International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	ROLE OF PRO- AND ANTI-INFLAMMATORY INTERLEUKINS IN PERIODONTITIS: MOLECULAR, IMMUNOLOGICAL, AND THERAPEUTIC SIGNIFICANCE
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6281
RECEIVED	26 May 2026
ACCEPTED	18 August 2026
PUBLISHED	26 August 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

ROLE OF PRO- AND ANTI-INFLAMMATORY INTERLEUKINS IN PERIODONTITIS: MOLECULAR, IMMUNOLOGICAL, AND THERAPEUTIC SIGNIFICANCE

Natasza Jankowska *(Corresponding Author, Email: jankowskanatasza@gmail.com)*
Specialized Dental Clinic, 5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0009-0491-3716

Marta Krzyżanowska
Mix-Med Arima Private Healthcare Institution, Radom, Poland
ORCID ID: 0009-0001-2932-0337

Agata Wnęk
Specialized Dental Clinic, 5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0004-5384-4597

Zuzanna Hucała
Specialized Dental Clinic, 5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0005-4859-1406

Natalia Dymel
5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0009-3928-5393

Weronika Jagiełło
5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0000-5200-9208

Natalia Le-Hong
5th Military Clinical Hospital with Polyclinic - Independent Public Healthcare Institution, Krakow, Poland
ORCID ID: 0009-0000-0540-8222

Alicja Biskup
University Dental Centre of the Silesian Medical University in Katowice, sp. z o.o., Bytom, Poland
ORCID ID: 0009-0001-2228-1478

ABSTRACT

Periodontitis is a chronic, biofilm-associated inflammatory disease in which tissue destruction reflects an altered host immune response more than the direct action of bacteria alone. This structured narrative review examines the molecular, immunological, diagnostic, and therapeutic significance of pro- and anti-inflammatory interleukins in periodontitis. A targeted literature search was performed in PubMed/MEDLINE, PubMed Central, Scopus, Web of Science, and Google Scholar for English-language publications from 2016 to 2026. Search terms combined 'periodontitis,' 'periodontal disease,' 'interleukin,' 'cytokine,' 'IL-1β,' 'IL-6,' 'IL-10,' 'IL-17,' 'IL-23,' 'IL-33,' 'IL-35,' 'IL-38,' 'inflammasome,' 'saliva,' and 'gingival crevicular fluid.' In the expanded search, 106 records were screened by title and abstract, 53 full-text papers were assessed, and 35 peer-reviewed publications were selected because they directly addressed interleukin expression, signaling, biomarker value, genetic variation, or therapeutic modulation in periodontal disease. Overall, IL-1β and IL-6 remain the most consistent salivary and gingival crevicular fluid biomarkers of disease severity. The IL-23/IL-17 pathway links adaptive immunity with neutrophil recruitment, RANKL expression, and osteoclastogenesis, whereas IL-10, IL-35, and IL-38 illustrate the importance of regulatory cytokine networks. Interleukin-directed therapy is not yet ready for routine periodontal use, but local, phenotype-guided immunomodulation may become a rational adjunct to conventional periodontal treatment.

KEYWORDS

Periodontitis, Interleukins, IL-1β, IL-6, IL-17, IL-10, Periodontal Immunology

CITATION

Natasza Jankowska, Marta Krzyżanowska, Agata Wnęk, Zuzanna Hucała, Natalia Dymel, Weronika Jagiełło, Natalia Le-Hong, Alicja Biskup. (2026). Role of Pro- and Anti-Inflammatory Interleukins in Periodontitis: Molecular, Immunological, and Therapeutic Significance. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6281

1. Introduction

Periodontitis is a chronic inflammatory condition affecting the gingiva, periodontal ligament, cementum, and alveolar bone. Although the disease begins in association with a dysbiotic subgingival biofilm, its clinical course is largely shaped by the magnitude, persistence, and quality of the host response. The 2017 World Workshop classification, with its emphasis on stage, grade, extent, distribution, and complexity, has made it easier to interpret biomarker studies within clinically meaningful disease phenotypes. Periodontitis is therefore best understood as a biofilm-induced and host-mediated disease rather than as a simple infection. This distinction matters in practice: scaling and root planing remain essential, but tissue breakdown and recurrence often reflect unresolved inflammatory dysregulation [1,2,3,4].

Interleukins are among the main molecular coordinators of this dysregulation. They relay danger signals from epithelial and myeloid cells, guide neutrophil trafficking, influence T-helper-cell differentiation, activate fibroblasts and osteoblast-lineage cells, and regulate osteoclastogenesis through the RANK/RANKL/osteoprotegerin system. Pro-inflammatory interleukins, including IL-1β, IL-6, IL-8, IL-17, IL-18, IL-23, and IL-33, can amplify periodontal inflammation. By contrast, IL-4, IL-10, IL-35, IL-37, and IL-38 contribute to counter-regulation and resolution. Advanced periodontitis develops when these opposing signals no longer maintain a stable tissue balance.

The translational relevance of interleukins has grown substantially during the last decade. Saliva and gingival crevicular fluid provide accessible, minimally invasive windows into the host response. IL-1β, IL-6, and IL-10 have repeatedly been assessed as biomarkers of disease stage and severity, while IL-17 and IL-23 have become central to current models of Th17-driven inflammation and bone loss. Meta-analytic evidence from gingival crevicular fluid studies supports increased IL-1β and IL-6 in chronic periodontitis and reductions in IL-1β and IL-17 after nonsurgical periodontal treatment. At the same time, biologic therapies used in rheumatoid arthritis, psoriasis, inflammatory bowel disease, and other immune-mediated disorders have encouraged interest in site-specific cytokine modulation as a possible periodontal adjunct. The challenge is

that interleukins are highly pleiotropic: a cytokine that supports mucosal defense in one setting may contribute to tissue destruction in another [4,5,6].

This review synthesizes the molecular, immunological, diagnostic, and therapeutic significance of pro- and anti-inflammatory interleukins in periodontitis, with particular attention to studies published during the last decade. The objectives are to outline how interleukins participate in periodontal immunopathogenesis, compare destructive and regulatory cytokine pathways, evaluate their potential value as biomarkers, and discuss the feasibility and limitations of interleukin-targeted therapeutic strategies.

2. Methodology

This article was prepared as a structured narrative review with a transparent search strategy, rather than as a registered systematic review. Literature was identified through PubMed/MEDLINE, PubMed Central, Scopus, Web of Science, publisher databases, and Google Scholar. The search covered English-language publications published between 2016 and 2026 and was last updated on June 2026. The search strategy combined terms related to periodontal disease, interleukin biology, cytokine signaling, biomarker assessment, and host-modulatory therapy. The following terms were used alone and in combination: periodontitis, periodontal disease, gingivitis, interleukin, cytokine, IL-1β, IL-6, IL-8, IL-10, IL-17, IL-18, IL-23, IL-33, IL-35, IL-37, IL-38, Th17, Treg, inflammasome, biomarker, saliva, gingival crevicular fluid, tocilizumab, cytokine-targeted therapy, photodynamic therapy, probiotics, omega-3 fatty acids, and host-modulation therapy. Priority was given to peer-reviewed publications, especially systematic reviews, meta-analyses, clinical observational studies, and mechanistic experimental work.

The initial search produced 106 candidate records. After title and abstract screening, 53 full-text publications were reviewed for eligibility, and 35 peer-reviewed studies were selected for citation in the final manuscript. Articles were included when they directlyaddressed periodontitis, the gingivitis-periodontitis transition, periodontal tissue inflammation, experimental periodontitis, interleukin expression, cytokine signaling, genetic variation, biomarker utility, or therapeutic modulation. Additional papers were considered when they clarified periodontal classification, inflammation-dysbiosis coupling, nonsurgical periodontal therapy, or adjunctive host-modulatory approaches.

Exclusion criteria included duplicate reports, conference abstracts without full peer-reviewed articles, studies focused exclusively on non-periodontal oral lesions, and papers centered on unrelated mediators unless they directly clarified interleukin-related mechanisms. Because this was a structured narrative review, no formal risk-of-bias assessment, duplicate independent screening, or quantitative synthesis was performed. The findings should therefore be interpreted as a conceptual and translational synthesis rather than as a systematic review or meta-analysis.

3. Results: Thematic Synthesis of the Evidence

The evidence was organized into interconnected thematic domains covering the transition from dysbiosis to tissue injury, pro-inflammatory interleukin pathways, anti-inflammatory and regulatory interleukin pathways, diagnostic and prognostic applications, therapeutic implications, molecular mechanisms of matrix breakdown and bone loss, systemic connections, clinical implementation, and limitations of the current evidence. This structure reflects the narrative-review design of the manuscript and allows mechanistic, diagnostic, and translational aspects of the evidence to be discussed together.

3.1. From Dysbiosis to Cytokine-Driven Periodontal Damage

Periodontal tissues are continuously exposed to microbial products and mechanical stress. In health, epithelial barriers, neutrophils, macrophages, dendritic cells, and resident stromal cells generate proportionate responses that preserve tissue integrity. Dysbiosis disrupts this equilibrium. Bacterial lipopolysaccharides, fimbriae, proteases, extracellular vesicles, and damage-associated molecular patterns activate pattern-recognition receptors, including Toll-like receptors and inflammasome-associated pathways. This triggers the release of IL-1 family cytokines, IL-6, IL-8/CXCL8, tumor necrosis factor, prostaglandin E2, chemokines, and matrix metalloproteinases. The resulting inflammation-dysbiosis loop is now regarded as a core element of periodontal pathobiology [2, 8, 9].

The shift from protective inflammation to destructive periodontitis is marked by a feed-forward cytokine circuit. IL-1β and IL-6 promote endothelial activation, leukocyte recruitment, fibroblast stimulation, and protease release. IL-6 contributes to Th17 differentiation, whereas IL-23 sustains IL-17-producing cells. IL-17 then acts on epithelial cells, fibroblasts, osteoblast-lineage cells, and macrophages to induce chemokines, matrix metalloproteinases, neutrophil recruitment, and RANKL-mediated osteoclastogenesis. In this way,

microbial dysbiosis is linked to the central pathological features of periodontitis: connective tissue breakdown and alveolar bone loss [10, 11].

Macrophage polarization and persistent neutrophil activity are also crucial. A rapid, balanced neutrophil response helps contain bacterial spread; chronic recruitment and activation, however, produce collateral damage through reactive oxygen species, extracellular traps, and proteases. M1-like macrophages amplify IL-1β, IL-6, IL-12, IL-18, and TNF-related signaling, while M2-like and regulatory macrophage phenotypes are associated with IL-10, repair, and resolution. Periodontitis can therefore be described not only as excessive inflammation, but also as a failure of resolution [3,11].

Table 1. Key interleukins in periodontitis and their major biological significance.

Interleukin / axis	Predominant role	Main periodontal effects	Clinical relevance
IL-1β / inflammasome	Pro-inflammatory	MMP induction, prostaglandin production, RANKL expression, osteoclastogenesis	Strong biomarker and therapeutic-target candidate
IL-6	Pro-inflammatory and systemic mediator	Th17 differentiation, acute-phase response, RANKL-related bone loss	Biomarker; possible target through IL-6R blockade
IL-8 / CXCL8	Chemotactic mediator	Neutrophil recruitment and persistence in periodontal pockets	Inflammatory activity marker, limited specificity
IL-23 / IL-17	Th17-maintaining and effector axis	Neutrophil recruitment, stromal activation, MMPs, RANKL, bone resorption	Risk stratification and experimental therapeutic target
IL-18	Inflammasome-related pro-inflammatory mediator	Th1 amplification and induction of IL-1β, IL-6, TNF-related cascades	Complementary biomarker in saliva/GCF/serum
IL-33 / ST2	Context-dependent	Barrier alarm signal; may support acute protection or chronic osteoclastogenic inflammation	Potential biomarker; timing-dependent function
IL-10	Regulatory / anti-inflammatory	Suppression of antigen presentation and pro-inflammatory cytokine production	Indicator of regulatory compensation and inflammatory balance
IL-35 / IL-37 / IL-38	Emerging regulatory interleukins	Th17 suppression, innate immune restraint, possible IL-1 family antagonism	Experimental biomarkers and future therapeutic candidates

3.2. Pro-Inflammatory Interleukins

3.2.1. IL-1β and Inflammasome-Dependent Inflammation

IL-1β is one of the cytokines most consistently linked with periodontal tissue destruction. It is produced by macrophages, dendritic cells, neutrophils, epithelial cells, and fibroblasts after stimulation by microbial products and endogenous danger signals. Unlike many cytokines, IL-1β requires post-translational activation through inflammasome-mediated processing, most often involving NLRP3-dependent caspase-1 activation. The inflammasome-IL-1β pathway therefore connects microbial sensing, pyroptotic cell death, and destructive inflammation. The wider IL-1 superfamily, including IL-18, IL-33, IL-37, and IL-38, adds both inflammatory amplification and regulatory counter-signals within periodontal lesions [12, 13, 14].

At the tissue level, IL-1β induces adhesion molecules, chemokines, prostaglandins, and matrix metalloproteinases. It also stimulates fibroblasts and osteoblast-lineage cells to express RANKL, thereby promoting osteoclast differentiation and alveolar bone resorption.

Meta-analytic evidence shows increased salivary and gingival crevicular fluid IL-1β in periodontitis, often together with MMP-8 and MMP-9, supporting its role as both a mechanistic mediator and a biomarker. A recent meta-analysis of adjunctive antimicrobialphotodynamic therapy used gingival crevicular fluid IL-1β as an inflammatory outcome in stage III and IV periodontitis, further illustrating its value for treatment-response monitoring. Experimental and translational evidence also suggests that inflammasome-related pathways may represent potential targets for future host-modulatory strategies, although patient phenotype, systemic status, microbial profile, and treatment modality are likely to influence the biological response [5,13,15,16].

3.2.2. IL-6 as a Local and Systemic Inflammatory Bridge

IL-6 is a pleiotropic cytokine produced by epithelial cells, macrophages, fibroblasts, endothelial cells, and osteoblast-lineage cells. It contributes to acute inflammation, B-cell differentiation, hepatic acute-phase responses, and Th17 polarization. In periodontitis, IL-6 is particularly important because it connects local periodontal inflammation with systemic low-grade inflammation and comorbidities such as diabetes, cardiovascular disease, and rheumatoid arthritis [17].

Molecularly, IL-6 signals through both classical membrane-bound IL-6 receptor pathways and trans-signaling mechanisms. In periodontal tissues it enhances inflammatory mediator production, supports Th17 differentiation, and contributes to RANKL-dependent osteoclastogenesis. Salivary biomarker studies frequently identify IL-6, often together with IL-1β and MMP-8, as a promising indicator of disease severity or early diagnosis. A 2024 clinical study found that salivary IL-1β, IL-6, and IL-10 were associated with periodontitis severity, with stronger associations for disease stage than for progression grade [6].

From a therapeutic perspective, IL-6 is attractive because IL-6 receptor blockade is already used in systemic inflammatory disorders. In periodontology, however, the available evidence remains preliminary and should not be interpreted as support for routine biologic therapy.

Experimental work indicates that local tocilizumab administration may reduce alveolar bone loss and inflammation in experimental periodontitis. These findings strengthen the concept of localized cytokine modulation as a possible future adjunct to conventional periodontal debridement in selected high-risk phenotypes, but dose, timing, delivery vehicle, safety, and patient selection require further investigation before clinical implementation [18].

3.2.3. The IL-23/IL-17 Axis

The IL-23/IL-17 axis occupies a central position in current models of periodontal immunopathogenesis. IL-17A, and to a lesser extent IL-17F, is produced by Th17 cells, γδ T cells, innate lymphoid cells, and other immune populations. IL-23 maintains the survival and pathogenicity of IL-17-producing cells, whereas IL-6, IL-1β, and TGF-β contribute to the early environment that favors Th17 differentiation [10, 19].

IL-17 has a dual biological role. In mucosal defense it promotes antimicrobial peptides and neutrophil recruitment, helping to control extracellular bacteria and fungi. In chronic periodontitis, persistent IL-17 signaling can instead amplify destructive inflammation. It stimulates epithelial cells and fibroblasts to produce chemokines, induces cyclooxygenase-2 and prostaglandin E2, increases matrix metalloproteinase activity, and promotes RANKL expression. This provides a mechanistic bridge between adaptive immunity, sustained neutrophil recruitment, and osteoclastogenesis.

Recent reviews and genetic analyses support the clinical relevance of this pathway. Salivary IL-17A and IL-23 vary according to periodontal status, while systematic review data suggest that IL-17A variants, especially rs2275913, may be associated with periodontitis or peri-implantitis in some populations. A separate meta-analysis of IL-17A polymorphism and chronic periodontitis highlights the importance of host genotype when cytokine profiles are interpreted. The evidence remains heterogeneous, which suggests that ethnicity, disease phenotype, environmental exposure, and comorbidity may modify these associations. Experimental studies further show that type I interferon signaling can restrain an IL-17-neutrophil axis and protect against bone loss, reinforcing the view that IL-17 functions within a wider regulatory network rather than as an isolated driver [19, 20, 21].

3.2.4. IL-18, IL-33, and IL-8/CXCL8

Several additional pro-inflammatory or context-dependent interleukins contribute to the periodontal cytokine network. IL-18, another IL-1 family cytokine, is generated after inflammasome-associated processing. It can amplify Th1 responses and induce IFN-γ in the presence of IL-12. A 2024 systematic review and meta-analysis reported significantly higher IL-18 levels in serum, saliva, and gingival crevicular fluid from patients with chronic periodontitis, supporting its potential as a complementary biomarker. Mechanistically, IL-18 may reinforce IL-1β, IL-6, and TNF-related pathways and thereby sustain a chronic inflammatory cycle [22].

IL-33 is more difficult to classify in a simple pro- or anti-inflammatory framework. It is released by epithelial, endothelial, and stromal cells and signals through the ST2 receptor. A 2024 meta-analysis found increased IL-33 in plasma, saliva, and gingival crevicular fluid in chronic periodontitis, suggesting biomarker potential. Experimental work, however, also indicates that the IL-33/ST2 axis may protect against acute periodontal inflammation. This apparent contradiction illustrates a broader principle of interleukin biology: cytokine effects depend on timing, cellular source, receptor expression, and inflammatory context. Early IL-33 may support barrier immunity and repair, whereas persistent expression may accompany or enhance osteoclastogenic inflammation [23,24].

IL-8/CXCL8 is often classified as a chemokine rather than a classical interleukin, but its historical name, interleukin-8, and its biological role make it highly relevant to periodontal neutrophil recruitment. Increased IL-8 in gingival crevicular fluid and serum has been investigated as a marker of inflammation. Clinically, it may be less specific than IL-1β or IL-6, yet it remains important for understanding how neutrophil accumulation persists within periodontal pockets.

3.3. Anti-Inflammatory and Regulatory Interleukins

Anti-inflammatory and regulatory interleukins do more than suppress immunity. They help recalibrate the inflammatory response so that microbial control can occur without unnecessary tissue damage. IL-10 is the best-characterized regulatory interleukin in periodontitis. It is produced by regulatory T cells, macrophages, dendritic cells, B cells, and some epithelial populations. IL-10 limits antigen presentation, reduces IL-1β, IL-6, IL-12, and TNF-related cytokine production, and restrains Th1 and Th17 polarization. Meta-analytic evidence suggests that IL10 polymorphisms may influence susceptibility to chronic or aggressive periodontitis, although associations differ across populations [25].

Clinical cytokine data suggest that IL-10 may increase as a compensatory response in some patients, but this response is often insufficient to halt tissue destruction. In diabetic periodontitis, the balance between IL-1β, TNF-α, and IL-10 may be especially relevant because hyperglycemia promotes oxidative stress, advanced glycation end-products, and exaggerated inflammatory signaling. Scaling and root planning can modify TNF-α, IL-1β, and IL-10 levels, supporting the idea that microbial disruption and immune recalibration are closely linked [27]. Psychological stress may further disturb this balance through neuroendocrine-immune pathways that interact with IL-10-mediated immunoregulation [26].

IL-4 and IL-13 are associated with Th2 responses, alternative macrophage activation, antibody regulation, and tissue repair. Their genetic polymorphisms have been studied in chronic periodontitis, including in Han Chinese populations. Although Th2 responses alone cannot explain periodontal disease, IL-4 and IL-13 may counterbalance excessive macrophage activation and favor more reparative tissue phenotypes [28].

Emerging regulatory interleukins have also become an important area of research. IL-35, produced by regulatory T and B cells, may suppress Th17 responses and support immune tolerance; systematic scoping and recent narrative reviews describe its possible biomarker, genetic, and treatment-response relevance in periodontal disease. IL-37 broadly suppresses innate and adaptive inflammation, although direct periodontal clinical evidence remains limited. IL-38, a member of the IL-1 family, may antagonize pro-inflammatory IL-1 family signaling. A recent cross-sectional study reported lower salivary IL-38 levels in periodontitis than in periodontal health, while IL-1β was higher, suggesting that insufficient IL-38-mediated regulation may contribute to periodontal inflammation [12, 29, 30, 31].

3.4. Diagnostic and Prognostic Significance

Interleukin-based diagnostics are appealing because periodontitis is currently staged and graded mainly through clinical and radiographic evidence of past destruction. Biomarkers could add information about current inflammatory activity, progression risk, and treatment response. Saliva is especially useful because it is non-invasive, repeatable, and compatible with future chairside or point-of-care technologies. Gingival crevicular fluid provides more site-specific information, but it is also more technique-sensitive.

The strongest biomarker evidence concerns IL-1β and IL-6, particularly when they are combined with MMP-8, MMP-9, MIP-1α, IL-8, IL-17, or clinical parameters. Systematic reviews of salivary and gingival crevicular fluid biomarkers show that no single mediator is robust enough for diagnosis across heterogeneous populations. Multi-marker panels appear more promising. In particular, combinations that include IL-1β, IL-6, MMP-8, and related inflammatory markers may distinguish periodontal health, gingivitis, and periodontitis more effectively than isolated cytokine measurements [5, 7, 16, 32].

IL-10 adds regulatory information to these panels. A high IL-1β/IL-10 or IL-6/IL-10 imbalance may represent destructive inflammation more accurately than absolute cytokine values alone. IL-17 and IL-23 could improve risk prediction in patients with Th17-dominant inflammation, while IL-18 and IL-33 may broaden inflammatory profiling. Emerging markers such as IL-35 and IL-38 may help identify defective resolution pathways. Important barriers remain, including inconsistent case definitions, variable saliva collection protocols, assay-platform differences, confounding by smoking, diabetes, and medication use, and limited longitudinal validation.

Table 2. Translational implications of interleukin research in periodontitis.

Application	Most relevant interleukins	Current status and limitations
Screening / risk assessment	IL-1β, IL-6, IL-17, IL-23, IL-10	Promising in multi-marker panels; needs longitudinal validation
Monitoring response to therapy	IL-1β, IL-6, IL-10, MMP-linked panels	Potential adjunct to clinical parameters; assay standardization required
Host modulation	IL-1β, IL-6, IL-17, IL-10, IL-35, IL-38	Mostly preclinical or indirect clinical evidence; local delivery preferred
Precision periodontology	Combined pro- and anti-inflammatory signatures	Requires integration with smoking, diabetes, microbiome, and genetic factors

Table 3. Evidence map linking major interleukin groups with mechanisms, evidence strength, and translational relevance.

Interleukin group	Mechanistic role	Evidence pattern	Translational use
IL-1 family: IL-1β, IL-18, IL-33	Inflammasome activation; epithelial and myeloid alarm signaling; MMP and prostaglandin induction	Generally elevated in periodontitis; strongest evidence for IL-1β, growing meta-analytic evidence for IL-18 and IL-33	Biomarker panels, inflammasome modulation, locally delivered host-modulatory strategies
IL-6 pathway	Classical and trans-signaling; acute-phase bridge; Th17 support; RANKL-associated bone loss	Consistently associated with severity in saliva/GCF; linked to systemic inflammatory comorbidities	Risk stratification and potential adjunctive IL-6R modulation in selected phenotypes
IL-23/IL-17 axis	Th17 maintenance; neutrophil recruitment; stromal activation; osteoclastogenic RANKL signaling	Clinical, salivary, genetic, and experimental evidence supports a role in destructive inflammation	Precision phenotyping; cautious local modulation because IL-17 supports mucosal defense
Regulatory interleukins: IL-10, IL-35, IL-37, IL-38	Suppression of excessive antigen presentation, Th17 activity, and IL-1-family signaling	IL-10 is best characterized; IL-35 and IL-38 remain emerging but biologically plausible	Restoration of resolution pathways, biomarker ratios such as IL-1β/IL-10, and future pro-resolving adjuncts

3.5. Therapeutic Significance

Conventional periodontal therapy reduces microbial load and disrupts dysbiotic biofilms, thereby indirectly lowering inflammatory cytokine production. Systematic evidence continues to support subgingival instrumentation as the foundation of periodontitis treatment. Nevertheless, persistent inflammatory activity after mechanical therapy has prompted interest in adjunctive host modulation. The key question is whether direct or indirect interleukin modulation can improve outcomes beyond debridement, oral-hygiene reinforcement, risk-factor control, and maintenance care. Current evidence is promising but still preliminary [5, 33].

Blocking IL-1β or inflammasome activation may reduce osteoclastogenic signaling, especially in patients with a strong IL-1β inflammatory signature. However, IL-1 pathways are important for host defense, and broad systemic inhibition could increase infection risk. Local delivery may limit systemic exposure and allow more precise site-specific modulation. Adjunctive antimicrobial photodynamic therapy has been evaluated using gingival crevicular fluid IL-1β as an inflammatory outcome, indicating that cytokine reduction can be a meaningful biological endpoint even when clinical outcomes vary. IL-6 receptor blockade is already

established in systemic inflammatory disease, and experimental local tocilizumab studies suggest reductions in periodontal inflammation and bone loss. Dose, timing, delivery vehicle, and patient selection still require careful study [15, 18].

Targeting the IL-23/IL-17 axis is biologically plausible because this pathway promotes neutrophil recruitment and RANKL-mediated osteoclastogenesis. Yet IL-17 also contributes to mucosal defense. Complete blockade could impair barrier immunity or alter the oral microbiome. A more realistic periodontal strategy may involve local, partial, or time-limited modulation rather than chronic systemic inhibition. Enhancing regulatory pathways offers another option. Interventions that increase IL-10, IL-35, IL-37, or IL-38 activity could support resolution without fully suppressing antimicrobial immunity. Biomaterials, nanoparticles, hydrogels, and host-modulation agents may eventually allow these signals to be delivered directly into periodontal pockets.

Adjunctive therapies also need to be integrated with systemic risk management. Glycemic control, smoking cessation, nutrition, stress reduction, and management of inflammatory comorbidities can influence cytokine tone and treatment response. Probiotics, omega-3 fatty acids, and other host-modulatory approaches may indirectly shift interleukin profiles toward resolution, although clinical effects remain variable and depend on study design, formulation, dose, and baseline inflammatory phenotype [34,35].

3.6. Molecular Pathways Linking Interleukins to Matrix Breakdown and Bone Loss

Interleukins convert periodontal dysbiosis into tissue destruction through several converging molecular pathways. First, IL-1β, IL-6, IL-17, and IL-18 activate NF-κB and MAPK signaling in epithelial cells, fibroblasts, macrophages, and osteoblast-lineage cells. These transcriptional programs increase chemokines, prostaglandins, matrix metalloproteinases, and inflammatory mediators. The result is a microenvironment in which connective-tissue degradation becomes self-sustaining.

Second, interleukins regulate the RANK/RANKL/osteoprotegerin system that controls osteoclast differentiation. IL-1β and IL-6 promote RANKL expression in periodontal ligament cells, osteoblasts, and activated T cells. IL-17 further amplifies RANKL and supports osteoclastogenic signaling. When osteoprotegerin is insufficient to buffer this response, the RANKL/osteoprotegerin ratio shifts toward bone resorption.

Third, inflammasome activity provides a maturation checkpoint for IL-1β and IL-18. NLRP3 and related inflammasomes detect microbial, metabolic, and danger signals, leading to caspase-1 activation, processing of pro-IL-1β and pro-IL-18, and pyroptotic cell death. In a periodontal pocket, repeated inflammasome activation can turn short-lived protective inflammation into chronic tissue injury.

Fourth, interleukins shape adaptive immunity. IL-6 and IL-1β promote Th17 differentiation, IL-23 stabilizes pathogenic Th17 responses, and IL-17 acts on non-immune stromal targets to perpetuate inflammation. Regulatory interleukins, particularly IL-10, IL-35, IL-37, and IL-38, counter these pathways. Disease progression can therefore be viewed as a failure of regulatory circuits to restrain destructive cytokine amplification.

3.7. Systemic Connections and Host Susceptibility

Periodontal interleukins have relevance beyond the oral cavity, although systemic associations should be interpreted cautiously. Inflamed periodontal pockets expose ulcerated epithelial surfaces to bacterial products and locally produced inflammatory mediators. IL-1β, IL-6, IL-17, and related cytokines may enter the circulation or stimulate systemic acute-phase responses. This provides a biologically plausible explanation for why periodontitis is frequently discussed in relation to diabetes, cardiovascular disease, adverse pregnancy outcomes, and inflammatory rheumatic disease; however, association should not be confused with causation [10,17].

Rheumatoid arthritis provides a clinically relevant example because it shares inflammatory pathways with periodontitis, including IL-6-related signaling, TNF-related signaling, Th17 activity, and RANKL-mediated bone loss. Observations from systemic inflammatory diseases and experimental periodontal models suggest that cytokine modulation can influence periodontal inflammatory parameters, but these observations remain hypothesis-generating rather than definitive. Medication use, oral hygiene, periodontal disease severity, systemic inflammatory burden, and comorbidities are difficult to separate in clinical populations [17,18].

Genetic susceptibility adds another layer of heterogeneity. Polymorphisms in IL10, IL4, IL13, IL17A, IL17F, IL17R, IL23R, IL33, and related genes may alter cytokine production, receptor signaling, or immune-cell differentiation. Genetic associations differ between populations and are often modest, but they may help explain why patients with comparable plaque exposure can show different inflammatory phenotypes and patterns of tissue destruction [19,21,25,28].

Psychological stress may also influence interleukin regulation through neuroendocrine-immune pathways. Cortisol, catecholamines, and stress-related behavioral

changes can affect IL-10-mediated feedback and increase pro-inflammatory signaling.These interactions are relevant because periodontitis develops in a complex host environment shaped by behavior, metabolism, genetics, microbiome composition, systemic inflammatory tone, and local plaque control [26].

3.8. Clinical Implementation and Future Research Priorities

Moving interleukin research into clinical practice requires careful attention to clinical utility. A biomarker is useful only if it improves decision-making beyond probing depth, bleeding on probing, attachment loss, radiographic bone loss, and established risk factors. For interleukin panels, useful applications could include identifying active inflammatory sites, monitoring response to nonsurgical therapy, estimating recurrence risk during maintenance, and selecting patients for host-modulatory adjuncts.

A practical diagnostic model may eventually combine three layers of information. The first would describe the clinical phenotype, including stage, grade, bleeding, pocket depth, and radiographic bone loss. The second would describe the biological phenotype, using salivary or gingival crevicular fluid markers such as IL-1β, IL-6, IL-17, IL-23, IL-10, MMP-8, and MMP-9. The third would integrate systemic and environmental modifiers, including smoking, diabetes, obesity, stress, medication use, and genetic background. This layered approach would be more realistic than relying on a single cytokine.

Therapeutic trials should be designed around phenotype as well. Patients with high IL-1β/inflammasome signatures may respond differently from those with Th17-dominant inflammation or inadequate regulatory cytokine activity. Future trials should therefore define baseline cytokine profiles, use standardized periodontal endpoints, include patient-centered outcomes, and evaluate local delivery methods that minimize systemic immunosuppression.

Future research should standardize sample collection, disease definitions, and assay platforms. It should also report confounders such as smoking, diabetes, body mass index, medication use, recent antibiotic exposure, and periodontal treatment history. Longitudinal studies are especially important because cross-sectional cytokine measurements cannot distinguish cause, consequence, compensation, and repair.

3.9. Limitations of Current Evidence

Although recent literature on interleukins in periodontitis is extensive, its interpretation remains difficult. The first limitation is biological variability. Cytokines fluctuate according to circadian rhythm, local site activity, plaque burden, recent oral hygiene, smoking, systemic disease, medication exposure, and recent periodontal treatment. A single saliva or gingival crevicular fluid sample may therefore fail to capture the inflammatory profile of the whole mouth or the activity of individual periodontal sites.

Because this manuscript is a structured narrative review, the search and selection flow should be interpreted as a transparent working method rather than as a registered systematic-review protocol. No formal risk-of-bias scoring, duplicate independent screening, or quantitative synthesis was performed. The review therefore supports conceptual and translational interpretation, but it should not be read as a definitive meta-analysis.

The second limitation is methodological heterogeneity. Studies use different periodontal classifications, sampling protocols, storage conditions, enzyme-linked immunosorbent assays, multiplex platforms, and normalization methods. Some report concentrations, others total amounts, and others ratios. These differences limit direct comparison and help explain why cytokine thresholds have not been standardized for clinical use.

The third limitation is causality. Increased IL-1β, IL-6, IL-17, IL-18, or IL-33 may indicate active pathogenic signaling, but cross-sectional studies cannot establish whether a cytokine drives disease, reflects tissue damage, or forms part of a compensatory repair response. Experimental models clarify mechanisms, but they cannot fully reproduce the complexity of human periodontitis.

The fourth limitation concerns therapeutic translation. Periodontal cytokine modulation cannot simply be copied from systemic immune-mediated diseases. Drugs that are safe and effective for rheumatoid arthritis or psoriasis may be inappropriate for chronic local use in periodontal pockets. Local delivery, short treatment windows, and careful patient selection will be essential if cytokine-targeted therapies are developed for periodontology.

A final limitation relates to publication patterns. Newer cytokines such as IL-35, IL-37, and IL-38 are biologically attractive, but their periodontal evidence base is still smaller than that for IL-1β, IL-6, and IL-17. Positive findings may also be more likely to be published than neutral or negative results. This should encourage cautious interpretation rather than dismissal of emerging pathways.

Such caution is necessary for a publication-quality synthesis and for responsible translation into clinical periodontology.

4. Discussion

Research from the last decade supports a model in which periodontitis is shaped by a dynamic interleukin network rather than by a single dominant cytokine. IL-1β, IL-6, and IL-17 act as central nodes because they connect microbial sensing, stromal activation, neutrophil recruitment, protease production, and osteoclastogenesis. IL-18, IL-23, and IL-33 broaden this inflammatory network, while IL-10, IL-35, IL-37, and IL-38 provide regulatory counterweights.

The molecular importance of interleukins lies in their ability to translate extracellular danger signals into intracellular transcriptional programs. NF-κB, JAK/STAT, MAPK, inflammasome, and RANKL-related pathways do not operate independently; they interact within epithelial cells, immune cells, fibroblasts, and bone-lineage cells. This explains why periodontitis can persist even after microbial reduction and why patients with comparable plaque levels may differ in disease severity.

Several caveats should nevertheless be emphasized. Cytokine levels differ by sampling fluid, assay method, disease definition, and patient characteristics. Many studies are cross-sectional, and most biomarker panels still lack longitudinal validation. Moreover, cytokines with destructive roles in chronic lesions may also contribute to mucosal defense, barrier integrity, and repair. For that reason, therapeutic inhibition must be selective, local, and guided by phenotype.

Future studies should use standardized periodontal classifications, longitudinal sampling, multi-omics profiling, and integrated clinical endpoints. Rather than searching for one universal 'periodontitis cytokine,' research should focus on cytokine signatures that correspond to distinct biological phenotypes, such as inflammasome-dominant, Th17-dominant, and resolution-defective disease. This approach is more likely to support precision periodontology.

5. Conclusion

Pro- and ant- inflammatory interleukins are central to the pathogenesis, progression, and potential treatment of periodontitis. IL-1β and IL-6 are among the most reproducible biomarkers and drivers of inflammation, while the IL-23/IL-17 axis links adaptive immunity with neutrophil recruitment and osteoclast-mediated bone loss. IL-18 and IL-33 expand the IL-1 family contribution to periodontal inflammation, although their functions are context-dependent. Regulatory cytokines such as IL-10, IL-35, IL-37, and IL-38 highlight the importance of resolution pathways and the consequences of inadequate immune restraint.

The most clinically relevant conclusion is that periodontitis reflects cytokine imbalance rather than simple cytokine excess. Diagnostic strategies should therefore move toward multi-marker profiles that combine pro-inflammatory, regulatory, microbial, genetic, and clinical information. Therapeutic strategies should focus on restoring immune balance while preserving host defense. At present, interleukin-targeted therapy remains experimental in periodontology, but local and phenotype-guided modulation may become a valuable adjunct to mechanical treatment, risk-factor control, and maintenance care.

Funding: The authors received no financial support, grants, or sponsorship for the research, authorship, and publication of this article.

Conflicts of Interest: The authors declare no potential conflicts of interest related to this manuscript.

Ethics Approval: Ethics approval was not required because this study is a review of previously published literature and did not involve human participants, animal experiments, or newly collected clinical data.

Data Availability: No new datasets were generated or analyzed during the preparation of this manuscript.

REFERENCES

1. Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., ... Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Clinical Periodontology, 45*(Suppl. 20), S162–S170. https://doi.org/10.1111/jcpe.12946
2. Van Dyke, T. E., Bartold, P. M., & Reynolds, E. C. (2020). The nexus between periodontal inflammation and dysbiosis. *Frontiers in Immunology, 11*, 511. https://doi.org/10.3389/fimmu.2020.00511
3. Neurath, N., & Kesting, M. (2024). Cytokines in gingivitis and periodontitis: From pathogenesis to therapeutic targets. *Frontiers in Immunology, 15*, 1435054. https://doi.org/10.3389/fimmu.2024.1435054
4. Martínez-García, M., & Hernández-Lemus, E. (2025). Pro-inflammatory and anti-inflammatory interleukins in periodontitis: Molecular roles, immune crosstalk, and therapeutic perspectives. *International Journal of Molecular Sciences, 26*(20), 10094. https://doi.org/10.3390/ijms262010094
5. Stadler, A. F., Angst, P. D. M., Arce, R. M., Gomes, S. C., Oppermann, R. V., & Susin, C. (2016). Gingival crevicular fluid levels of cytokines/chemokines in chronic periodontitis: A meta-analysis. *Journal of Clinical Periodontology, 43*(9), 727–745. https://doi.org/10.1111/jcpe.12557
6. Relvas, M., Mendes-Frias, A., Gonçalves, M., Salazar, F., López-Jarana, P., Silvestre, R., & Viana da Costa, A. (2024). Salivary IL-1β, IL-6, and IL-10 are key biomarkers of periodontitis severity. *International Journal of Molecular Sciences, 25*(15), 8401. https://doi.org/10.3390/ijms25158401
7. Arroyo, E., Oliveira-Alves, M. G., Chamorro-Petronacci, C. M., Marichalar-Mendia, X., Bravo-López, S. B., Blanco-Carrión, J., & Pérez-Sayáns, M. (2023). Protein-based salivary biomarkers for the diagnosis of periodontal diseases: Systematic review and meta-analysis. *Journal of Taibah University Medical Sciences, 18*(4), 737–747. https://doi.org/10.1016/j.jtumed.2022.12.004
8. Marchesan, J. T., Girnary, M. S., Moss, K., Monaghan, E. T., Egnatz, G. J., Jiao, Y., et al. (2020). Role of inflammasomes in the pathogenesis of periodontal disease and therapeutics. *Periodontology 2000, 82*(1), 93–114. https://doi.org/10.1111/prd.12269
9. Murakami, T., Takahata, Y., Hata, K., & Nishimura, R. (2020). Role of interleukin-1 and inflammasomes in oral disease. *Journal of Oral Biosciences, 62*(3), 242–248. https://doi.org/10.1016/j.job.2020.07.003
10. Bonsmann, T., Mochol, M., Bonsmann, E., Jablonowski, L., Pawlik, A., Rasławska-Socha, J., Lipski, M., & Mazurek-Mochol, M. (2025). The role of IL-17 in periodontitis and its systemic connections. *International Journal of Molecular Sciences, 26*(22), 10902. https://doi.org/10.3390/ijms262210902
11. Zhang, J., Ding, Q., Wang, A. X., Lin, M., Yu, N., Moss, K., Williamson, M. A., Miao, D., Marchesan, J. T., Zeng, E., Shi, W., Sun, H., Lei, Y. L., & