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The Role of Oxidative Stress in Periodontitis

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ABSTRACT

Periodontitis and noncommunicable diseases share an overall inflammatory state often sustained by concomitant oxidative stress as one of the main processes involved. A huge amount of literature supports such a main pathogenic process, which is also considered the therapeutic target. The attempt to control inflammation by acting on oxidative stress has given largely unsatisfactory results, either as preventive or as treatment approaches. To propose new ideas that will help in this field, the paper reviewed all physiological processes involved in oxidative stress in periodontitis. The discussion considers all of them, considering whether they come from endogenous sources, that is, all the intracellular physiological devices and/or processes that are involved in oxidative stress, such as mitochondria, rough endoplasmic reticulum, peroxisomes, autophagy, and aging, or from exogenous sources, that is, the external factors that affect oxidative stress, such as nutrition, physical activity, psychological status, environmental conditions, microbiome, and drugs. The most important conclusion is that all of them should be taken into consideration in future research since we need to address oxidative stress as part of a specific biological and metabolic cellular state in a multicellular organism. To understand the cellular physiology that underlies oxidative stress and consider this point in treating each of our periodontal patients according to a specific oxidative state could be called personalized/precise oxidative stress therapy (POST) and should include the following points: (1) environmental conditions, (2) individual characteristics, and (3) oxidative state of different intracellular organelles.

1 | Introduction

The pathogenesis of periodontitis presents more questions than certainties. The main role of bacteria, and the concept of dysbiosis as an imbalance or disruption of the oral bacterial community, are well established. However, the above cannot thoroughly explain all the aspects. Bacterial infection produces a reaction in all multicellular organisms, which is a defense mechanism: inflammation. It tries to eliminate the bacteria, isolate the damaged tissue, and recover with tissue regeneration. Inflammation involves multiple metabolic and molecular mechanisms that depend on the characteristics and systemic health of the host organisms. When this reaction is exacerbated or reduced, many diseases can occur. Systemic inflammation is the main mechanism behind disease onset, such as cardiovascular diseases, Type 2 diabetes, cancers, and periodontitis among others. All these diseases are grouped in the so-called noncommunicable diseases that kill 41 million people each year, equivalent to 74% of all deaths globally [1].

One of the main processes, giving rise to inflammation, involved in all these diseases is oxidative stress (OS).

A huge amount of literature deals with OS as a main pathogenic process and therapeutic target for all inflammatory diseases and, of course, for periodontitis. The results behind the effort to

Summary

- Oxidative stress involves multiple processes that should be known and considered as part of a therapeutic strategy.

control inflammation have been largely unsuccessful either as a preventive or a curative measure. The reason is that we need to know what is behind the concept of OS and the relationship with cellular physiology. According to the National Cancer Institute [2] OS is defined as: "A condition that may occur when there are too many unstable molecules called free radicals (FR) in the body and not enough antioxidants to get rid of them. This can lead to cell and tissue damage." This concept includes an equilibrium between the production of FR, but also reactive oxygen/nitrogen species (ROS/RNS) and the presence of antioxidant mechanisms that try to control it.

FR, ROS, and RNS can damage molecular cellular components. To counteract this action, antioxidants are involved. Antioxidants are any substance that significantly delays or prevents oxidation of the substrate. Three kinds of antioxidants exist: (i) preventive antioxidants, (ii) radical scavengers, (iii) repair and de novo enzymes [3]. Redox processes take place in all bioenergetics processes, metabolism and life functions: they are involved in pH control, phosphorylation–dephosphorylation reaction, acetylation/deacetylation, and in methylation/demethylation, as well as in central mechanisms for controlling the genome and epigenome [4].

Oxygen, the most successful oxidative molecules, is used in all aerobic organisms to produce energy with the oxidation of nutrients rich in carbon and hydrogen. In contrast, an anaerobic organism does not require oxygen; cellular respiration utilizes electron acceptors such as inorganic compounds (e.g., hydrogen gas, hydrogen sulfide) or ferrous ions as a source of energy. The first form of life, known as the last universal common ancestor (LUCA), is the node on the tree of life where the different domains of life diverge. Through phylogenetic reconciliation methods, LUCA has been demonstrated to be a prokaryote-grade anaerobic acetogen that possessed an early immune system and used ATP as a common energy currency [5]. It is thought that it appeared in the absence of light and oxygen in the hydrothermal vents of the sea floor. Lately, this way of anaerobic living started to produce oxygen that is toxic, but some bacteria used it due to a most efficient way to produce energy. Anaerobic metabolism produces four ATP molecules from one glucose molecule, and aerobic metabolism produces 34 ATP molecules. This energy production takes place with five groups of proteins that constitute the electron transport chain embedded in the inner mitochondrial membrane. A transfer of electrons from electron donors to electron acceptors via redox reaction takes place together with a concomitant translocation against the gradient of protons (H+, hydrogen ions) across the membrane and couples the following phenomenon of gradient dissipation through ATPase to produce ATP from ADP.

However, cells use this oxidative reaction not only to produce energy but also as a defense mechanism. Bacteria, mainly in the endocytosis process, are engulfed by the plasma membrane and give rise to phagosomes that are linked to the lysosome and degraded. It takes place mainly in neutrophils and macrophages. These lysosomes contain many hydrolytic enzymes: proteases, nucleases, and phosphatases with their maximum enzymatic activity at a low pH ($pH \leq 5$) that degrades bacteria [6]. The initial product of NADPH oxidase that causes this respiratory burst in leukocytes is superoxide, which is released by the oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). ROS production is part of the neutrophil defense mechanism, and its hyperresponsiveness is related to periodontitis [7].

Cells not only use this degradation process as a defense device against bacteria but also to control dysfunctional cellular components by degrading them in a process called autophagy. In addition, some oxidants can act as a redox second messenger in redox biology and as a signal for gene expression. For instance, hydrogen peroxide (H_2O_2), an uncharged oxidant molecule, is well suited for redox sensing and redox signaling [8], reactive sulfide species are prevalent in intracellular redox signaling [9], and nitric oxide, a gaseous signaling molecule, is a key regulator of cardiovascular function [10] (Box 1).

Many papers, including systematic reviews and meta-analyses, have studied the role of oxidative stress in the pathogenesis of inflammatory diseases and the treatment of periodontitis, suggesting sometimes treating periodontitis as an inflammatory disease with oxidative stress as the target and using, for example, resveratrol and curcumin as therapeutic antioxidant agents in conjunction with conventional therapies [11]. However, scientific research has not yet been able to implement any type of antioxidant treatment in periodontal therapy. In our opinion, a new approach is needed. The administration of an antioxidant cannot be based on the same principle as the administration of a vitamin, enzyme, or hormone when these are lacking in the body. It is known that in certain diseases caused by their deficiency, the administration of these products achieves a cure.

The objective of this narrative review was to highlight the cellular mechanisms that underlie these aspects and could provide clues that may inform future research. Oxidative stress is a balance derived from aerobic metabolism, which is part of cellular homeostasis. If an excessive number of antioxidants are provided, their action can interfere with energy production or defense mechanisms or signaling. Redox processes depend on the type of

BOX 1 | Oxidative stress.

- Oxidative stress can occur when there are too many unstable molecules called free radicals (FR) in the body and not enough antioxidants to eliminate them [2].
- Antioxidants are any substance that significantly delays or prevents oxidation of the substrate [3].
- Redox processes take place in all bioenergetic processes, metabolism, and life functions [4].
- The oxidative reaction produces energy, is part of the defense mechanism, and is involved in the degradation process [6].

BOX 2 | Endogenous and exogenous oxidative sources.

Endogenous sources	Exogenous sources
• Mitochondria • Rough endoplasmic reticulum • Peroxisomes • Autophagy • Aging	• Nutrition • Physical activity • Psychological status • Environmental conditions • Microbiome • Drugs

BOX 3 | Essential aspects of mitochondria.

General aspects	Periodontal aspects
• Essential organelles in oxidative energy production [14]. • Generate most cellular ROS [15]. • Play a central role in the regulation of oxidative stress and cellular redox homeostasis, as well as intracellular calcium and apoptosis [16]. • Related to immunity and inflammation [17]. • Great adaptation to energy demands [18]. • Contain circular DNA [19]. • They form a highly dynamic network [20]. • Mitochondrial dysfunction leads to an undesirable inflammatory response [21].	• Mitochondrial dysfunction is present in periodontitis [22]. • mtDNA increases periodontitis susceptibility [23]. • Oxidative stress produces variants of mtDNA in periodontitis and cardiovascular disease [24]. • Periodontal treatment decreases mitochondrial ROS production [25]. • *P. gingivalis* and *F. nucleatum* influence mitochondria [26]. • Mitochondria promote tissue regeneration [27].

specific cell, tissue, or organ. The optimal pH varies according to the cellular or subcellular space, and there is an optimal pattern of pro-oxidants and antioxidants for each physiological process. This way of thinking is the basis of the concept of personalized/precision medicine: Diagnostic testing employed to select appropriate and optimal therapies based on the patient's genetics or their other molecular or cellular characteristics [12, 13].

All these aspects should be highlighted if we treat an inflammatory disease considering oxidative stress as the main target of the therapeutic approach. All physiological processes involved in oxidative stress have been reviewed. They are analyzed, considering whether they originate from exogenous or endogenous sources. The former considers all intracellular physiological processes that are involved in oxidative stress, while the latter are external factors that affect oxidative stress. All organisms are influenced by the environment and must adapt to all external stimuli capable of modulating their characteristics and determining their deterioration through oxidative stress (Box 2).

2 | Endogenous Sources

2.1 | Mitochondria

We are aerobic multicellular organisms that produce energy in the most productive way with oxygen that oxidizes nutrients in a controlled burning process. The whole process takes place in one of the most important intracellular organelles, the mitochondrion (Box 3).

Energy production, as the main characteristic of our living form, has an important undesirable side effect. The electron transport chain produces ROS, mainly by Complex I and III [14], controlled by antioxidant mechanisms, but sometimes oxidants are overproduced, and antioxidants are overwhelmed, thus damaging different molecules and organelles and leading, finally, to mitochondrial dysfunction and different diseases [15]. Oxidative stress damages mitochondrial structures and function, disrupts mitochondrial membrane integrity that releases damage-associated patterns (DAMPs), activates the pattern recognition receptors (PPRs) of the innate immune system, and triggers inflammation with the activation of the inflammasome [28]. Mitochondria generate most cellular ROS and play a central role in the regulation of oxidative stress and cellular redox homeostasis [16]. Therefore, the regulation of innate immunity and inflammatory responses against infection pathogens is considered a central signaling hub for integration and transduction of the cell response [29], for regulating the innate and adaptive immunity [17], and communication with distant tissues in a noncell-autonomous manner through different molecules [30]. Macrophages, which eliminate microorganisms by phagocytosis and play an important role in innate and adaptive immunity, produce reactive mitochondrial species during Toll-like receptor (TLR)-dependent inflammatory responses that trigger mitohormesis as a negative feedback mechanism to restrict inflammation through tolerance [31]. Mitohormesis is a mechanism in which exposure to low doses of ROS enhances systemic defense mechanisms by inducing an adaptive response, in contrast to high levels of ROS that cause cell damage [32].

The most important characteristic of mitochondria is their ability to adapt to energy demands. They are highly dynamic and can be remodeled in seconds [18]. The number of mitochondria can vary from absence, as in mature red blood cells, to their presence in large quantities, as in liver cells (more than two thousand), and they can migrate from one cell to another [33]. The coexistence of several mitochondrial subpopulations has been observed in different tissues and even within the same cell [34]. Mitochondria have other essential functions for cell survival, such as heat production, fatty acid synthesis, calcium concentrations, programmed cell death, and innate immunity [35]. The containing of circular DNA held the hypothesis of an endosymbiotic origin. Mitochondrial DNA (mtDNA) is distinct from the nucleus, as it has a lack of cytosine and guanine methylation [19]. The mitochondrial ancestor could have been a bacterium or an Asgard archaeon (a group of uncultivated archaea) engulfed by a proteobacterium [36]. Then some portions of mtDNA were transferred to the cellular nucleus, maybe to protect them from a high oxidative environment; therefore, two DNAs control the mitochondrial proteins. Around 1500 mammalian mitochondrial proteins are synthesized from nuclear genes, and 13 from mtDNA [37]. Both are related; continuous changes in mtDNA heteroplasmy result in discontinuous remodeling of nuclear DNA and mtDNA gene expression profiles due to alterations in both the signal transduction and epigenetic regulatory processes [38]. Another way to avoid the oxidative environment is with continuous replication of mtDNA with a half-life of 7–10 days [39]. Oxidized mtDNA is a key danger signal that triggers sterile inflammation through activation of the NLRP3 inflammasome, which has been linked to many chronic diseases [40].

Mitochondria are inherited only from the mother; this leads to the basis for studying population genetics and evolutionary biology [41]. They form a highly dynamic network that undergoes constant fission, fusion, biogenesis, and autophagy processes according to the needs of cellular metabolism. Fusion mitigates stress and is stimulated by energy demand, while fission creates new mitochondria and facilitates quality control [20]. Mitochondrial fission and fusion contribute to their functions and ROS production [42]. Mitochondrial production involves multiple signals; one of them is peroxisome proliferator-activated receptors (PPARs). Its genes and its activation have been associated with typical bone loss from periodontitis and could be a meeting point with metabolic disorders [43].

Mitochondria also exist outside cells in platelets, in extracellular vesicles; also, a cell-free circulating mitochondrial DNA exists [44]. Small extravesicular vesicles that contain respiration-competent but oxidatively damaged mitochondrial particles can enter the circulation and provide mitochondrial transfer between tissues that can restore the metabolic activity of cells with impaired metabolism [45].

Inflammation includes complex multifaceted mechanisms, and mitochondria are involved in the onset and development of inflammatory conditions. Mitochondrial dysfunction leads to an undesirable inflammatory response [21] and can cause systemic disorders such as neurological ones, but also myopathies, endocrinopathies, and is related to aging, too. Genomic studies found several associations between changes in mtDNA and nuclear mitochondrial genes in cardiometabolic diseases [46]. mtDNA controls the mitochondrial protein machinery, and the link >40% of the mitochondrial proteome to human diseases has been identified [47].

In periodontitis, some data provide some evidence of the relationship between periodontitis and mitochondria. Various bacteria and viruses can affect mitochondrial dynamics and functions in host cell metabolism and immune response as a pathogenic mechanism [48]. As an example of this effect, some studies suggest that mitochondrial dysfunction may be present in periodontitis, linking it with systemic diseases [22]. Recent reviews showed an overview of the interplay between mitochondria and periodontitis [49–51]. Morphometric studies in gingival fibroblast mitochondria from patients with cardiac disease showed a reduced number and increased volume normalized by nifedipine and diltiazem [52]. Mitochondrial structure and function of human gingival fibroblasts are impaired in patients with chronic periodontitis compared to healthy patients [53]. The mitochondrial membrane potential and oxygen consumption of gingival cells were reduced and the mtDNA showed novel mutations [54]. In a Chinese population, a significant association was observed between aggressive periodontitis and eight mtDNA polymorphisms, making periodontitis susceptibility increase [23]. A total of 162 unique variants in the mtDNA sequences were described in patients suffering from periodontitis and cardiovascular disease, and 12 of them were the result of oxidative stress [24]. In an animal model, mitochondrial dysfunction was positively correlated with aggravated periodontitis in diabetes [55]. In a randomized clinical control study, intensive periodontal treatment markedly decreased mitochondrial ROS production in patients with periodontitis and Type 2 diabetes [25].

Porphyromonas gingivalis can promote mitochondrial fission in endothelial cells with upregulation of Drp1 [56], reduce the expression of PINK1, a mitophagy gene, and impair the clearance of damaged mitochondria in macrophages [57]. *P. gingivalis* and *Fusobacterium nucleatum* regulate the expression of mitochondria-ER contact-related genes that are part of host–microbiome interactions [26]. The lipopolysaccharide of *P. gingivalis* in fibroblasts produces a decrease in mitochondrial protein expression, mitochondrial mass, and mitochondrial membrane potential [58].

The role of mitochondria in the regenerative process has also been studied. Induced pluripotent stem cells have been applied to regenerative medicine, but success depends on cellular mechanisms, which in turn depend on mitochondria to maintain pluripotency and develop functional, differentiated cell types [27]. Mesenchymal stem cells are involved due to angiogenic and antiapoptotic functions, mediated by their paracrine effects and sharing their mitochondria with target cells [59]. Platelets are used in regenerative therapy and can improve the regenerative capacity of mesenchymal stem cells with the transfer of respiratory competent mitochondria that improve wound healing [60]. The osteogenic differentiation of mesenchymal stem cells is impaired under inflammatory conditions due to mitochondrial dysfunction and can be restored by activating the cannabinoid receptor I [61]. Changes in mitochondrial metabolism are a critical mechanism for macrophage functions during wound healing. A subpopulation of early-stage wound macrophages

showed mitochondrial ROS production that promotes proper vascularization; on the contrary, the late phase is mediated by mitochondrial respiration and mitohormesis [62]. Even mitochondrial replacement therapy has been implemented in in vitro fertilization to avoid the transmission of diseases. Recently, this mitotherapy has represented an attractive paradigm for the treatment of nervous system disorders [63]. In addition, mitochondrial transfer and transplantation have been proposed to treat skin aging [64]. All of these points could be considered in the future to treat periodontitis.

2.2 | Rough Endoplasmic Reticulum

The endoplasmic reticulum (ER) is an interconnected network of cisternae that can be covered by ribosomes (rough endoplasmic reticulum RER) or not (smooth endoplasmic reticulum SER). The membranes are continuous with the outer nuclear membrane, and the cisternal space is continuous with the perinuclear space. SER is involved in lipid synthesis, production of steroid hormones, and detoxification. The functions of RER include protein folding and maturation of proteins produced by RER ribosomes and their transport to the Golgi apparatus. More than a third of all proteins made in the cell enter the RER lumen, fold in a three-dimensional shape, and undergo various post-translational modifications that include glycosylation and disulphide bond formation. Both processes need the special molecular environment of ER, different from the cytosol, with a higher calcium concentration, essential for glycosylation, and a more reducing redox potential, essential for the formation of disulphide bonds [65]. This disulphide bond formation, between polypeptide chains, is assisted by chaperones and involves the transfer of two electrons provided by the enzyme protein disulphide isomerase, in a redox process [66]. ROS are produced, and it is estimated that around 25% of ROS production in the endoplasmic reticulum is generated by disulphide bonds during oxidative protein folding [67]. Generally, H_2O_2 is produced, and 25% of the oxygen used in the cell is estimated to be spread by the endoplasmic reticulum [68]. In addition, other mechanisms are involved in the stress of the endoplasmic reticulum, such as NADPH oxidase 4, NADPH-P450 reductase activities, and glutathione (GSH), highlighting the significant roles in the pathogenesis of human disorders [69]. But the protein-folded machinery has a limited capacity, and when it is overwhelmed, it produces misfolded proteins that accumulate in cells suffering RER stress [70, 71]. During RER stress, the carefully coordinated redox system is disrupted, causing the accumulation of unfolded proteins with distention of the RER lumen, increased ROS production, and depletion of intracellular GSH by oxidation [72]. Some disturbances can promote this accumulation, such as nutrient deprivation, hypoxia, mutated proteins, and loss of calcium homeostasis [73] (Box 4).

The balance in protein-folding capacity is essential, and when misfolded protein increases, an unfolded protein response (UPR) starts to remedy the situation. This is an essential adaptive intracellular signaling pathway triggered by metabolic stress, oxidative stress, and inflammation [74]. Using the measurement of RER redox status and UPR, various stressors show a compromised RER protein oxidation that contributes to diabetes, neurodegeneration, and cancer [82]. When this adaptive response is inadequate to control ER stress, the cell death process is activated, sometimes involving a mitochondrial apoptotic mechanism pathway [83]. Indeed, the most important organelle related to RER is the mitochondrion. There are mitochondria-associated membrane regions that reversibly bind RER to mitochondria. They are involved in the transaction (exchange) of lipids, calcium homeostasis, autophagy, apoptosis, and how mtDNA is replicated and segregated [84]. The ER is the most significant calcium storage site, with an interaction with the mitochondria [75].

Periodontitis, as an inflammatory chronic disease, has been associated with RER stress highlighting different aspects [76]. Periodontal tissues are highly dynamic and need an adequate function of all cellular mechanisms and especially the appropriate synthesis of proteins. The production of collagen and cellular differentiation are essential to maintain periodontal homeostasis. When human gingival fibroblasts are exposed to RER stress, they exhibit protein degradation and induced cell death [77]. Also, the induction of gingival fibrosis found in drug-induced gingival overgrowth might be a consequence of ER stress [78]. *P. gingivalis* LPS activates ER stress in human periodontal ligament cells [79] and is involved in alveolar bone resorption in experimental periodontitis [80]. Recently, through machine learning methods, three potential biomarker genes involved in RER stress, SERPINA1, ERLEC1, and VWF, have been identified in periodontitis [81].

BOX 4 | Essential aspects of rough endoplasmic reticulum.

General aspects	Periodontal aspects
• It has functions in protein folding and maturation [65]. • It involves a reduced redox potential environment [66]. • It produces ROS [67]. • ROS and unfolded proteins increase RER stress [72]. • An unfolded protein response (UPR) starts to remedy the situation [74]. • It is related to mitochondria through membrane mitochondria regions associated with mitochondria [75].	• Stress from RER related to periodontitis [76]. • Gingival fibroblasts exposed to RER stress show protein degradation and cell death [77]. • Drug-induced gingival overgrowth might be a consequence of ER stress [78]. • *P. gingivalis* LPS activates ER stress in human periodontal ligament cells [79] and produces alveolar bone resorption [80]. • Biomarker genes involved in RER stress have been identified in periodontitis [81].

BOX 5 | Essential aspects of peroxisomes.

General aspects	Periodontal aspects
• They contain oxidases that produce H_2O_2 using oxygen and catalase [85]. • They play key role in the synthesis and turnover of complex lipids, the reduction of ROS, and oxidative injury [86]. • They have an expected role in cholesterol transport [87]. • They are involved in immune disorders, inflammation, and cancer [90].	• PPARs induce the proliferation of peroxisomes [91]. • They influence bone metabolism [92]. • They could be a meeting point with the periodontal related systemic diseases [92]. • They inhibit the LPS-induced inflammatory response [92].

2.3 | Peroxisomes

The peroxisome is a poorly known organelle that can induce diseases called peroxysomopathies related to neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis. It is a single membrane-bounded organelle present in all eukaryotic cells that vary in size, number, and functions, adapting to metabolic requirements and environmental conditions. It contains some oxidases that produce H_2O_2 using oxygen and catalase and play key roles in the synthesis and turnover of complex lipids, the reduction of ROS, and oxidative injury [85]. The main functions are the breakdown of very long chain fatty acids through beta oxidation and their transfer to mitochondria and the production of plasmalogen, the most abundant myelin phospholipid [86]. Cholesterol, an essential lipid in eukaryotic cells, is transported among organelles mainly from the lysosome to the peroxisome. Peroxisome gene alterations have an expected role in cholesterol transport, and cholesterol accumulates in cells as part of the peroxisomal disorder [87]. Peroxisomes play a role in cellular ROS metabolism with the glutathione antioxidant as a crucial component that maintains redox homeostasis [88]. They are often juxtaposed with other organelles, such as RER, mitochondria, and lipid droplets, that allow functional cooperation between organelles [89]. Apart from being a metabolic organelle, it is involved in immune disorders, inflammation, and cancer. Polyunsaturated fatty acids, as peroxisomal lipid metabolites, are precursors of leukotrienes and resolvins as immune mediators. Peroxisomal redox metabolism modulates cellular immune signaling such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation. Therefore, these aspects highlight the importance in the activation of innate and adaptive immune cells linked to inflammatory diseases [90] (Box 5).

