Received: 18 March 2023 | Revised: 6 November 2023 | Accepted: 31 December 2023

DOI: 10.1002/jcla.25002

REVIEW ARTICLE

WILEY

Periodontal disease in down syndrome: Predisposing factors and potential non-surgical therapeutic approaches

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Abstract

Background: Periodontal diseases (PDs) have been documented to be significantly more prevalent and severe in patients with Down syndrome (DS). Different immunological and microbiological factors contributed to predisposing these patients to progressive and recurrent PDs.

Aim: The aim of this review was to investigate the altered immunological responses and oral microbiota disorders as well as focus on adjunctive non-surgical methods for the treatment of PDs and its applicability in patients with DS.

Material and Methods: A literature review was conducted addressing the following topics: (1) the altered immunological responses, (2) orofacial disorders related to DS patients, (3) oral microbiota changing, and (4) adjunctive non-surgical treatment and its efficacy in patients with DS.

Results: Due to the early onset of PDs in children with DS, the need for prompt and effective treatment in these patients is essential.

Discussion and Conclusion: So, investigating underlying factors may open a new window to better understand the pathology of PDs in DS people and thus, find better strategies for treatment in such group. Although non-surgical treatments such as photodynamic therapy and probiotic consumption represented acceptable outcomes in different examined patients without DS, data about the application of these convenience and no need for local anesthesia methods in patients with DS is limited.

KEYWORDS
dentistry, down syndrome, immunological defects, oral microbiota, periodontal disease, periodontology, photodynamic therapy, probiotics

1 | INTRODUCTION

Down syndrome (DS), also known as trisomy 21, stands out as the most prevalent chromosomal separation disorder in humans. The estimated incidence of DS is nearly 1 in 1000 live births worldwide.[1] Individuals with DS are characterized by intellectual disabilities, phenotypical alterations in face, and systemic disorders, including heart and immune system defects. These factors contribute to an increased susceptibility to periodontal diseases (PDs).[2,3] PDs encompass various inflammatory conditions affecting the tooth-supporting structures (periodontium).[3] Notably, DS children exhibit significantly elevated PDs compared to normal

age-matched controls.[4-6] The increased incidence and severity of PDs in DS cases is related to genetic polymorphisms in inflammatory factors and immune deficiency,[6] aberrant orofacial morphology in gingival epithelium and tooth formation,[5] and altered oral microbiome due to early colonization with periodontopathogens.[6] Therefore, delving into immunological defects, anatomical changes in oral cavity, and oral microbiome may enhance our understanding of individuals with DS, paving the way for improved strategies in both surgical and non-surgical treatments for this group. Given the challenges associated with surgical treatments, such as local anesthesia and prolonged durations, especially in recurrent PDs,[7] opting for adjunctive non-surgical methods with minimal side effects appears to be a more practical approach to enhance tissue repair and control PDB in DS patients. The objective of this review article was to provide a comprehensive summary of the existing literature on PDs in individuals with DS. To identify relevant studies, a literature search was conducted across databases, including PubMed, MEDLINE, and Embase, utilizing keywords pertinent to the topic: "Down syndrome" OR "Trisomy 21," "periodontal disease" OR "gingivitis," "predisposing factors," and "non-surgical therapy." The aim was to encompass observational, interventional, and case–control studies, as well as systematic reviews, focusing specifically on individuals with DS within the last 20 years. Moreover, the inclusion criteria considered studies exploring non-surgical therapeutic approaches for managing PDs in individuals with DS. This encompassed investigations into photodynamic therapy, the use of probiotics/prebiotics or symbiotics, and the utilization of melatonin and chlorhexidine as adjunctive therapies for PDs.

2 | PREDISPOSING FACTORS

2.1 | Immune factors

According to the recent classification, PDs in individuals with DS are categorized as systemic diseases, exhibiting chronic and progressive manifestations that are responsible for the damage to periodontal attachment and the destruction of alveolar bone.[4] Trisomy 21 is associated with abnormalities in both the innate and adaptive immune systems, including mild to moderate T-cell lymphopenia (characterized by decreased naïve lymphocyte), reduced antibody responses, and impairments in chemotaxis and neutrophils phagocytosis.[8] Furthermore, increased levels of proteolytic enzymes and inflammatory factors in DS patients lead to the destruction of periodontal tissue.[9] These conditions contribute to an additional risk of infections, chronic inflammation, and oxidative stress, which, in turn, lead to tissue damage and predispose DS patients to PDs.[10] This section of the review aims to highlight some crucial immune response defects in DS patients that elevate the risk of developing PDs (Figure 1).

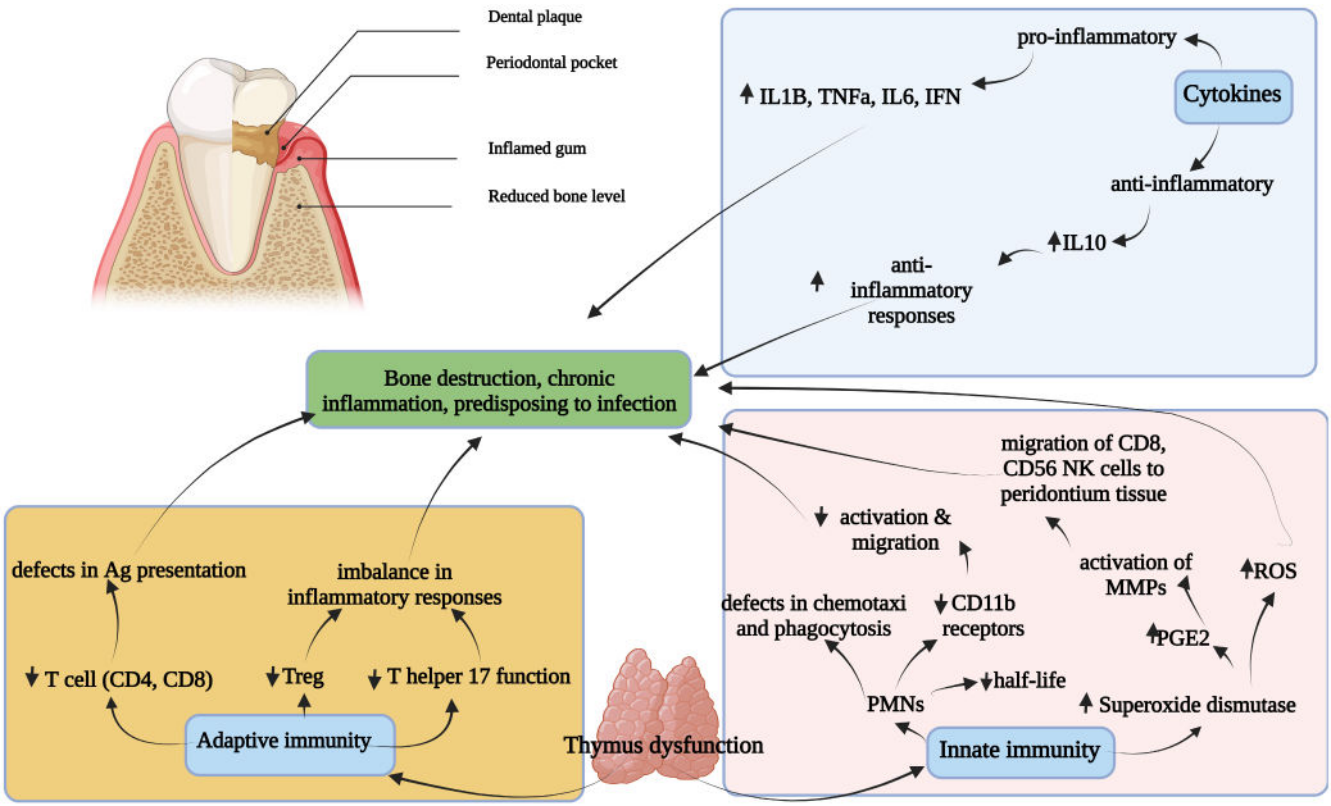

FIGURE 1 Immune function in Down syndrome. Abnormalities of the cytokines, innate, and adaptive immune system in Down syndrome that result in predisposing periodontitis. Ag, antigen; MMP, matrix metallo proteinase; NK cell, natural killer cell; PGE2, prostaglandin E2; PMN, polymorphonuclear; Treg, T regulatory.

2.1.1 | Polymorphonuclears (PMNs) defects

PMNs, particularly neutrophils, as the most abundant circulating blood cells, possess the ability to undergo phagocytosis and destroy the microbial agents. Neutrophils achieve intracellular killing through the mediation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which generates reactive oxygen species (ROS).[10] The infiltration and accumulation of activated PMNs, notably a rich source of ROS, result in the destruction of the proteoglycans and macromolecules present in alveolar bone and gingival tissues.[11] Based on previous studies, chemotaxis in PMNs is disturbed in individuals with DS.[10,12,13] Despite sufficient hydrogen peroxide (H_2O_2) production in DS patients, chemotaxis, phagocytosis, and intracellular killing are compromised. Additionally, the half-life of PMNs in DS subjects is reduced, increasing the risk of infections.[10] Because the genes encoding amyloid precursor protein and Cu/Zn superoxide dismutase (Cu/Zn SOD), which are associated with the regulation of ROS, are located on chromosome 21, DS patients experience heightened inflammation and tissue damage due to the increased production of ROS.[14] The increased production of reactive oxygen metabolites such as 8-hydroxy-20-deoxyguanosine and hydroperoxides in saliva of DS individuals with PD compared to healthy controls is well documented.[15,16] The elevated production of ROS, which is associated with the depolymerization of extracellular matrix components, apoptosis in deepest area of the sulcular pocket,[17] the induction of pro-inflammatory cytokines, and DNA damage[18] can potentially increase the severity and development of PDs in DS patients. Furthermore, a recent study demonstrated that in the presence of lipopolysaccharide (LPS), an endotoxin in Gram-negative bacteria, the frequency of CD11b receptors (adhesion receptor in neutrophils and monocytes) increased and resulted in neutrophil hyper-responsiveness and detrimental inflammatory effects in DS subjects.[19]

2.1.2 | Imbalance of interleukin 10 (IL-10)

IL-10, an anti-inflammatory cytokine, inhibits the induction of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-6, and IL-12,[20] which are mediated by LPS and bacterial products.[20] In the gingival crevicular fluid (GCF) of affected periodontium, the concentration of IL-10 is lower compared to healthy sites. Therefore, the increased levels of IL-10 could potentially be associated with a decreased susceptibility to PDs.[21] Cytokine dysregulation, leading to imbalances in pro- and anti-inflammatory responses, is associated with tissue destruction and chronic infections. However, the decreased expression of IL-10 in DS patients with PDs has been reported,[22,23] other studies have represented the increased level of IL-10 that predisposes DS patients to other infections, such as respiratory tract infections.[24,25] Further studies are needed to explore the role of IL-10 in inflammation and to compare its involvement in different infections, including PDs.

2.1.3 | Matrix Metalloproteinases (MMPs)

The inflammatory responses in gingival tissues lead to the activation of proteolytic enzymes, particularly matrix metalloproteinases (MMPs), which are associated with tissue remodeling, and the destruction of the extracellular matrix.[26] The expression of MMPs is significantly increased in the periodontium following inflammation compared to non-inflamed tissues.[27] MMPs play a role in the transmigration and influx of inflammatory cells to the site of inflammation by processing extracellular matrix components, growth factors, cytokines, and chemokines. Based on substrate specificity, MMPs are classified into various groups including collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -10), and so on.[28,29] Higher levels of MMP-2, MMP-3,[30] MMP-8,[30,31] and MMP-9[30,32] have been reported in the GCF and saliva samples collected from DS children compared to healthy controls. These findings suggest that alterations in the regulation of MMP activity are associated with a higher risk of inflammation in the periodontium of DS patients.

2.1.4 | T Cells malfunction

However, T lymphocyte abnormalities are commonly associated with various infections in DS patients.[33] In this section, we will focus on the most important abnormalities related to PDs. T lymphocytes play a critical role in cell-mediated immunity within the gingival barrier.[34] DS individuals, due to thymus alterations, have been reported to exhibit a reduced expression of α and β chain T cell receptors (TCRs).[33,35,36] Furthermore, the antigen recognition and development of immune response in T cells are disrupted in DS patients.[35] In DS patients, there is a lower proliferation and accumulation of T cells in the periodontium compared to healthy individuals.[5] Regulatory T cells (Tregs) modulate the immune response in the inflammation and have an important role in PD development. The increased accumulation of Tregs has been associated with alveolar bone loss in PDs.[37,38] The function of Treg, follicular helper T, and peripheral helper T cell is dysregulated, and remarkably, the modulating role of Tregs is reduced In DS subjects.[35,36] Moreover, Th17 cells-derived cytokines in gingiva of DS subjects are higher than normal subjects. Regarding the role of Th17 lymphocyte and IL-17 in PDs and alveolar bone destruction, the increased level of IL-17 in DS patients may result in more osteoclastogenesis.[39]

2.2 | Orofacial features in DS patients

Certain orofacial features observed in individuals with DS are often associated with a higher incidence and severity of PDs.[8] The dentofacial manifestations of DS patients present as mild mandibular prognathism, a hypoplastic maxilla with a high, short, and narrow palate, macroglossia, and dental anomalies.[40] The hypoplastic maxilla,

combined with an enlarged tonsillar volume, can lead to upper airway obstruction and open mouth breathing.[5] The results of a recent systematic study indicated that fissured tongue and lip lesions were the oral mucosal findings most frequently reported in children with DS compared to the general population. Furthermore, it was observed that the prevalence of these findings tends to increase with age.[41] In DS children, the incidence of dental anomalies is five times higher compared to other children.[42] The most common dental anomalies include variations in the number and morphology of teeth, such as microdontia, enamel hypocalcification or hypoplasia, taurodontism, delayed tooth eruption, and hypodontia.[43,44]

Microdontia, which is observed in 35–55% of DS patients, refers to a decrease in the size of the crown, resulting in reduced enamel and dentine thickness.[44] The reduced amount and hardness of the enamel lead to enamel hypocalcification.[45] DS cases often exhibit elongated pulp chambers and apical displacement, a condition known as taurodontism, which commonly affects the second lower molar.[40]

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Other factors including short roots, mucogingival problems, and changes in saliva components, contribute to an increased risk of PD in DS patients.[8,48,49] Both short roots and taurodontism can reduce the extent of periodontal attachment and result in tooth mobility, which is commonly observed in DS cases and can potentially contribute to PD development in these patients.[45] Notably, the extensive and rapid gingival inflammation observed in DS children, when compared with healthy children, could be attributed to an unfavorable gingival morphology associated with the genetic abnormalities present in these patients. Habashneh et al. reported that DS children had a significantly higher percentage of surfaces with a severe gingival index and a higher mean probing pocket depth compared to children without DS.[50] Extensive research has been conducted on the alteration of salivary components and their role in increasing or decreasing of PDs and dental caries. The primary culprit of PD is bacterial plaque, which causes progressive tissue damage. Saliva contains numerous organic and inorganic components that maintain the delicate balance of the oral microbiota and prevent the adhesion and penetration of bacteria into the teeth.[51,52] Salivary components such as pH, buffering capacity, and salivary flow volume play an important role in reducing the harmful effects of metabolites produced by the oral microbiota.[51,53] Adequate Salivary flow can effectively dilute and eliminate the products of bacterial metabolism in the oral cavity. The low salivary flow in DS children may contribute to the accumulation of bacterial products, gingivitis and an increased risk of PD.[54] The reduction in salivary flow results in a thin mucosa in the oral cavity, which could potentially interfere with the antibacterial effect of mucus.[51]

Due to the open mouth posture, protruded tongue, and hypotonic orofacial muscles, DS patients experience drooling, which contributes to a decrease in stimulated salivary flow from the parotid gland and results in dryness of the mucous membranes.[55,56] Several studies have indicated that salivary flow rates are lower in DS children compared to healthy individuals.[57–60] The oral pH range in the healthy population typically falls between 6.8 and 7.2. Several studies have demonstrated significant differences in salivary pH values between individuals with DS and those without,[57,58,61] while other studies have reported no statistically significant difference.[51]

The ability of saliva to stabilize a normal pH, which contributes to oral health, is known as buffering capacity. DS cases generally exhibit higher buffering capacity of saliva compared to the general population.[61] Salivary proteins and lipids, which form buffers, antibacterial substances, and a protective film on the surface of the tooth, play critical roles in bacterial aggregation, hydrogen peroxide oxidation, antiviral and antifungal activities.[62] Although some studies reported no statistically significant differences in salivary components compared with data from individuals without DS,[51,62] certain early studies have reported alterations in saliva in DS patients.[57,59] In general, the anatomical changes in the oral cavity of children with the syndrome contribute to an increased risk of periodontal disease in these patients.

2.3 | Microbiota changes in individuals with DS

The human oral cavity contains a diverse range of microbial species, and the disturbance of homeostasis between the host and the microbiome is strongly linked to oral disease processes.[63] Environmental factors and immune deficiencies in DS patients can increase their risk of microbial imbalance, colonization by pathogenic bacteria, and the subsequent development of PD.[5]

A comparison of microbiota changes between DS and healthy groups has revealed an increase in certain species such *Propionibacterium acnes*, *Selenomonas noxia*, *Streptococcus gordonii*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus constellatus*, and *Treponema socranskii* in DS patients.[4] In DS patients who habitually suck their thumbs and other fingers, *P. acnes*, which is a commensal of human skin, can lead to apical periodontal infections.[64] *S. noxia*, *T. socranskii*, and *S. constellatus* are periodontal pathogens that cause destruction of periodontal tissue and contribute to resistant forms of PD.[65] *S. gordonii*, *S. mitis*, and *S. oralis* play a primary role in the initial microbial colonization that promotes plaque development and serve as a foundation for the attachment of other bacteria to the plaque.[66] The prevalence of periodontal pathogens may depend on the age of the DS patient. *Peptostreptococcus micros*,

Eikenella corrodens, and *Prevotella nigrescens* are significantly more prevalent in DS young adults, whereas *A. actinomycetemcomitans*, *Porphyromonas gingivalis*, *Campylobacter rectus*, *Capnocytophaga sputigena*, and *Prevotella intermedia* are more commonly found during puberty. Additionally, *Actinomyces naeslundi* and *Tannerella forsythia* are present in DS patients regardless of age.[67]

According to one study, the composition of the oral microbiome in DS individuals was significantly altered, showing an increased presence of *S. aureus* and periodontal pathogens such as *Kingella*, *Cardiobacterium*, *Gemella*, and *Rothia*.[68] Several studies have reported an association between the increased population of *Kingella*[69,70] and *Cardiobacterium*[71,72] in the oral cavity and a higher incidence of PD. Although *S. aureus*,[73–75] *Rothia*,[76] and *Gemella*[77,78] have been associated with periodontal health, their synergistic effect with periodontal pathogens has been documented.[79]

Furthermore, *Candida* species have been found to be more prevalent in DS.[80] Several species, including *C. parapsilosis* and *C. dubliniensis* are opportunistic pathogens in the oral cavity and have been associated with PD.[81,82] The combination of low salivary flow, impaired immune response, and altered electrolyte concentrations in DS creates a favorable environment for the growth of *C. parapsilosis* and *C. dubliniensis*.[80]

Additionally, DS patients exhibit high production of aspartyl proteolytic, proteinases, and phospholipases, which predispose them to more virulent *Candida* spp. infections.[4,80] Some acidogenic species such as *C. parapsilosis*, contribute to a decrease in salivary pH and trigger the activation of aspartyl proteinases.[80] Overall, the increased presence of *Candida* species in the oral cavity of DS subjects appears to be associated with a higher incidence of PD.

3 | THERAPEUTIC STRATEGIES

For several decades, the treatment strategies for PD, which involved the removal of dental biofilm and use of surgical and nonsurgical therapies, served as the foundation of periodontal treatment.[83,84] Presently, we possess a more profound comprehension of the etiological factors associated with PD and the mechanisms that regulate host immune responses. Most importantly, technological advancements have provided dentists with a wide range of options for PD treatment.

Non-surgical techniques for plaque and calculus removal, such as scaling and root planing (SRP), along with the adjunctive use of non-steroidal anti-inflammatory drugs and antioxidant dietary supplements,[85] have the potential to enhance periodontal ligament health and yield clinical benefits. Table 1 provides a list of various non-surgical treatment modalities employed in the management of PDs. A systematic review reported that both surgical and non-surgical preventive therapies had a significant improvement in the clinical parameters of DS patients. Moreover, a higher frequency of interventions was found to be closely associated with better outcomes, especially in younger age groups.[48]

Due to learning disorders in DS patients, lengthy treatments, such as periodontal surgical therapy under local anesthesia, which requires high patient tolerance and long treatment duration, are generally impractical. In addition, the escalating issue of antimicrobial resistance has led to increased efforts in seeking alternative therapies.[86] Therefore, periodontal treatment approaches that primarily focus on pathogen eradication, plaque control and utilize simpler methods are undeniably more suitable for DS patients. In this section, we present several nonsurgical treatment approaches that target pathogenic bacteria and the immune mechanisms involved in the development of PD.

3.1 | Photodynamic therapy

Antimicrobial photodynamic therapy (PDT) was introduced in the late 1990s as a complementary treatment to SRP. PDT is a noninvasive therapeutic method that involves targeting microorganisms with a photosensitizer using appropriate low-power light energy.[87] The mechanism of action can be described as follows: when the

TABLE 1 Non-surgical therapeutic approaches and adjunctive methods for periodontal disease treatment.

Treatment approach	Description
Oral Hygiene Education[134]	Educating patients about proper oral hygiene practices, including brushing, flossing, and interdental cleaning. Emphasizing the importance of regular dental check-ups
Scaling and Root Planing (SRP)[135]	A non-surgical procedure performed by a dentist or dental hygienist to remove plaque, calculus, and bacteria from the tooth surfaces and root surfaces below the gumline
Antibacterial Mouthwash[136]	Use of antimicrobial or antibacterial mouthwash to reduce bacterial growth and inflammation in the oral cavity. May contain chlorhexidine or other active ingredients.
Systemic and local Antibiotics[136,137]	Application of systemic antibiotics (doxycycline, amoxicillin, and metronidazole) or local antibiotics (minocycline microspheres, chlorhexidine chips) directly into periodontal pockets to control infection and inflammation
Antimicrobial photodynamic therapy[138]	Use of a low-level light (led or laser) to remove infected tissue, promote gum reattachment, and reduce periodontopathogens particularly *P. gingivalis* in periodontal pockets
Probiotics, prebiotics, symbiotics[139]	Use of probiotics (live microorganisms), prebiotics (non-digestible substances), and symbiotics (a combination of probiotics and prebiotics) to the restoration of microbial balance, immune modulation and reduction of pathogens

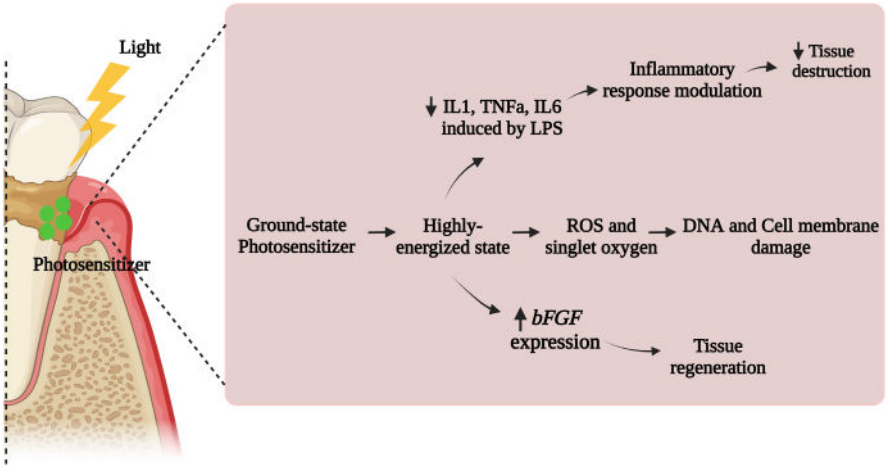

FIGURE 2 Photodynamic therapy inhibits periodontal pathogens and promotes tissue regeneration in periodontal pockets. bFGF, basic fibroblast growth factor; LPS, lipopolysaccharide; ROS, reactive oxygen species; TNF, tumor necrosis factor.

photosensitizer is exposed, it transitions into a high-energy triplet state, which interacts with surrounding molecules. These interactions generate ROS such as superoxide, hydrogen peroxide, hydroxyl radicals, as well as singlet oxygen ($^1O_2$), another highly reactive form of oxygen. These reactive species can cause damage to the DNA and cell membrane of bacteria[88] (Figure 2).

PDT offers benefits beyond eradicating bacteria. It can also reduce the levels of pro-inflammatory cytokines such as IL-1, TNFα, and IL-6 induced by LPS, leading to the modulation of inflammatory responses and reduced tissue destruction.[89] Moreover, PDT enhances the expression of basic fibroblast growth factor (bFGF) genes, which contribute to tissue regeneration, angiogenesis, osteogenesis, fibroblast proliferation, and reduction of cell death in periodontal tissues.[90] PDT possesses several advantages over conventional antimicrobials, including its ability to broadly and rapidly eliminate target organisms, minimal side effects due to localized treatment, and the prevention of resistance development through lethal photosensitization.[91]

The primary objective of periodontal therapy is to eliminate bacterial deposits by removing the supragingival and subgingival biofilms.[92] Due to the intricate anatomy of tooth roots, particularly in deep periodontal pockets, conventional mechanical therapy may not completely eliminate all periodontal pathogens.[93] Local infections in the oral cavity, including PD, can be potential targets for antimicrobial PDT. Dental plaque biofilms on tooth surfaces are easily accessible for flushing with a photosensitizer and subsequent activation by light.[87] In vitro studies have demonstrated the effectiveness of PDT in inhibiting biofilm formation and reducing periodontopathogens such as *S. mutans*, *P. gingivalis*, *A. actinomycetemcomitans*, and *P. acnes*.[94,95] Furthermore, following a reduction in the bacterial load in PD, improvements in clinical indicators of inflammation, including redness and bleeding upon probing have been demonstrated.[93]

Table 2 shows that adjunctive PDT in patients with and without DS can improve clinical attachment levels, reduce bleeding, periodontal pathogens, and probing pocket depth (PPD) in chronic and aggressive PD. Although few studies have been published on the efficacy of PDT in DS patients, it appears that PDT may be a potential candidate for nonsurgical treatments in this population.

3.2 | Probiotic uses for treatment

Probiotics are living microorganisms that, when administered in sufficient quantities, provide health benefits to the host. The term "prebiotic" refers to non-digestible oligosaccharides that stimulate the growth or activity of beneficial bacteria.[96] Probiotics act by interfering with the colonization of pathogens through various mechanisms, including prevention of tissue binding, inhibition of virulence factors, and production of antimicrobial compounds such as bacteriocins.[97] Probiotics can also reduce immune cell immigration and inflammation. Furthermore, probiotics have the ability to repair inflammation-related epithelial damage by upregulating structural proteins.[98] The most commonly used probiotics in the treatment of oral diseases belong to the *Lactobacillus*, *Streptococcus* and *Bifidobacterium* species.[99] Many strains of *lactobacilli* and *streptococci* isolated from healthy oral cavities exhibit antibacterial activity against *P. gingivalis*, *P. intermedia*, and *A. actinomycetemcomitans*.[100] Certain *Lactobacillus* strains, including *L. paracasei* and *L. acidophilus*, demonstrate an inhibitory effect on the growth of *S. aureus*, an important periodontopathogen in aggressive PD.[101] Remarkably, the modulation of immune responses by *Lactobacillus* and *Bifidobacterium* strains leads to a decrease in the level of inflammatory cytokines such as IL -1β, IL -6, and TNF-α.[102] *Lactobacillus* strains also reduce the inflammatory response to *P. gingivalis* by decreasing IL-8 expression in gingival epithelial cells.[103] Numerous studies have shown that supplemental administration of probiotics, in comparison to mechanical procedures alone, leads to improved clinical outcomes, including reductions in probing pocket depth, gingival index, gingival bleeding index, plaque index, bleeding on probing, and clinical attachment.[104–107] These remarkable results have been demonstrated also in patients with implants.[108] In these cases, oral microbiota showed some differences[109] but probiotic therapy has been demonstrated to be an efficient adjuvant therapy. A recent meta-analysis reported that administration of probiotics, particularly *Lactobacillus* species, results in a significant reduction in the number of periodontopathogens, including *P. gingivalis*, *T. forsythia*, *P. intermedia*, and *A. actinomycetemcomitans* in the subgingival and supragingival environments and saliva.[110] Prebiotics exert a significant beneficial effect on the alteration of bacterial communities, promoting a more favorable composition and reducing the presence of pathogenic species such as *P. gingivalis* and

TABLE 2 The recent studies on the application of photodynamic therapy in periodontal diseases.

Study	Sample size	Bacterial population	Disease	Photosensitizer	Outcome	Reference
Novaes et al. (2012)	10 patients (8 F, 2 M)	*Aggregatibacter* actinomycetemcomitans, *Tannerella forsythia*, *Porphyromonas gingivalis*, *Treponema denticola*	Aggressive periodontitis	Phenothiazine chloride	Adjunctive PDT was more effective in reducing *A. actinomycetemcomitans* than SRP	140
Theodoro et al. (2012)	33 patients (21 F, 12 M)	*A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, *Prevotella intermedia*, *Prevotella nigrescens*	Chronic periodontitis	Toluidine blue	Adjunctive PDT showed a significant reduction in the percentage of sites positive for all bacteria compared with SRP	141
Berakdar et al. (2012)	22 patients (10 F, 12 M)	–	Chronic periodontitis	Methylene blue	Adjunctive PDT showed a significant CAL reduction compared with SRP	142
Campos et al. (2013)	13 patients (8 F, 5 M)	–	Chronic periodontitis	Methylene blue	Adjunctive PDT showed a significant PPD, BOP reduction, and CAL compared with SRP	143
Petelin et al. (2014)	27 patients (12 F, 15 M)	*A. actinomycetemcomitans*, *P. gingivalis*, *T. denticola*, *P. intermedia*, *T. forsythia*	Chronic periodontitis	Phenothiazine chloride	Adjunctive PDT showed a greater reduction of *A. actinomycetemcomitans*, *T. forsythia* and *T. denticola* in medium pockets compared with SRP	144
Chitsazi et al. (2014)	24 patients (15 F, 9 M)	*A. actinomycetemcomitans*	Aggressive periodontitis	Toluidine blue	Adjunctive PDT showed a significant reduction in the counts of *A. actinomycetemcomitans* at 90 days compared to baseline	145
Moreira et al. (2015)	20 patients (18 F, 2 M)	*A. actinomycetemcomitans*, *T. forsythia*, *P. gingivalis*, *T. denticola*, *F. nucleatum*, *P. intermedia*, *Streptococcus constellatus*	Aggressive periodontitis	Phenothiazine chloride	Adjunctive PDT showed a significantly less periodontal pathogens, a decrease in PPD and a lower ratio IL-1β/IL-10 than SRP	146
Martins et al. (2016)	13 DS patients (4 F, 9 M)	–	Periodontitis	Methylene blue	Similar PPD in adjunctive PDT and control group	147
Al Ahmari et al. (2019)	83 patients (15 F, 14 M)	–	Chronic periodontitis	Methylene blue	Similar PI, BOP, and CAL in adjunctive PDT and control group	148
Joshi et al. (2019)	29 patients (15 F, 14 M)	–	Chronic periodontitis	Indocyanine green	Adjunctive PDT showed a significant reduction in PPD and CAL	149
Derikvand et al. (2020)	50 patients	–	Chronic periodontitis	Methylene blue	Adjunctive PDT showed a significant reduction in PI, GI and PD	150
Aabed et al. (2022)	34 patients	*A. actinomycetemcomitans*, *P. gingivalis*	Chronic periodontitis	Methylene blue	Similar PI, GI, PD, CAL and bacterial count in adjunctive PDT and control group	151
Silva et al. (2022)	8 DS patients (6 F, 2 M)	–	Periodontitis	Methylene blue	Adjunctive PDT showed a significant reduction in BOP	152

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; DS: Down syndrome; F, Female; GI: gingival index; IL, interleukin; M, Male; PDT, photodynamic therapy; PI, plaque index; PPD, probing pocket depth; SRP, scaling and root planing.

TABLE 3 Studies on the application of probiotics in the treatment of periodontitis.

Study	Population	Disease	Probiotic	Main treatment	Periodontal assessment	Main outcomes
Teughels et al. (2013)[105]	30 patients (15 F, 15 M)	Chronic periodontitis	*Lactobacillus reuteri* DSM17938, *L. reuteri* ATCC PTA5289	SRP	PPD, GI, PI, BOP, CAL; microbial parameters	Significant reduction of PPD, *P. gingivalis* count and greater gain of CAL in the probiotic group
Vicario et al. (2013)[153]	19 patients (7 F, 12 M)	Chronic periodontitis	*L. reuteri* ATCC 55730, *L. reuteri* ATCC PTA5289	SRP	PPD, PI, BOP	Significant reduction of PPD, PI, BOP in the probiotic group
Shah et al. (2013)[154]	30 patients (16 F, 14 M)	Aggressive periodontitis	*L. brevis*	SRP + Antibiotic therapy	PPD, GI, PI, CAL microbial parameters	Similar clinical improvements in control and test groups., increasing of *Lactobacilli* counts in saliva in the probiotic group
Tekce et al. (2015)[104]	40 patients (22 F, 18 M)	Chronic periodontitis	*L. reuteri*	SRP	PPD, GI, PI, BOP, CAL; microbial parameters	Significant reduction of PI, GI, BOP and PPD and reduction of the proportions of obligate anaerobes in the probiotic group
Ince et al. (2015)[107]	30 patients (13 F, 17 M)	Chronic periodontitis	*L. reuteri*	SRP	PPD, GI, PI, BOP, CAL; biochemical parameters	Significant reduction of PI, GI, BOP, and PPD, and GCF MMP-8 and increasing of TIMP-1 levels in the probiotic group
Laleman et al. (2015)[106]	48 patients (22 F, 26 M)	Advanced periodontitis	*Streptococcus oralis* KJ3, *S. uberis* KJ2, *S. rattus* JH145	SRP	PPD, REC, CAL, BOP, PI, GI, microbial parameters	Significant reduction of PI in the probiotic group. Reduction of *P. intermedia* counts in the probiotic group
Morales et al. (2016)[155]	28 patients (14 F, 14 M)	Chronic periodontitis	*L. rhamnosus* SP1	SRP	PPD, CAL, PI, BOP	Similar clinical improvements in control and test groups
Costacurta et al. (2018)[156]	40 patients (20 F, 20 M)	Chronic periodontitis	*L. reuteri* ATCC PTA 5289	SRP	PPD, CAL, BOP	Significant reduction of BOP, and PPD in the probiotic group
Invernici et al. (2018)[157]	41 patients	Chronic periodontitis	*Bifidobacterium lactis* HN019	SRP	PI, BOP, microbial parameters	Significant reduction of PPD, CAL and significantly fewer periodontal pathogens of red and orange complexes in the probiotic group
Ikram et al. (2019)[158]	28 patients (11 F, 17 M)	Chronic periodontitis	*L. reuteri*	SRP	PPD, CAL, PI, BOP	Significant reduction in PPD and BOP and more gain in CAL in the probiotic group
Laleman et al. (2019)[159]	39 patients	Chronic periodontitis	*L. reuteri* ATCC PTA 5289, *L. reuteri* DSM 17938	SRP	PPD, CAL, PI, BOP, microbial parameters	Significant reduction in PPD in the probiotic group
Pelekos et al. (2019)[160]	41 patients (26 F, 15 M)	Chronic periodontitis	*L. reuteri*	SRP	PPD, CAL	Similar clinical improvements in control and test groups
Grusovin et al. (2019)[161]	20 patients (12 F, 8 M)	Aggressive periodontitis	*L. reuteri* DSM 17938, *L. reuteri* PTA 5389	Guided Bone Therapy	PPD, CAL, BOP	Significant reduction in PPD, PAL, BOP in the probiotic group
Theodoro et al. (2019)[162]	28 patients (13 F, 15 M)	Chronic periodontitis	*L. reuteri* DSM 17938	SRP	PPD, CAL, BOP	Significant reduction in BOP in the probiotic group
Pudgar et al. (2020)[163]	40 patients	Chronic periodontitis	*L. brevis*, *L. plantarum*	SRP	PPD, BOP, CAL, PI, microbial parameters	Similar clinical improvements in control and test group
Vohra et al. (2020)[164]	62 patients (62 M)	Chronic periodontitis	*L. reuteri* ATCC PTA 5289, *L. reuteri* DSM 17938	SRP	PPD, PI, BOP, CAL	Similar clinical improvements in control and test group
Alshareef et al. (2020)[165]	25 patients (13 F, 15 M)	Chronic periodontitis	*L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. salivarius*, *B. bifidum*	SRP	PPD, CAL, PI, biochemical and microbial parameters	Significant reduction in BOP and GCF/ MMP-8 levels in the probiotic group

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; F, Female; GCF, gingival crevicular fluid; GI, gingival index; M, Male; MMP-8, Matrix metalloproteinases; PI, plaque index; PPD, probing pocket depth; SRP, scaling and root planing; TIMP-1, Tissue inhibitor matrix metalloproteinase.

P. intermedia.[100] In addition, prebiotics have demonstrated a direct impact on the host by increasing the secretion of immunoglobulin A (IgA) and stimulating the expression of IL-10 and IFNs, thereby modulating inflammatory responses against pathogens.[111] The inhibitory properties of prebiotics such as xylitol, xylose, and arabinose on *S. mutans* and *C. albicans* have already been documented.[112–114]

As shown in Table 3, the efficacy of probiotics as an adjunctive method in the treatment of PD has been confirmed. To the best of our knowledge, no study has specifically investigated the use of probiotics or prebiotics in the treatment or prevention of oral disease in DS patients. However, considering the positive impact of probiotics in balancing oral flora and reducing periodontopathogens, it is plausible that this complementary treatment could be beneficial for these patients, particularly in cases involving dysbiosis of the oral microbiota. Additionally, other compounds such as postbiotics and lysates are objects of research.[115]

3.3 | Melatonin therapy

Melatonin, a natural hormone, possesses immunomodulatory and antioxidant effects that help combat inflammation and cell damage.[116] Within the oral cavity, melatonin functions as a paracrine factor on cells and contributes to the proliferation and synthesis of type I collagen, thereby promoting bone formation and reducing bone resorption.[117,118] Melatonin also down-regulates osteoclastogenesis mediated by the receptor activator for nuclear factor kappa B ligand (RANKL).[119] The interaction between the TNF superfamily, RANKL, RANK, and osteoprotegerin plays a crucial role in osteoclastogenesis and alveolar bone resorption.[120] The administration of melatonin treatment is associated with improvement in gingival index and pocket depth, a reduction in salivary RANKL concentrations, and an increase in salivary concentrations. These findings indicate that melatonin retards osteoclastogenesis, improves alveolar bone quality, and prevents the progression of PD.[121] Consequently, melatonin has the potential to enhance important periodontal aspects such as collagen fiber preservation, diminished alveolar bone resorption, and attachment to the root surface. Several studies have demonstrated that melatonin levels in GCF, saliva, and serum are lower in patients with chronic and aggressive PD compared to healthy controls or those with mild gingivitis, suggesting that melatonin may exert a protective role in PD.[122–124] Melatonin directly reduces oxidative stress by scavenging ROS and nitrogen radicals and indirectly by increasing antioxidant enzymes such as superoxide dismutase (SOD), catalase and peroxidases.[125] The antibacterial properties of melatonin against common PD pathogens like *S. aureus* and *C. albicans* have been confirmed. Melatonin assumes an immunomodulatory role by regulating the secretion of IL-2 and interferon α (IFNα), as well as the subsequent activation of Th1 lymphocytes. The immunomodulatory effects of melatonin in response to LPS result in the reduction of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-12, and increase of anti-inflammatory IL-10.[126] Limited research has been conducted on the evaluation of melatonin's effects on immune responses in DS children with PD. Huggard et al. reported that melatonin has the potential to reduce LPS-induced inflammatory responses in DS children compared with healthy subjects by decreasing the expression of CD11b and toll-like receptor 4 (TLR4), as well as genes involved in the inflammasome (NLRP3, IL-1β).[127] Although many studies have been conducted on the effects of melatonin on reducing ROS and pro-inflammatory responses in healthy individuals, the use of melatonin as a non-surgical therapy for DS individuals with PD requires careful consideration due to the elevated levels of SOD and IL-10 in DS patients, which may result in an imbalance between pro- and anti-inflammatory responses.

3.4 | Prevention of periodontal and treatment with chlorhexidine

Chlorhexidine gluconate (CHX) is a broad-spectrum anti-microbial compound belonging to the biguanide family. Its use as an antiseptic mouthwash effectively prevents bacterial biofilms in PD, plaque-induced gingivitis, dental caries, and oral soft tissue disease.[128] The antimicrobial properties of CHX also prevent the adherence of *C. albicans* to the surface of dentures and oral mucosa.[129]

Recent reports have demonstrated the effectiveness of CHX in the treatment of chronic PD.[130,131] Despite confirming its benefits as an adjunctive treatment in healthy individuals with PD, the use of CHX in the prevention and treatment of PD in individuals with DS has not been extensively studied. However, a systematic review conducted by Ferreira et al. revealed that among various chemical agents, CHX exhibited a reduction in bacterial plaque and gingival bleeding in DS patients.[48] Another meta-analysis conducted by Zhou et al. supported the use of CHX to prevent gingivitis in children and adolescents with intellectual disabilities, with over half of the reviewed studies yielding positive results. However, the authors emphasized the need for further research to determine the effectiveness of chemical interventions, such as CHX, in treating severe and advanced stages of PD.[132]

The clinical guideline for oral health care of patients with learning disabilities recommended the application of 1% CHX gel as a potentially effective adjunctive therapy to reduce PD in DS patients.[133] It is important to note that CHX is not suitable for treating all cases of PD and plaque-induced gingival diseases. Additionally, for established PD, adjunctive chemical agents may also be utilized.[128] As previously noted, the exploration of adjunctive non-surgical methods in individuals with DS remains incompletely investigated, with limited studies available in this area. The sole adjunctive treatment examined in individuals with DS is the utilization of chlorhexidine for the prevention and treatment of PDs.[48] Due to the distinctive conditions of these patients, including oral and orofacial abnormalities, immune system defects, and a specific composition of the oral bacterial community, it becomes imperative to undertake dedicated studies

to assess the effects and potential side effects of these adjunctive treatments. Furthermore, the necessity for systematic studies and meta-analyses to facilitate a comprehensive review of these treatment methods, coupled with informed decision-making regarding their application in the treatment of PDs in individuals with DS, is deemed beneficial for advancing clinical understanding.

4 | CONCLUSION AND FUTURE PROSPECTS

In conclusion, this review delved into the intricate relationship between DS and PDs, shedding light on predisposing factors and exploring potential non-surgical therapeutic approaches. Both endogenous factors, like genetics and host immune responses, and exogenous factors, like oral hygiene, are involved in the occurrence of PDs as a multifactor disease in these patients. Moreover, there are numerous reports on the altered oral microbiota and their impact on the rates of PD in subjects with DS. This review not only provides a foundational understanding but also highlights the imperative for future research to enhance our knowledge and guide evidence-based interventions for optimal periodontal care in individuals with DS. Due to the early onset of PDs in children with DS, the imperative for prompt and effective treatment in this demographic is evident. While there remains ample scope for future advancements in assessing the efficacy of these treatments in individuals with DS, it appears promising that adjunctive non-surgical treatments may offer a viable option for the prevention and treatment of PDs. This is owing to their convenience, lack of necessity for local anesthesia, and a reduced risk of antibiotic resistance. By addressing these research gaps, we can pave the way for tailored therapeutic approaches that consider the distinct challenges presented by DS, ultimately advancing the field of non-surgical treatment and improving the oral health outcomes for this vulnerable population.

ACKNOWLEDGMENTS

All authors have read the journal's authorship agreement and that the manuscript has been reviewed and approved by all named authors.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest in this study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Ghaffarpour M, Karami-Zarandi M, Rahdar HA, Feyisa SG, Taki E. Periodontal disease in down syndrome: Predisposing factors and potential non-surgical therapeutic approaches. *J Clin Lab Anal*. 2024;38:e25002. doi:10.1002/jcla.25002