue destruction in PD.
14	Patent Mining on the Use of Antioxidant Phytochemicals in the Technological Development for the Prevention and Treatment of Periodontitis.	Jos et al., 2024	Brazil	Review	Dental technological development	Free-radical neutralization, KEAP1-NRF2 pathway.	Growing interest in patents involving phytochemicals (vitamin C, quercetin, etc.) to neutralize OS in PD.	Adjunctive antioxidant therapies applied in gels or dentifrices improve the clinical response to conventional treatment.
15	Targeting Nrf2 with Probiotics and Postbiotics in the Treatment of Periodontitis.	Karaca et al., 2022	Finland	Literature review	Patients with suppressed immune responses	Nrf2 activation, cytotoxic respiratory burst.	Probiotics and postbiotics may activate antioxidant mechanisms through Nrf2 to suppress excessive OS.	Restoring impaired Nrf2 responses is a promising strategy for high-risk or treatment-resistant patients.
16	Modern views on the etiology and role of microbial persistence in the development of inflammatory processes in the periodontal complex (review).	Marfiian et al., 2024	Ukraine	Review	Periodontal complex	Free-radical oxidation, lipid and protein peroxidation.	OS and impairment of the antioxidant system are key pathogenic links that remain insufficiently studied.	Microbial persistence dysregulates local and systemic oxidative balance in generalized PD.
17	Salivary Redox Homeostasis in Human Health and Disease.	Čižmarová et al., 2022	Slovakia	Review	Human health and disease	MDA, 8-OHdG, SOD enzymes.	Saliva reflects local redox imbalance: increased MDA and 8-OHdG in patients with chronic periodontitis.	Periodontal treatment does not always significantly or immediately improve salivary OS levels.
18	Avoiding implant-related complications in medically compromised patients with or without unhealthy lifestyle / Elevated oxidative stress.	Guabello et al., 2023	Italy	Review	Systemically compromised patients, with or without harmful habits	ROS generated by friction and corrosion.	Implant placement inevitably generates ROS due to disruption of the titanium oxide layer.	Elevated OS in systemically compromised patients increases the risk of peri-implant complications.
19	Effect of Hesperidin on Barrier Function and Reactive Oxygen Species Production in an Oral	Maquera et al., 2023	Canada	Experimental (in vitro)	Oral epithelial cells and macrophages	ROS production by P. gingivalis, NF-κB activation.	Hesperidin reduces ROS production in stimulated epithelial cells and attenuates	The flavonoid hesperidin may act as an adjunctive agent by protecting

No.	Title	Authors and Year	Country	Study Type	Population/Model	Oxidative Stress (OS) Biomarkers or Mechanism Evaluated	Main Findings	Periodontal Implications
	Epithelial Cell Model, and on Secretion of Macrophage-Derived Inflammatory Mediators during Porphyromonas gingivalis Infection.						the secretion of pro-inflammatory cytokines.	the epithelial barrier against oxidative damage.
20	Reactive oxygen species can be traced locally and systemically in apical periodontitis: A systematic review.	Georgiou et al., 2021	Netherlands	Systematic review	Patients with apical periodontitis (AP)	MDA expression, serum antioxidants.	AP induces local ROS production and increases systemic OS in blood and saliva.	Nitric oxide plays a fundamental role in periapical bone resorption and lesion progression.
21	Research efficacy of gaseous ozone therapy as an adjuvant to periodontal treatment on oxidative stress mediators in patients with type 2 diabetes: a randomized clinical trial.	Rapone et al., 2023	Italy	Randomized clinical trial	Diabetic patients with moderate or severe PD	TOS, TAS, GSH, plasma MDA.	Gaseous ozone treatment as an adjunct to mechanical therapy improved clinical parameters but did not significantly improve plasma OS markers.	Although ozone is theoretically a potent antioxidant, clinical evidence still requires further standardized research in diabetic patients.
22	Influence of Reactive Oxygen Species on Wound Healing and Tissue Regeneration in Periodontal and Peri-Implant Tissues in Diabetic Patients.	Buranasin et al., 2023	Thailand	Review	Diabetic patients with PD	ROS-induced insulin resistance, Akt activation.	Excess ROS damages proteoglycans and collagen, impairing healing in diabetic patients.	Antioxidants may improve tissue regeneration impaired by hyperglycemic conditions.
23	Ferroptosis: A New Development Trend in Periodontitis.	Chen et al., 2023	China	Review	Basic medical research	Ferroptosis, iron overload, lipid peroxidation (MDA).	The development of PD is accompanied by iron overload and glutathione (GSH) depletion, suggesting the presence of ferroptosis.	Ferroptosis acts as a novel mechanism of oxidative cell death and tissue damage in the periodontium.
24	Mitochondrial function in oral health and disease.	Ramos et al., 2022	United States	Review	Mitochondrial proteomics and metabolomics	Dysfunction of oxidative phosphorylation (OXPHOS).	PD is an inflammatory disease of the attachment apparatus associated with excessive ROS production.	Periodontal health strongly depends on mitochondrial homeostasis in host cells.
25	The role of Mitofusin-1 and Mitofusin-2 in periodontal disease: a comprehensive review.	Varma et al., 2025	United Arab Emirates	Review	Periodontal tissue homeostasis	Mitochondrial integrity, MFN1 and MFN2, mitochondrial fusion.	Reduced MFN1 and MFN2 levels correlate with increased OS, inflammation, and mitochondrial fragmentation.	Targeting mitofusins therapeutically may improve regeneration and management of PD.
26	Mitochondrial Dysfunction in the Pathogenesis and Treatment of Oral Inflammatory Diseases.	Dong et al., 2023	China	Review	Oral inflammatory diseases	Mitochondrial membrane potential, OPA1 cleavage, mtROS.	Mitochondrial dysfunction contributes to PD by affecting OS and regulating the inflammatory response.	Strategies aimed at restoring mitochondrial function reduce osteoblast apoptosis.
27	Ferroptosis and cuproptosis in periodontitis: recent biological insights and therapeutic advances.	Zheng et al., 2025	China	Systematic review	Synthesis of findings	Ferroptosis and cuproptosis, GSH pathway, copper/iron imbalance.	Pathogen-driven metal homeostasis imbalance increases periodontal OS.	OS is a unifying mechanism linking ferroptosis and cuproptosis in periodontal destruction.
28	Molecular hydrogen: Mechanism against oxidative stress and application in periodontitis: A review.	Ying et al., 2025	China	Literature review	Periodontal treatment	Selective scavenging of hydroxyl radicals and peroxynitrite; Nrf2 pathway.	Molecular hydrogen acts as a potent antioxidant by reducing excessive ROS levels.	Its application before, during, and after periodontal surgery helps

No.	Title	Authors and Year	Country	Study Type	Population/Model	Oxidative Stress (OS) Biomarkers or Mechanism Evaluated	Main Findings	Periodontal Implications
29	Hyperhomocysteinaemia aggravates periodontitis by suppressing the Nrf2/HO-1 signalling pathway.	Yang et al., 2025	China	Literature review	Periodontal and systemic health	Nrf2 pathway, 8-OHdG levels, ROS.	Hyperhomocysteinemia inhibits Nrf2 translocation, increasing oxidative damage (8-OHdG).	restore redox balance. Elevated homocysteine levels act as a contributing factor to periodontal bone loss through OS.
30	The Periodontal–Cardiovascular Disease Association: Molecular Mechanisms and Clinical Implications.	Ferrara et al., 2025	Italy	Review	Patients with PD and cardiac risk	NOX2 activation, peroxynitrite, NO bioavailability.	NOX2-mediated OS increases superoxide production, reducing NO and causing endothelial dysfunction.	The molecular link between PD and cardiovascular disease is based on the systemic propagation of oxidative and pro-inflammatory mediators.
31	Hypochlorous acid solution serves as a potential anti-biofilm therapy for periodontitis via targeting quorum sensing of periodontal pathogens.	Lv et al., 2025	China	Experimental (in vitro and in vivo)	Periodontal biofilm	Hypochlorous acid (HOCl), bacterial oxidative stress.	The imbalance between bacterial plaque and host defense generates toxic products and OS.	Bacterial resistance to OS perpetuates periodontal infection.

Source: own elaboration.

LITERATURE REVIEW

Periodontal Diseases and Oral Microbiota:

Periodontal disease (PD) affects 10% to 15% of the population^{1,3}, although up to 90% of individuals have experienced some manifestation of the disease^{8,14}. It is characterized by chronic inflammation and progressive destruction of the tooth-supporting tissues, and its primary etiology is associated with microorganisms present in dental plaque; however, its progression and severity depend on the host's immunoinflammatory response^{15–18}.

The accumulation of dysbiotic biofilms, with a predominance of pathogens belonging to the “red complex” (*Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*) and *Aggregatibacter actinomycetemcomitans*, initiates the process^{16,19}. However, tissue destruction results from the host response and the underlying redox imbalance. Therefore, PD is a dysbiotic condition in which the microbial community becomes imbalanced and potentiates inflammation^{2,5,14}.

Oxidative Stress and Reactive Oxygen Species:

Free radicals are chemical species with unpaired electrons that participate in metabolic processes, cellular signaling, and defense responses when maintained at controlled levels^{8,17,20,21}. However, their high reactivity represents a risk to cellular integrity if their production is not adequately regulated⁸. To counteract their harmful effects, cells possess antioxidant systems that preserve redox balance, the dynamic equilibrium between free radicals and the body's capacity to neutralize them^{2,17}, thereby preventing or delaying structural and functional damage to essential biomolecules^{2,17}.

OS occurs when there is an imbalance between the production of oxidizing agents and antioxidant capacity^{9,17,18}, a situation in which regulatory mechanisms become insufficient to maintain homeostasis due to excessive free radical production^{8,17,20}. Consequently, cellular damage is triggered through the oxidation of lipids, proteins, and nucleic acids, altering cellular function and promoting the development of pathological processes⁸. Therefore, OS has been implicated in various chronic diseases, including periodontitis^{16,17,20}.

Reactive Oxygen Species:

Exogenous and Endogenous Sources:

ROS are highly reactive by-products of aerobic metabolism, originating from approximately 5% of the oxygen consumed by cells². They may originate from exogenous sources (radiation, cigarette smoke, intense exercise, and tissue injury) or endogenous sources (by-products of metabolic pathways, immune cell activity, and connective tissue processes)^{2,17,18}. When their production exceeds cellular regulation, they become central mediators of oxidative imbalance and inflammatory tissue damage^{1,13,17,22}.

ROS Production in Periodontal Disease:

Neutrophils:

Polymorphonuclear neutrophils (PMNs) are the primary source of ROS in PD^{1,2,15,23}, accounting for 50% to 60% of immune cells in the gingival sulcus and periodontal tissues under inflammatory conditions^{1,2,5,22}. Although they maintain homeostasis under healthy conditions, bacterial stimulation induces a hyperactive phenotype⁵. This bactericidal increase in ROS generates a collateral cytotoxic effect that promotes tissue deterioration and bone loss^{1,5,12,14,22}.

Respiratory Burst:

PMNs and macrophages generate massive amounts of ROS through the respiratory burst, a process dependent on the NADPH oxidase enzyme complex^{5,8}. Its excessive or prolonged activation extends oxidative damage to the surrounding periodontal tissues⁵.

Mitochondrial ROS Production:

Aerobic Metabolism:

During oxidative phosphorylation, electron leakage reduces O₂ to the superoxide anion (O₂⁻), which subsequently gives rise to hydrogen peroxide (H₂O₂) and the hydroxyl radical (·OH)^{2,11,24}.

Mitochondrial Dysfunction:

Alteration of quality-control mechanisms such as mitophagy, which is common under conditions of hyperglycemia, prevents the elimination of damaged mitochondria, resulting in sustained elevation of ROS^{11,24-26}. This is compounded by local hypoxia, infection with *P. gingivalis*^{6,19}, and ferroptosis, which depletes antioxidant capacity and intensifies the inflammatory process^{23,27}.

Oxidative Stress in Periodontal Disease:

OS acts as a link between the inflammatory response and tissue destruction^{13,22}. In periodontitis, an increase in local ROS is observed together with depletion of antioxidant systems^{3,10,17,22}, establishing OS as a key etiopathogenic factor in this disease^{1,2,18} (Table 2).

Molecular Mechanisms of Periodontal Damage:

Excessively generated ROS trigger harmful reactions that affect fundamental biological components, compromising the structural and functional integrity of periodontal tissues^{2,3,17}:

Lipid Peroxidation (LPO):

The attack on polyunsaturated fatty acids in cell membranes produces lipid hydroperoxides and reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). In addition, LPO promotes the production of prostaglandin E₂ (PGE₂), a mediator involved in bone resorption, thereby contributing to alveolar bone loss in periodontitis^{2,3}.

Protein Damage:

Oxidation of carbon double bonds and side chains induces the formation of protein carbonyls, altering essential cellular processes such as migration, proliferation, and maintenance of periodontal tissues^{1,2,18,22}.

DNA Damage:

Radicals such as ·OH and peroxynitrite induce strand breaks and the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG)². These genetic lesions may result in insertions, deletions, sequence amplification, and DNA strand breaks, affecting genomic stability and cellular viability in periodontal tissues^{2,3,17}.

Role of Oxidative Stress in the Progression of Periodontal Disease:

Alteration of Periodontal Cell Function:

OS directly compromises cellular physiology by inhibiting the migration and proliferation of gingival fibroblasts and periodontal ligament cells, which are essential for tissue maintenance and repair^{13,18,26}. Furthermore, ROS overproduction induces apoptosis in these cells, limiting the regenerative capacity of the periodontium and accelerating the progressive degradation of the extracellular matrix^{2,22}.

Amplification of the Inflammatory Response:

ROS modulate the inflammatory response by activating redox-sensitive transcription factors, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs)^{2,28}. This signaling triggers the massive release of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α)^{2-4,8}, which, in turn, stimulates further ROS production by immune cells, establishing a self-sustaining interaction between inflammation and oxidative damage².

Imbalance in Bone Remodeling:

At the bone level, OS alters the regulatory RANKL/osteoprotegerin (OPG) axis¹⁴. RANKL overexpression stimulates osteoclast differentiation and activation, while oxidative damage induces dysfunction and apoptosis of osteoblasts^{5,7}. As a result, an imbalance favoring alveolar bone resorption occurs, accelerating the bone loss characteristic of PD^{3,4,7,22}.

Perpetuation of Tissue Damage:

A persistent oxidative microenvironment promotes the activation of matrix metalloproteinases (MMP-8 and MMP-9), enzymes responsible for degrading collagen and the extracellular matrix of the attachment apparatus^{1,3,4,20}. The sustained activity of these proteases contributes to progressive tissue destruction and perpetuates the progression of PD^{20,29}.

Table 2: Biomarkers of oxidative damage in periodontal disease.

Marker	Type of Damage	Finding in PD	Periodontal Implication
Reactive oxygen species (ROS)	General process of OS and cellular signaling ^{1,2} .	Massive overproduction, mainly by hyperactive PMNs ^{2,5} .	Direct damage to macromolecules ^{2,8} . Enhancement of bone resorption ^{2,7,22} .
Malondialdehyde (MDA)	Lipid peroxidation (LPO) ² .	Significantly elevated levels in saliva, gingival crevicular fluid (GCF), and serum ^{3,14,30} .	Positive correlation with probing depth and severity of periodontal destruction ^{2,12,18} .
Protein carbonyls	Oxidative damage to proteins ^{1,18,22} .	Significantly higher levels in patients with PD ^{1,22,30} .	Positive correlation with advanced clinical attachment loss and collagen degradation ^{1,22} .
8-OHdG	Oxidative DNA damage ² .	Increased levels in saliva and GCF of patients with periodontitis ^{3,7,22} .	Promotes apoptosis of osteoblasts and fibroblasts ^{3,13,30} . Positive correlation with disease severity ^{3,13,18,22} .
Total oxidative status (TOS)	Global measure of the total oxidant burden in a given environment ^{10,21} .	Significant increase in serum, GCF, and saliva of affected patients ^{10,21} .	Reflects the magnitude of local and systemic oxidative burden and the status of disease activity ^{1,10} .
Total antioxidant capacity (TAC)	Status of total antioxidant defenses ^{10,18,21} .	Decreased levels in saliva, GCF, and serum, indicating depletion of the defense system ^{3,10,21,22} .	An imbalance favoring oxidation predisposes to progressive degradation of supporting tissues ^{10,22} .

Source: own elaboration.

Systemic Factors Associated with Oxidative Stress:

Various systemic conditions exacerbate oxidative stress (OS) and promote the progression of periodontitis by intensifying the host's inflammatory and oxidative response^{1,10,26,30}. This interaction highlights the bidirectional nature of periodontitis with multiple systemic diseases²⁷. The main mechanisms involved in this interaction are summarized in Table 3.

Diabetes Mellitus:

Diabetes mellitus, a metabolic disorder characterized by persistent hyperglycemia, maintains a close bidirectional relationship with periodontitis and is the sixth most common complication in patients with diabetes^{1,7,8}. Chronic hyperglycemia increases ROS production at the periodontal level, promoting osteoblast apoptosis, osteoclast activation, and alveolar bone loss^{1,7,18,22}. Likewise, the accumulation of advanced glycation end products (AGEs) and their binding to the receptor for advanced glycation end products (RAGE) activates the NF-κB pathway in macrophages and endothelial cells, amplifying the release of ROS and pro-inflammatory cytokines^{1,8,18,22}. This is accompanied by PMN dysfunction and a hyperinflammatory state that accelerates tissue destruction⁷.

Smoking:

Tobacco consumption exacerbates periodontal OS, increasing the risk and severity of periodontitis^{1,18}. Although nicotine causes vasoconstriction, thereby reducing bleeding on probing and masking active inflammation, it promotes a dysfunctional immune response characterized by PMN hyperactivation and ROS overproduction¹. At the bone level, it alters the RANKL/OPG axis by reducing OPG and increasing the RANKL/OPG ratio, thereby stimulating osteoclastogenesis and alveolar bone loss^{1,18}. In addition, hydrocarbons in tobacco smoke activate the aryl hydrocarbon receptor, stimulating osteoclastic differentiation, while nicotine increases ROS generation in gingival fibroblasts and decreases local antioxidant capacity in a dose-dependent manner^{1,18}.

Hyperhomocysteinemia:

Hyperhomocysteinemia (HHcy), characterized by elevated concentrations of homocysteine in the blood, is associated with endothelial dysfunction, chronic inflammation, and increased OS²⁹.

HHcy promotes OS by increasing ROS accumulation, enhancing the expression of pro-inflammatory mediators, and suppressing the body's antioxidant defenses. In patients with periodontitis and HHcy, greater clinical attachment loss and bone resorption have been observed, accompanied by increased local and systemic inflammation, suggesting a synergistic effect between both conditions²⁹.

This phenomenon is explained, in part, by the fact that elevated homocysteine concentrations inhibit the Nrf2/HO-1 signaling pathway, the principal cellular antioxidant defense mechanism. Alteration of this pathway promotes increased ROS production and osteoclastogenesis in periodontitis^{28,29}.

Table 3: Systemic diseases associated with oxidative stress and their periodontal effects.

Systemic Disease	Mechanism Related to OS	Periodontal Effects
Diabetes mellitus	Hyperglycemia with increased ROS ^{1, 7, 18, 22} , activation of NF-κB ^{1, 18, 22} , PMN dysfunction, and a persistent state of hyperinflammation ⁷ .	Intensification of the periodontal inflammatory response, increased osteoblast apoptosis, osteoclast activation, and greater alveolar bone loss ^{7, 22} .
Smoking	Increased total oxidant status induced by components of tobacco smoke ^{1, 18} ; ROS overproduction by hyperactivated PMNs; reduction in total antioxidant capacity; alteration of the RANK/RANKL/OPG system ¹ .	Increased osteoclastogenesis and alveolar bone loss; local immune dysfunction; accelerated progression of periodontal destruction with less clinical expression of inflammation ^{1, 18} .
Hyperhomocysteinemia	Elevated ROS, suppression of antioxidant defenses; inhibition of the Nrf2/HO-1 pathway; endothelial dysfunction and chronic systemic inflammation ²⁹ .	Greater clinical attachment loss and alveolar bone resorption; increased periodontal tissue damage due to a synergistic effect between OS and inflammation ²⁹ .

Source: own elaboration.

Therapeutic Strategies Related to Oxidative Stress:

Non-surgical periodontal therapy has demonstrated a positive impact on redox balance, as evidenced by a reduction in oxidative stress (OS) markers and an increase in total antioxidant capacity, confirming that biochemical parameters reflect periodontal status and the response to treatment^{1, 10, 17}. However, in addition to the conventional approach, various studies^{3, 7, 14} have proposed the use of adjunctive therapeutic strategies aimed at modulating OS, including antioxidant supplementation^{7, 14} and the development of emerging therapies^{19, 28, 31}, which have shown promising results for the treatment of periodontitis.

Antioxidants in Periodontal Therapy:

Pharmacological and natural antioxidants have demonstrated considerable potential as adjunctive therapies in the treatment of periodontitis by counteracting OS and modulating the inflammatory response^{1, 4, 22}. Drugs such as metformin, in addition to their antihyperglycemic effect, promote gingival healing and angiogenesis³. Similarly, natural compounds such as vitamin C, quercetin, resveratrol, and coenzyme Q10 have demonstrated antioxidant and anti-inflammatory effects in the periodontal context^{4, 7, 14, 22}. The main agents evaluated and their clinical evidence are summarized in Table 4.

Table 4: Antioxidants evaluated as adjuncts in periodontal therapy.

Agent	Type	Suggested Use	Mechanism Related to OS	Evidence in PD
Metformin	Pharmacological	Commonly used in type 2 diabetes mellitus ³ . Its potential cytoprotective effect is under investigation ³ .	Reduces intracellular levels of free radicals ³ . Modulation of OS and improvement of tissue response, promoting healing and angiogenesis ³ .	Improves healing and periodontal parameters ³ .
Vitamin C	Natural (vitamin)	500–2000 mg/day as an adjunct to scaling and root planing ^{14, 22} . Local application in gel ⁷ .	Potent ROS scavenger and prevents endothelial dysfunction ¹⁴ . Neutralization of ROS and attenuation of inflammatory pathways ¹⁴ .	Reduction of periodontal inflammation ¹⁴ . Improvements in periodontal parameters ^{14, 22} .
Quercetin	Natural (flavonoid)	Natural extracts or incorporation into membranes for tissue regeneration ¹⁴ .	Activation of Nrf2, increasing cellular antioxidant capacity; inhibition of macrophages ¹⁴ . Stimulates the expression of endogenous antioxidant enzymes ¹⁴ .	Prevents oxidative damage in periodontal ligament cells ¹⁴ . Reduces alveolar bone loss (animal models) ^{14, 27} .
Resveratrol	Natural (polyphenol)	Oral administration: 500 mg/day (effective high dose) ¹⁴ .	Nrf2 activation ^{1, 4} ; reduction of pro-inflammatory cytokines ¹⁴ . Direct action against ROS overproduction ^{1, 4} .	Improves clinical attachment level, probing depth, and bleeding index ¹⁴ . Prevents disease progression and bone loss (animal models) ^{1, 22} .
Coenzyme Q10 (CoQ10)	Natural (endogenous)	Topical application in gel ⁴ .	Protects mitochondria, proteins, and DNA against oxidative damage ⁴ . Reduces inflammation activation induced by OS ⁴ .	Effective in improving gingival index, probing depth, and clinical attachment level ⁴ . Inhibits bone loss ⁴ . CoQ10 levels are reduced in 80% of patients with periodontitis ⁴ .

Source: Own elaboration.

Emerging Therapies:

Innovative strategies, such as the use of molecular hydrogen²⁸, postbiotics¹⁵, flavonoids¹⁴, nanomaterials¹⁴, and local delivery systems²⁶, represent promising approaches for modulating OS and improving therapeutic efficacy in PD^{4,22}. Likewise, some therapies seek to act directly on the biofilm through controlled oxidative mechanisms, offering new alternatives as adjunctive treatments^{2,13,14}. The main emerging strategies aimed at modulating OS are detailed in Table 5.

Table 5. Emerging Strategies Targeting Oxidative Stress in Periodontal Therapy

Strategy	Approach	Suggested Use	Relationship with OS	Periodontal Effects	Status
Molecular hydrogen (H₂)	Selective antioxidant ²⁸ .	Consumption of hydrogen-rich water ²⁸ . Mouthwash for disinfection ²⁸ . Inhalation or local injection ²⁸ .	Neutralizes ·OH ²⁸ . Activates Nrf2 and inhibits MAPK and NF-κB pathways ²⁸ .	Reduces osteoclast differentiation and DNA damage ²⁸ . Improves probing depth and clinical attachment level ²⁸ .	Experimental.
Postbiotics	Host modulation ¹⁵ .	Local administration or administration of bacterial metabolites ¹⁵ .	Activation of the Nrf2 pathway ¹⁵ . Reduces intracellular ROS levels ¹⁵ .	Reduces inflammatory burden and oxidative damage ¹⁵ . May prevent recurrence in susceptible patients ¹⁵ .	Experimental.
Flavonoids (hesperidin)	Anti-inflammatory ¹⁹ .	Slow-release gels or oral hygiene products ¹⁹ .	Inhibition of P. gingivalis-mediated ROS production ¹⁹ . Inhibition of the NF-κB pathway ¹⁹ .	Protects the integrity of the gingival epithelial barrier ¹⁹ . Reduces secretion of proinflammatory cytokines and MMPs ¹⁹ .	Preclinical.
Nanomaterials	Local delivery ^{4,26} .	Locally administered nanoparticles in periodontal pockets ^{4,26} .	Eliminate ROS at sites with elevated OS ^{4,26} . Enable greater antioxidant bioavailability ^{4,26} .	Improve osteogenic differentiation capacity in stem cells ^{4,26} . Restore mitochondrial function and promote tissue repair ^{4,26} .	Experimental.
Hypochlorous acid	Controlled oxidant ³¹ .	Solution (100 mg/L) for periodontal irrigation.	Targeted production of OS against biofilm ³¹ .	Effective biofilm destruction ³¹ . Significant reduction in bone resorption and inflammation ³¹ . High biocompatibility with host cells ³¹ .	Experimental/Adjunctive.

Source: Own elaboration.

DISCUSSION

Overall, the reviewed evidence confirms that oxidative stress (OS) constitutes a relevant component of the pathogenesis of periodontal disease (PD); however, its interpretation varies according to the study approach. Whereas Zhao et al.⁷ and Mirnic et al.⁸ position OS as a central axis capable of integrating systemic factors, Jia et al.⁴ and Marfian et al.¹⁶ analyze it as a phenomenon secondary to bacterial dysbiosis. The findings of the present analysis indicate that there is no definitive consensus as to whether OS acts as an initiator of tissue damage or as an amplifier of a previously dysregulated inflammatory response.

One of the main discrepancies identified concerns the nature of redox imbalance. Sczepanik et al.¹ and Georgiou et al.²⁰ raise a fundamental question regarding whether decreased total antioxidant capacity (TAC) in gingival crevicular fluid (GCF) is a cause or a consequence of inflammation. On the one hand, some studies, such as those by Guabello et al.¹⁸ and Patil et al.², argue that OS acts as an active mediator by enhancing proinflammatory cytokines and promoting tissue destruction; on the other hand, Karaca et al.¹⁵ reported that oxidative damage is an inevitable consequence of neutrophil hyperactivity in response to the biofilm. This distinction is critical because it determines whether the therapeutic approach should focus on eliminating the bacterial stimulus or additionally modulating the redox environment.

Regarding biomarkers, although the meta-analysis conducted by Mohideen et al.¹⁰ reported a consistent increase in oxidative damage markers in patients with periodontitis, their diagnostic utility remains limited when different biological matrices are compared. This is attributable to notable discrepancies concerning whether saliva accurately reflects the processes occurring in GCF: whereas Guabello et al.¹⁸ and Lv et al.³ found a direct correlation with clinical severity, Papadakis et al.⁹ warned that exposure of the oral cavity to environmental factors, such as tobacco and diet, destabilizes the local redox balance and reduces the diagnostic utility of these biomarkers.

Nevertheless, the measurement of these OS markers cannot currently be recommended for routine clinical practice because of the lack of methodological standardization and defined reference values. Furthermore, a relevant methodological aspect identified in this review is the predominance of narrative and experimental studies, together with the scarcity of clinical trials and longitudinal studies. This distribution indicates that, although the role of OS in PD is broadly supported, its clinical validation and diagnostic applicability still require stronger scientific evidence.

Another factor complicating the interpretation of OS is the adaptive capacity of certain periodontopathogens to oxidative environments. In the review by Jiang et al.⁵, it was established that species such as *P. gingivalis* express antioxidant enzymes that neutralize reactive oxygen species (ROS) and promote their survival in an inflammatory environment. This suggests that OS is not merely a consequence of the host response, but also a dynamic component of the interaction with microorganisms that contributes to bacterial persistence and maintenance of the inflammatory process.

On the other hand, an important aspect identified in the literature is the difference in OS levels between systemically healthy patients and those with associated systemic diseases. Studies such as those by Sczepanik et al.¹ and Guabello et al.¹⁸ indicate that conditions such as diabetes mellitus and smoking may intensify the host oxidative state, promoting a more pronounced inflammatory response and greater periodontal destruction. In these patients, increased ROS production has been observed, together with reduced antioxidant defenses, generating a tissue environment that is more susceptible to oxidative damage and disease progression. Similarly, Zhao et al.⁷ and Buranasin et al.²² show that systemically healthy individuals appear to have a more regulated oxidative response, which could explain a slower progression of periodontal damage. This reinforces the concept that OS does not act in isolation but may be significantly modulated by the patient's systemic status.

Regarding PD progression following conventional treatment, sustained activation of pathways such as nuclear factor kappa B (NF- κ B) could perpetuate an inflammatory state that is partially independent of the initial bacterial stimulus. A difference in clinical interpretation arises here: some authors, such as Lv et al.³ and Jia et al.⁴, maintain that scaling and root planing is sufficient to restore the local oxidative balance, whereas more recent research, such as that by Zhao et al.¹¹, suggests that in patients with a high oxidative burden or systemic comorbidities, conventional therapy does not always completely restore tissue homeostasis. This could explain why mechanical treatments are unsuccessful at certain sites, as OS may create a microenvironment that favors chronicity and limits inflammatory resolution.

Likewise, a gap persists between experimental evidence and clinical outcomes in the therapeutic field. According to Sczepanik et al.¹, resveratrol has demonstrated potent inhibitory effects on bone damage in animal models; however, clinical trials in humans have yielded inconsistent results, according to Buranasin et al.²². Furthermore, although studies such as that by Jos et al.¹⁴ have reported additional benefits from the use of adjunctive antioxidants, others, such as Sczepanik et al.¹, have found no significant advantages from adding supplemental doses of vitamin C to conventional therapy. Consequently, current evidence does not support the routine use of antioxidants as standard therapy in periodontics, although they may be considered adjunctive strategies in specific clinical contexts.

Finally, a potential transition is suggested from an approach focused exclusively on infection control toward a more individualized view of the disease. The current debate is oriented toward understanding each patient's oxidative profile and how it influences disease progression and treatment response. Research into regulatory pathways such as Nrf2/HO-1, as described by Lv et al.³, opens new perspectives for the development of more specific therapeutic strategies. However, the available clinical evidence remains limited for the routine translation of these advances into clinical practice.

Despite the findings described above, the present literature review has certain limitations that should be considered when interpreting its results. First, the search was restricted to articles published exclusively in English within a specific time range (2020–2025), which may have resulted in the omission of relevant evidence published in other languages or seminal studies conducted before this period. In addition, there is considerable heterogeneity in the methodologies used by the included studies, ranging from animal models and *in vitro* cell cultures to clinical trials with diverse diagnostic criteria for periodontitis and different methods for measuring oxidative stress markers, which makes direct comparison between findings difficult. Finally, the possibility of publication bias must be acknowledged, as studies reporting statistically significant results tend to be published more frequently than those with null or non-significant findings.

CONCLUSIONS

Oxidative stress plays a relevant role in the etiopathogenesis of periodontal disease by contributing to the amplification of the inflammatory response and the progressive destruction of the tooth-supporting tissues. However, current evidence does not allow a clear determination of whether OS acts as an initiating factor in tissue damage or as a consequence of a previously established inflammatory process.

On the other hand, oxidative damage biomarkers are associated with disease severity; however, their diagnostic use is limited by methodological heterogeneity, variability among biological matrices, and the absence of standardized reference values.

Finally, conventional periodontal therapy contributes to improving the local redox balance, but the available evidence does not support the routine use of antioxidants as part of standard treatment. Although they represent a promising alternative in specific contexts, clinical studies are required to establish their actual efficacy and to define their clinical indications more precisely.

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“Conceptualization and design: María Carrasco, Carlos Naula; Literature review: María Carrasco, Carlos Naula; Methodology and validation: María Carrasco, Carlos Naula; Formal analysis: María Carrasco, Carlos Naula; Investigation and data collection: María Carrasco, Carlos Naula; Resources: María Carrasco, Carlos Naula; Data analysis and interpretation: María Carrasco, Carlos Naula; Writing – original draft preparation: María Carrasco, Carlos Naula; Writing – review and editing: María Carrasco, Carlos Naula; Supervision: María Carrasco, Carlos Naula; Project administration: María Carrasco, Carlos Naula; Funding acquisition: Not applicable.”

CONFLICTS OF INTEREST

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