One of the most studied molecules that induce the proliferation of peroxisomes in cells is peroxisome proliferator-activated receptors (PPARs). They are nuclear receptor proteins that function as transcription factors that regulate the expression of genes. Three types of PPAR have been identified, which regulate cellular differentiation, development, and metabolism (carbohydrate, lipid, protein), and tumor production [91]. Furthermore, they promote the expression of antioxidant enzymes that produce a reduction in the concentration of ROS that regulates the cellular response to oxidative stress conditions [93]. They are related to metabolic syndrome, cardiovascular disease, and cancer, and the use of specific agonists/antagonists has potential therapeutic usefulness in infectious diseases [92]. PPARs are related to periodontitis as an inflammatory disease due to the ability to modulate inflammation, inhibit the LPS-induced inflammatory response, influence bone metabolism, and could be a meeting point with related systemic diseases [43].

2.4 | Autophagy

The main cellular organelles involved in the production of different oxidative molecules have been reviewed. But the cell needs to eliminate the faulty molecules, or those that come from outside, or break down the normal molecules to produce energy in starvation situations. Autophagy is a degradation pathway and a recycling process that cleans up the cell, preserves cellular functionality, and plays an important role in the homeostasis of cells (Box 6).

Therefore, it plays an important role in adaptation to metabolic demands, immunity, inflammation, and it is related to innumerable diseases, especially neurodegenerative, inflammatory disorders, and cancer [94]. Four forms of autophagy have been described: macroautophagy, microautophagy, chaperone-mediated autophagy, and crinophagy.

Macroautophagy engulfs a portion of the cytoplasm or an organelle with a thin membrane, called a phagophore, and then forms a double membrane organelle called an autophagosome. This autophagosome fuses to the lysosome and degrades its content. The process involves the action of multiple proteins encoded by autophagy-related genes (ATG) [108]. A specific macroautophagy is called mitophagy. Mitophagy degrades damaged and superfluous mitochondria that are essential to maintain cellular homeostasis. Dysregulation of mitophagy is a contributing factor to the pathogenesis of metabolic diseases [109]. Also, it is an essential component of mammalian developmental and differentiation processes, for instance, the elimination of paternal mitochondria from the fertilized egg [110]. Microautophagy involves the direct engulfing of cytoplasmic material into lysosomes, excluding the involvement of autophagosomes [111]. Chaperone-mediated autophagy is a selective form that modulates the turnover of a specific pool of soluble cytosolic proteins recognized by the containing complex of hsc70. These identified proteins are targeted, engulfed, and degraded by lysosomes. It modulates glucose and lipid metabolism, DNA repair, cell

BOX 6 | Essential aspects of autophagy.

General aspects	Periodontal aspects
• Autophagy is a cellular degradation pathway and a recycling process [94]. • It depends on extracellular stimuli, cell type, microenvironment, nutrients, and oxygen supply [95]. • Oxidative stress as the main stimulus that sustains autophagy [96]. • Mitochondria and RER ROS induce autophagy [97]. • It is involved in cancer, cardiovascular disease, obesity, and Type II diabetes [98]. • Lysosomes are essential organelles for autophagic degradation [99]. • Lysosomal storage diseases are related to ROS [100].	• RER stress induces autophagy in human gingival fibroblasts and osteoblasts [101]. • Autophagy in periodontal disease is mediated by RER stress [102]. • Autophagy increases inflammation in periodontitis with the production of cytokines [103]. • Peripheral blood mononuclear cells from periodontitis patients show an increased level of autophagic gene expression [104]. • Gingival epithelial cells show lysosomal dysfunction in periodontitis [105]. • Cathepsin C is associated with severe periodontitis present in Papillon–Lefevre syndrome [106]. • Cathepsin K, the most potent mammalian collagenase, plays a special role in bone resorption [107].

reprogramming, and cellular response to stress [112]. The least known degradation process is crinophagy. It controls abnormal, excess, or obsolete secretory granules, maintaining the proper intracellular pool of secretory granules. It is considered a quality control checkpoint in the maturation of secretory vesicles. Some human disorders, such as insulin secretion in diabetes, have been associated with defective lysosomal clearance of secretory materials [113].

Autophagy is a selective process inhibited or activated due to a variety of intra- and extracellular stimuli, depending on the type of cell, its microenvironment, nutrients, and oxygen supply [95]. Numerous data have been published arguing for oxidative stress as a main stimulus that sustains autophagy [96]. ROS generation occurs mainly in mitochondria, RER, and cytosolic NADPH oxidases, which are interrelated and influenced by exogenous ROS. Mitochondria represent the main source of ROS that induce autophagy as signaling molecules that lead to either survival or cell death [114]. An increase in the level of cellular ROS is also known to trigger mitophagy [97]. It has been demonstrated by measuring the cellular content of hydrogen peroxide and superoxide that the latter is correlated with the extent of autophagy and therefore is the major ROS autophagic regulator [115]. RER stress induces autophagy in human gingival fibroblasts through a large number of autophagic vesicles and autophagic markers such as Beclin-1 and LC-3 [101].

The crosstalk between autophagy and oxidative stress modifies inflammatory conditions that lead to the development of noncommunicable disease [98]. In periodontitis, different aspects have been studied. The bone cells oxidative stress-induced autophagy is regulated through different pathways such as ROS/FOXO3, ROS/AMPK, ROS/Akt/mTOR, and ROS/JNK/c-Jun that influence bone formation and resorption [116]. The adaptation to biomechanical loading in human periodontal ligament fibroblasts involved autophagic mechanisms [117]. The role of autophagy in periodontal disease has been known due to the interaction with periodontal inflammation mediated by RER stress [102]. Lower mtDNA levels, increased ATG5, LC3-II, lower PDK2 protein levels, and mitochondrial destruction have been shown in gingival periodontitis fibroblasts [53]. Autophagy increases inflammation in periodontitis with the production of cytokines mediated by mTOR inactivation [103]. Peripheral blood mononuclear cells from periodontitis patients show an increased level of autophagic gene expression and a high level of mitochondrial ROS [104].

Lysosomes are essential organelles for autophagic degradation. These can degrade extracellular material by endocytosis or intracellular material by autophagy. Also, other roles in nutrient sensing and metabolic adaptation have a major role in cellular physiology [99]. They are single membrane-bound spherical vesicles that contain different enzymes capable of digesting many kinds of molecules. As in the stomach, the enzymes are activated in an optimal acidic environment (pH 4.5–5.0) due to pumping in protons (H^+ ions) through proton pumps and chloride ion channels. Lysosomes must perform their activity through the endosomal-autophagic-lysosomal system in which they fuse to autophagosomes or in a microautophagy and chaperone-mediated autophagy process. Lysosomal enzymes and membrane proteins are synthesized in the RER and controlled by transcription factors. These transcription factors act as a master regulator of lysosomal function, are activated by ROS, and govern cell homeostasis in response to oxidative stress [118], also regulate cellular stress under starvation and ER stress conditions [119]. Even for an antioxidant, the sulforaphane induced its protection through a moderate increase in ROS [120]. When one of the genes that controlled these enzymes is mutated, an accumulation of a specific substrate produces lysosomal storage diseases.

These include neurodegenerative disorders, cardiovascular disease, cancer, and age-related diseases [100]. The hyperinflammatory response in gingival epithelial cells in diabetes-associated periodontitis involved a lysosomal dysfunction due to compromised acidity [105].

BOX 7 | Essential aspects of aging.

General aspects	Periodontal aspects
• Aging is related to inflammation and oxidative stress [124]. • Immune activation includes inflammasome activation that drives IL-1β, IL18, and pyroptotic cell death [127]. • NLRP3 inflammasome activation depends on ROS production and is activated in aging [128]. • Aging produces mitochondrial impairment [129]. • Suppression of NLRP3 prevents age-associated changes in the heart [130]. • Oxidized mtDNA activates NLRP3 [40].	• The inflammasome has a regulatory function in periodontal cells [131]. • NLRP3 concentration increases both in serum and saliva in periodontitis [132]. • mtDNA mutations are present in gingival and cardiac tissues in periodontitis [24]. • Gingival fibroblasts in periodontitis acquire a senescent phenotype produced by oxidative stress [133]. • Excess ROS production, mitochondrial dysfunction, and deficient mitophagy are present in periodontitis [134].

The major class of hydrolytic lysosome enzymes is cathepsins; in humans, 11 cysteine cathepsins have been described [121]. The mutated gene of one of these cathepsins, cathepsin C, is associated with severe periodontitis present in the Papillon–Lefevre syndrome. The production of a recombinant cathepsin C protein by a baculovirus system in insect cell cultures can restore lysosomal function [106]. Cathepsin K is the most potent mammalian collagenase, which is highly expressed in osteoclasts and has a special role in bone resorption [107]. Furthermore, lysosomes are essential in lipid degradation, especially in the control of cholesterol homeostasis [122].

2.5 | Aging

Aging is the most important characteristic of our population that is determinant of the health system. It is a universal process present in all multicellular organisms caused by the deterioration of the normal function of the cells. Cells lose their ability to proliferate and replace damaged cells accumulated over time, in a process known as cellular senescence, which causes organismal aging and dysfunction [123]. Biological aging is the result of multiple cooccurrence hallmarks, which encompass a wide range of biological processes, two of them related to periodontitis, chronic inflammation, and dysbiosis [124], whose presence suggests an increased risk of periodontitis [125]. The links between aging and oxidative stress were first proposed in 1956 [126]. Oxidative stress damages cell physiology due to an excessive amount of ROS that affects different molecules (Box 7).

All organisms must deal with many environmental dangers that threaten their survival; it activates inflammation, a self-protection machinery that includes innate and adaptive response, which are both tightly influenced by oxidative stress [135]. The adaptive immune system responds to a specific antigen, and the innate immune system responds quickly to a diverse set of microbial and sterile insults. The first step is then to recognize threats through the pattern recognition receptors (PRRs) that are sensitive to pathogen- and damage-associated patterns (PAMPs and DAMPs). PAMPs include microbial cell wall components, bacterial and viral DNA, as well as fungal signatures. DAMPs are host-derived and include molecules coming from injured or dying cells, as well as molecules released upon injury and lifestyle molecular patterns accumulated over time, such as cholesterol or oxidized low density lipoprotein [136]. PRR activation induces NF-κB activation of inflammatory genes such as TNF and IL-6 and the assembly of inflammasome that drives caspase, IL-1β and IL18 production and pyroptotic cell death [127]. Recent literature provides data that ROS are integral to the initiation and propagation of inflammasome signaling promoting the immune response [137]. One of the most studied inflammasome, namely NLRP3, depends on ROS production, and it has been demonstrated that ROS scavengers impair its assembly and activation [128]. So, the inflammasome is an essential part of the innate immune system, but its continued activation can be harmful to an organism.

An aging process that includes continuous oxidative stress can be detrimental to cellular homeostasis [138]. Redox status plays a crucial role in regulating cellular senescence, where persistently elevated oxidative stress produces a significant increase [129]. Suppression of NLRP3 prevents age-associated changes in the heart, preserves cardiac function, and increased lifespan [130]. ROS production has a double effect. Mild elevation leads to adaptation to external insults and prevents age-dependent decline. Persistent oxidative stress is related to inflammaging that is harmful and related to aging diseases [139]. The role of the inflammasome in oral diseases and the development and therapy of periodontitis have been widely discussed. It has regulatory functions in periodontal cells, especially in osteoclasts and osteoblasts, and some drugs have potential for treating periodontitis [131, 140]. In periodontitis patients, the concentration of NLRP3 increases in both serum and saliva [132].

Aging produces impaired mitochondrial function and a breakdown of mitocellular communication; therefore, strategies to improve mitochondrial function can increase lifespan [141]. In senescent cells, lysosomes contain lipofuscin, a source of hydroxyl radicals, which show decreased autophagic degradation capacity, enhanced oxidative stress, and mitochondrial dysfunction [142]. Mitochondrial adaptations are associated with both acute and chronic inflammation by restricting fatty acid oxidation that induces optimal activation of the NLRP3 inflammasome [143]. Damaged mitochondria and their oxidized mtDNA signaling released by necrotic cells can be sensed by TLR receptors and are associated with activation of NLRP3 [40]. Also, fusion, fission, molecular biogenesis, and Krebs cycle molecules, such as succinate, fumarate, and citrate engage in processes related

BOX 8 | Essential aspects of nutrition.

General aspects	Periodontal aspects
• Adipose tissue plays an important role as a regulator of energy, Homeostasis, and as an energy depot [144]. • Nutrients excess generates intracellular H_2O_2 from NOX and initiate adipose inflammation [145]. • Obesity increases the population of macrophages with a high level of NOX [146]. • The storage of triglycerides in adipocytes develops RER stress [147]. • Specific nutrients, diet, and time can influence the oxidative status [15]. • Intermittent fasting reduces oxidative stress [148]. • Caloric restriction ameliorates inflammation due to aging and reduces oxidative stress [149].	• There is a positive association between obesity and periodontitis [150]. • Obesity is associated with bone remodeling and is related to periodontitis [151]. • An increase in periodontal oxidative stress in obese patients is associated with clinical attachment loss [152]. • There exists a significant negative association between adherence to the Mediterranean diet and periodontitis [153]. • The oxidative balance score is associated with periodontitis [154]. • Fasting regimens have shown in periodontitis patients lesser bone loss [155].

to innate and adaptive immune cells [17]. Analysis of mtDNA mutations shows multiple variants shared by gingival and cardiac tissues in periodontitis patients, and some of them resulted from oxidative forces [24]. Gingival fibroblasts from periodontitis patients acquire a senescent phenotype produced by oxidative stress-induced DNA and mitochondrial damage [133]. Excessive ROS production, mitochondrial dysfunction, and deficient mitophagy are some of the hallmarks of cellular senescence in periodontitis and type II diabetes mellitus [134].

3 | Exogenous Sources

3.1 | Nutrition

Nutrients are sources of energy; therefore, their availability directly influences the oxidative status of each organism. If there is an excess of any of them, it will accumulate as fat reserves in adipose tissue for later use, causing obesity, which is associated with some diseases. If there is a shortage, they can stimulate certain health mechanisms, and in extreme situations, organisms use their own structural molecules to obtain energy through autophagy (Box 8).

3.1.1 | Obesity

One of the most widespread characteristics of our society is the abundance of nutrients that accumulate in adipose tissue under droplets of triglycerides and finally contribute greatly to the production of obesity. Obesity is defined as body mass index (BMI) greater than 30 kg/m^2. The percentages of obese and overweight adults are expected to increase to 50% by 2030 [156]. Excess energy intake impairs mitochondrial function with reduced ATP synthesis due to ROS accumulation mainly in metabolically active tissues such as adipose tissue, muscle, and liver [157]. Adipose tissue plays an important role as a regulator of energy homeostasis as an energy storage and with endocrine function [144]. Obesity is associated with increased ROS production [158]. The excess of nutrients does not increase mitochondrial oxidative phosphorylation in adipocytes but rather a generation of intracellular H_2O_2 from nicotinamide adenine dinucleotide phosphate oxidase (NOX) that causes the expression of chemotactic factor and promotes an inflammatory phenotype. These effects of NOX are dependent on their localization in lipid rafts that increase ROS production, intracellular NF-κB activation, and chemotactic signaling. It appears that adipocyte NOX-derived H_2O_2 is essential for its physiological condition and may initiate adipose inflammation [145]. Obesity is characterized by an increasing population of macrophages that express high levels of NOX and excess nutrients that produce a drive toward proinflammatory polarization [146]. These inflammatory macrophages reduce the production of adiponectin by adipocytes in a dose-dependent manner by exogenous H_2O_2 [159]. Diminished adiponectin production contributes to higher NOX expression and ROS production [160]. Interestingly, macrophages NOX exhibit a time-dependent metabolic phenotype during diet-induced obesity: an 8-week protective effect can be observed while after 16 weeks a detrimental effect occurs with no benefit [161]. The storage of triglycerides in adipocytes develops a hypertrophy that interferes with ascorbate and oxygen-dependent disulfide bonding and protein folding in the RER lumen, RER stress, and a maladaptive UPR [147]. Additionally, mitochondrial dysfunction due to hypertrophy reduced lipolysis, increased triacylglycerol synthesis, and inflammatory cytokine production, decreased insulin sensitivity, and increased ROS production [162].

A positive association between obesity and periodontitis was found regardless of country or age in meta-analysis studies [150, 163]. Some data suggest that obesity is associated with osteoporosis, indicating a negative impact of obesity on bone quality and in the jawbone [164]. Obesity-associated bone remodeling is related to hyperinflammation, immune dysregulation, and microbial dysbiosis in periodontitis [151]. Animal experiments show a decrease in the ratio of reduced/oxidized glutathione in obesity [165]. In human studies, an increase in periodontal oxidative stress in obese patients has been reported, associated with clinical attachment loss [152]. Systematic reviews of the literature showing the effects of obesity on nonsurgical periodontal therapy are still controversial. An inferior healing response in patients with high body mass index has been reported [166],

and no statistical differences have been found in clinical periodontal measures, but significant differences in inflammatory parameters in obese patients were found [167].

3.1.2 | Specific Nutrients/Diet

Not all nutrients and their consumption schedule have the same influence on oxidative stress. Two main aspects have been highlighted: One is a specific diet pattern, such as the Mediterranean diet as healthy, and a high cholesterol content diet as detrimental; the other is the use of time restricting eating and caloric restriction as protective mechanisms. The consumption of bioactive compounds via oral food has been used extensively in the treatment of metabolic disorders due to their therapeutic properties and safety [168]. Since mitochondria are the main users of nutrients and the cause of mitochondrial defects, the antioxidant properties of bioactive food compounds may be suitable for therapeutic approaches [15]. The types of diet influence systemic metabolic health; the most studied is the Mediterranean diet due to its anti-inflammatory effects [169]. It emphasizes plant-based foods, mainly vegetables, fruits, whole grains, and healthy fats. The idea is to consume healthy bioactive food components as much as possible. The most studied beneficial components are resveratrol, quercetin, coenzyme Q, curcumin, and astaxanthin, which produce their effects attenuating mitochondrial dysfunction via regulating ROS generation [170]. The mediterranean diet rich in vegetables and fruits shows beneficial effects on oxidative gene expression [171]. Noncommunicable diseases have been related to diet, above all metabolic syndrome and cardiovascular disease. The risk of metabolic syndrome and its related diseases can be reversed by reducing body weight through specific diets such as the Mediterranean diet [172]. A significant negative association has been shown between adherence to this diet and periodontitis, with the mediating role of obesity in this association, with data from the National Health and Nutrition Examination Survey (2009–2014) [153]. Oxidative balance score is used to assess the effects of diet in relation to oxidative stress; a negative association with periodontitis was established and is useful as a biomarker of risk [154]. When the specific nutritional intake has been studied, periodontitis shows an inverse association between cholesterol and iodine and a direct association with saturated fat, monounsaturated fat, and folic acid [173]. A study developed a microfluidic system to evaluate the effects of flavonoids on the inflammatory factors and ROS contents in human gingival fibroblasts and in mesenchymal stem cells. It has been demonstrated that flavonoids used to treat periodontitis can reduce cellular inflammation, decrease ROS, and promote bone formation [174].

Not only have types of diet been studied, but also the effects of dietary restriction have been studied. Intermittent fasting is an eating schedule that switches between fasting and eating on a regular schedule. It appears to promote weight loss, may improve metabolic health, and is related to reducing oxidative stress [148]. Caloric restriction is defined as a 20%–40% caloric reduction without reducing essential nutrients. In humans, it leads to body weight and a decrease in inflammatory markers, as well as a low incidence of cancer, cardiovascular, and degenerative diseases, but it does not increase lifespan as demonstrated in monkeys and rodents [149]. It can ameliorate senescence and inflammation secondary to aging [175], and reduce oxidative stress and simulate mitochondrial biogenesis through PPAR [153]. Some data highlight an interesting aspect of the existence of tissue specificity in response to caloric restriction. Tissues composed predominantly of postmitotic cells, such as the brain, heart, and skeletal muscles, have the highest influence due to fasting, also in plasma and spleen, while in the liver the beneficial effects were not clear [176]. Fasting regimens have shown in periodontitis patients lesser bone loss due to an increase in osteoprogenitor cells compared with the nonfasting regimen [155].

3.2 | Physical Activity

Nutrients influence oxidative stress, so it is essential that they are adequately consumed through physical exercise to prevent their accumulation. One of the main characteristics of our society is a sedentary lifestyle and physical inactivity. The demands of energy in all organisms clearly depend on their physical activity. All cellular mechanisms can adapt to all energy requirements by increasing or decreasing mitochondrial production of ATP. Also, the production of radicals and the activation of antioxidants depend on physical demands. It is well known that the deleterious effects of sedentary behavior and physical inactivity can produce numerous diseases, especially cardiovascular disease [177]. In an experimental study, inactivity increases vascular superoxide production and atherosclerotic lesions [178]. Immobilization-induced atrophy depends on ROS and RNS production [179]. Numerous studies have demonstrated, in humans, that physical inactivity promotes insulin resistance and that it is related to both reactive species [180–182]. During exercise, reactive species are produced, especially after an acute bout, which leads to important training adaptations; chronic exercise promotes the body's antioxidant mechanism [183]. Regular exercise increases cardiorespiratory fitness and influences oxidative stress [184] (Box 9).

In epidemiological studies, it has been demonstrated that increased sedentary behavior was associated with higher odds of periodontal disease, but it could be explained by systemic inflammation, obesity, and comorbidities [188, 189]. An inverse linear association was observed between the presence of physical activity and the severity of periodontitis in the Japanese women's population, but not in men [185]. A lifestyle characterized by the combination of low adherence to the Mediterranean diet and lack of regular exercise had 10 times the odds of severe forms of periodontitis [190]. Another lifestyle study related obesity and physical fitness, measuring the estimation of maximal oxygen consumption, and showed that there are some interactive effects on periodontal health status [186]. Physical activity, measured with a subject-completed questionnaire, was not associated with periodontitis, but the measure of Il1-beta and CRP in gingival crevicular fluid indicated protection against an excessive inflammatory response in periodontitis [191]. However, these results were not supported by genetic studies that did not show a relationship between physical activity and the risk of periodontitis [192]. An experimental animal study investigated the effects of moderate physical training on the inflammatory response. Physical training reduced levels of IL-1β, IL-6, TNF-α C-reactive protein, and lipid peroxidation and caused a decrease in vertical bone loss [187].

BOX 9 | Essential aspects of physical activity.

General aspects	Periodontal aspects
• Radicals production and the antioxidants activation depend on physical demands [178]. • Physical inactivity increases vascular superoxide production and atherosclerotic lesions [179]. • It is inversely related to cardiovascular disease and insulin resistance [182]. • Physical exercise produces reactive species and training adaptation [183].	• There exists an inverse linear association between physical activity and the severity of periodontitis [185]. • Physical fitness showed that there are some interactive effects on periodontal health status [186]. • Physical training reduces levels of IL-1β, IL-6, TNF-α, C-reactive protein, and lipid peroxidation, as well as decrease vertical bone loss [187].

BOX 10 | Essential aspects of psychological status.

General aspects	Periodontal aspects
• Chronic stress produces oxidative stress and impaired immune system [193]. • Antidepressant drugs have shown an antioxidant effect [194]. • Major depression disorders are related to mitochondrial dysfunction, impaired antioxidant defense system, and oxidative neuronal damage [195]. • Schizophrenia altered mitochondrial activity, increased RER stress, and misfolded proteins [196].	• The association between stress and periodontitis has been demonstrated [197]. • Chronic stress induces oxidative stress related to alveolar bone loss [198]. • Higher attachment loss was observed in cases of periodontitis and psychological stress [199]. • Melatonin prevents the destructive effects of stress on periodontal bone loss, lowering oxidative stress [200]. • An NHANES study demonstrated a negative link between depressive disorder and periodontitis in obese individuals [201].

3.3 | Psychological Status

The nervous system detects environmental changes and responds to such events, maintaining or regaining physiological homeostasis. Stress is the defense mechanism of an organism to face aggression or high energy demand. Two major systems are involved: the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, with the two main hormones adrenalin and cortisol produced in the adrenal gland. Acute and sporadic stress is not harmful, but prolonged stress without breaks is one of the main sources of human pathology in western countries. Chronic stress causes dysregulation of the HPA axis that increases the circulating level of glucocorticoids, resulting in oxidative stress and impairment of the immune system [193] (Box 10).

High levels of oxidative stress have been observed in psychiatric disorders such as schizophrenia, bipolar disorder, and depression, and some benefits of antioxidants have been observed as adjunctive therapy. Antidepressant drugs have been demonstrated to have an antioxidant effect through inhibition of oxidative phosphorylation and increased activity of antioxidant enzymes. Therefore, it is possible to modulate the redox system as a therapeutic strategy to counteract the detrimental effects of the imbalance in brain oxidative mechanisms [194]. In major depression disorder, mitochondrial dysfunction has been demonstrated to impair the antioxidant defense system, resulting in oxidative neuronal damage due to an imbalance in antioxidant status [195]. In patients with schizophrenia, a study showed altered mitochondrial activity that generates free radicals, increased RER stress, and misfolded proteins, but it cannot conclude if it is the cause or the consequence of the disease [196]. Lymphocytes from bipolar disorder patients have RER stress associated with decreased cellular response and illness progression [202].

Association between stress and periodontitis has been demonstrated [197]. In an experimental study, chronic stress induced a decrease in antioxidant activity and increased oxidant activity related to alveolar bone loss [198]. Furthermore, a higher attachment loss was observed in cases of periodontitis and psychological stress compared to only periodontitis, and it was related to increased ROS content and a decrease in antioxidant enzyme activity [199]. Additionally, melatonin, which has antioxidant effects, prevented the destructive effects of stress on periodontal bone loss, lowering oxidative stress [200]. An NHANES study demonstrated a negative link between depressive disorder and periodontitis in obese individuals [201].

3.4 | Environmental Conditions

All living organisms live in different environments that modulate their physiology. One of the main harmful effects is the contribution of free radicals produced by air pollution, ultraviolet radiation from the sun, ionizing radiation, and smoking [203]. Air pollution comprises a mixture of particulate matter, gases, organic compounds, and metals that contain 300 times

BOX 11 | Essential aspects of environmental conditions.

General aspects	Periodontal aspects
• Environmental conditions modulate the physiology of living organisms [203]. • Air pollution causes oxidative deterioration of biological macromolecules [204]. • Ultraviolet light affects antioxidants, leading to high levels of ROS [206]. • Ionizing radiation from medical diagnostic imaging produces oxidative stress [207]. • Tobacco smoke contains ROS and RNS that damage cells and produce lipid peroxidation [208].	• An association has been demonstrated between air pollutants and periodontitis [209]. • Epigenetic mechanisms but not markers of oxidative stress are downregulated in periodontitis smokers [210].

more free radicals than tobacco smoke. It causes oxidative deterioration of biological macromolecules, depletion of enzyme activities, and metabolism affecting mainly the respiratory system [204]. Sunlight photoexcitation affects endogenous or exogenous sensitizer molecules leading to the formation of reactive species, notably singlet molecular oxygen, electronically excited carbonyls, and superoxide anion radicals; these may cause molecular damage [205]. Ultraviolet light affects antioxidants, such as catalase and nitric oxide synthase, protein kinase, leading to high levels of ROS [206]. A low dose of ionizing radiation from medical diagnostic imaging produces oxidative stress that causes epigenetic modifications and cellular damage [207]. Tobacco smoke contains ROS and RNS that damage cells and produce lipid peroxidation, post-translational modification of proteins, nucleic acid adduction, epigenetic alterations, and activate the inflammatory response [208] (Box 11).

A South Korean study demonstrates that air pollution contains levels of particulate matter of 10 μm, ozone, sulfur dioxide, and nitrogen dioxide. They found an association between air pollutants and periodontitis and proposed them as a modifiable risk indicator [209]. A study evaluated the epigenetic markers and oxidative stress in smokers and nonsmokers patients and periodontitis. Epigenetic mechanisms, but not markers of oxidative stress, were downregulated in periodontitis smokers [210].

3.5 | Microbiome

The microbiome is defined as a characteristic microbial community occupying a reasonably well-defined habitat that has distinct physiochemical properties. It refers to microorganisms and the theater of activity that results in specific ecological niches [211]. Another related term is the microbiota, which is defined as all living members that form the microbiome. Now it is considered that each multicellular organism is a unit composed of cells and the microbiota in a holistic approach [212]. According to this concept, holobiont's disease is linked to dysbiosis and the healthy state to eubiosis. The Human Microbiome Project has been carried out to provide resources, methods, and discoveries that link interactions between humans and their microbiomes with health-related outcomes [213]. One of the most studied microbiomes is the gut microbiome, which has been related to some diseases such as mental disorders, diabetes, and obesity, so some therapeutic approaches that change the bacterial composition have been proposed [214]. The enteric nervous system controls gastrointestinal disorders and is related to neurointestinal diseases with oxidative stress as a critical player [215]. Some antioxidant nutrients can modulate this enteric nervous system by alleviating oxidative stress [216] (Box 12).

Oral microbiome dysbiosis is a key player in the pathogenesis of periodontitis. Some studies have shown that bacterial periodontal pathogens, especially the red complex, have a wide range of effects on the structure and function of mitochondria [49]. *P. gingivalis* lipopolysaccharide induces mitochondrial dysfunction that involves increased oxidative stress, impaired energy production, and disrupted biosynthesis [217]. Also, it has been shown that its ability to overcome oxidative stress in the inflammatory environment of the periodontal pocket is mediated by the bacterioferritin comigratory protein (bcp) gene that is critical for its survival [218].

3.6 | Drugs

Not only have antioxidants been studied as part of the composition of nutrients, but also as drugs. Reducing oxidative stress present in chronic inflammation, restoring ATP production, and counteracting damage from ROS production can be a therapeutic targets [219]. We have mentioned the beneficial effects of some antioxidants that are part of the Mediterranean diet. A group of antioxidants has been widely used as drugs, for instance, the supplementation with Coenzyme Q10, vitamin E, vitamin C, and β-carotene. Although oxidative stress is a component of many diseases and antioxidants have shown therapeutic potential in preclinical studies, clinical trials have shown disappointing results [220]. One of the reasons for the lack of clinically significant benefits could be the inability of antioxidants to enter mitochondria [221]. Almost all antioxidant drugs should be administered orally, then absorbed into the gastrointestinal tract, enter the enterohepatic circulation, and be metabolized in the liver. Here, they can be metabolized by cytochrome P450 oxidases enzymes that catalyze a high diversity of reactions through oxidative, peroxidative, and reductive metabolism. In humans, it plays a central role in Phase I drug metabolism, as 90% of it influences drug interactions and interindividual metabolism variability [222, 223]. Cytochrome P450 enzymes are

BOX 12 | Essential aspects of microbiome.

General aspects	Periodontal aspects
• Each multicellular organism is a unit composed of cells and the microbiota in a holistic approach [212]. • Holobiont's disease is linked to dysbiosis and healthy state to eubiosis [213]. • The gut microbiome has been related to mental disorder, diabetes, and obesity [214]. • The enteric nervous system is related to neurointestinal diseases with oxidative stress as a critical player [215].	• Oral microbiome dysbiosis is a key player in the pathogeny of periodontitis [49]. • The *P. gingivalis* lipopolysaccharide induces mitochondrial dysfunction and increases oxidative stress [217]. • Oxidative stress has been shown in the inflammatory environment of the periodontal pocket [218].

BOX 13 | Essential aspects of drugs.

General aspects	Periodontal aspects
• Antioxidants have shown therapeutic potential in preclinical studies, but clinical trials showed disappointing results [220]. • Antioxidants administrated orally must be metabolized in the liver [222]. • Oral antidiabetic drugs reduce oxidative stress [225]. • Metformin which can inhibit Complex 1 of the respiratory chain, improves mitochondrial function, extending health and lifespan [226]. • Anticancer drugs induce RER stress [227]. • Nonsteroidal anti-inflammatory drugs and methamphetamine increase oxidative stress [228].	• Green tea, quercetin, melatonin, lycopene, resveratrol, and curcumin neutralize free radicals and reduce oxidative stress which are useful as an adjunctive in periodontal treatment [229]. • The above substances can be used in different preparations for local applications [230]. • Resveratrol is proposed as an alternative to chlorhexidine in nonsurgical periodontal treatment [231]. • These compounds, due to their antioxidant properties, in animal models can prevent periodontal tissue damage, however, in humans the efficacy is poor [232].

a significant source of ROS in the biological system, especially in the liver. These are contained in microsomes, in a vesicle-like artifact derived from pieces of endoplasmic reticulum produced when eukaryotic cells are homogenized [224] (Box 13).

Not only have antioxidant nutrients been studied, but also some other drugs with different effects. Some of them have beneficial effects. The most studied are oral antidiabetic drugs. For instance, metformin, pioglitazone, vildagliptin, liraglutide, and exenatide cause a reduction in oxidative stress [225]. The most studied drug is metformin, which can inhibit Complex 1 of the respiratory chain, activate the AMPK signal, induce muscle to absorb glucose, improve mitochondrial function, extend health span and lifespan [226]. Some anticancer drugs can exert their benefit through induction or inhibition of RER stress [227].

Other drugs have detrimental effects. Nonsteroidal carboxylic acid anti-inflammatory drugs are widely used, and their adverse effects are related to mitochondrial dysfunction and oxidative stress [228]. Long-term abuse of methamphetamine increases oxidative stress, produces mitochondrial dysfunction, and increases inflammation [233]. Doxycycline rescues cell death and inflammatory signatures in mitochondrial diseases through partial and selective inhibition of mitochondrial translation, resulting in an independent mitohormetic response of ATF-4 and is proposed as a potential treatment [234].

Some antioxidants and drugs have been studied as adjuvants to improve periodontal treatment outcomes. The most studied were green tea, quercetin, melatonin, lycopene, resveratrol, and curcumin. They can be used in different presentations, such as gels, membranes, dentifrices, chewing gum, orally disintegrating film, mouthwash, mouth spray, and mouth massage cream. They neutralize free radicals and reduce oxidative stress and can be useful as an adjunctive in periodontal treatment [229]. Data from a study show that lycopene and green tea improve clinical parameters such as plaque index, gingival index, bleeding on probing, and clinical attachment level, so they decrease inflammatory periodontal levels [230]. Another recent meta-analysis demonstrated that lycopene is useful in improving the treatment of periodontal disease [235]. Additionally, it is proposed that the use of a mouthwash of resveratrol can be an alternative to chlorhexidine [231]. Melatonin supplementation can play a role in periodontal disease by reducing levels of periodontal inflammation [236]. In animal models, quercetin reduced oxidative stress and senescent cells, and reduced inflammation [237]. The local application of curcumin can be considered as an adjunct to periodontal mechanical debridement [238]. Oral coenzyme Q10 supplements as an adjunct to scaling and root planing reduced gingival inflammation [239]. The efficacy of topical metformin in periodontitis and dental implants has been reviewed and some benefits can be shown [240]. However, in a metanalysis, antioxidants exhibited moderate evidence of benefits as an adjunct to nonsurgical periodontal therapy, possibly due to the use of different clinical parameters

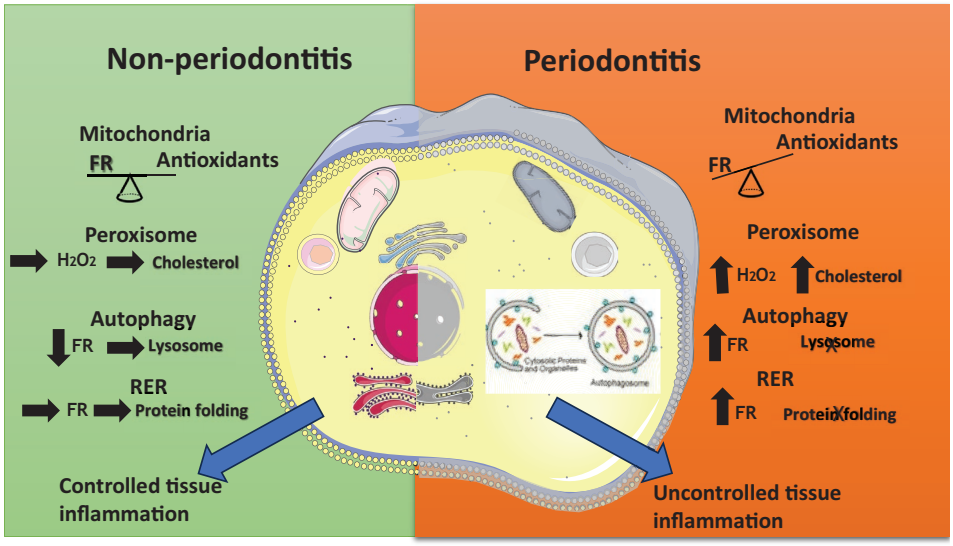

FIGURE 1 | Our review highlights that the following points should be considered.

FIGURE 2 | Personalized/precise oxidative stress therapy (POST). This approach incorporates the environments, individual characteristics, and cell physiology concepts into the oxidative stress therapy in periodontitis.

and types of antioxidants [230]. Another review shows that the effects of these compounds, due to their antioxidative properties, in animal models can prevent periodontal tissue damage; however, in humans the efficacy is poor [232].

4 | Conclusions and Future Research Guidelines Proposals

This review shows that oxidative stress is involved in multiple chemical reactions that take place in different intracellular organelles and can be influenced by numerous exogenous factors (Graphical abstract). The future is exciting due to the implementation of new techniques that allow us to use microscopes that can handle angstrom measurements and molecular technologies that can analyze their components with extreme precision. Oxidative stress implies the imbalance of pro-oxidants and antioxidants that produces macromolecular damage and the disruption of thiol redox circuits, leading to aberrant cell signaling and dysfunctional redox control. However, we must assume that it is part of the normal functioning of cellular metabolism. Our most important conclusion that should be taken into

consideration in future research is that oxidative stress is part of the biological and metabolic cellular statement in a multicellular organism. Understanding the cellular physiology behind oxidative stress is essential (Figure 1). Not all our patients and their different organs have the same oxidative conditions. On the one hand, it depends on specific tissue, but also our whole body has a specific metabolic background that differentiates one patient from another and depends on the specific moment, general systemic conditions, and the environment. Treatment of oxidative stress simply by administering antioxidants, as is the case with administering vitamins or hormones when they are lacking, should be changed. Antioxidants may not produce the desired effect; they may improve one organelle, but they may affect another, damaging it or interfering with free radical signaling. Our key message is that it is above all a new window into the pathogenesis of periodontitis, and this new understanding of the physiological and molecular basis of the disease will transform treatment. Our goal should be to treat our patients according to the specific oxidative statement. Based on our data to implement this therapy, we should apply a specific therapy; it could be called personalized/precise oxidative stress therapy (POST). Our review highlights that the following points should be considered (Figure 2):

1. Environmental conditions: air pollution, ultraviolet radiation, and ionizing radiation.
2. Individual characteristics: age, nutritional status, physical activity, psychological state, microbiome, and drug intake.
3. Intracellular physiology: mitochondria, RER, peroxisomes, and autophagy.

Oxidative stress therapy should incorporate the concept of POST dealing with these aspects to be successful. Artificial intelligence could be helpful to study all these parameters together.

Author Contributions

P.B. write the paper, F.G. review the paper, B.B. bibliographic search, M.B. write the paper and review the paper.

Disclosure

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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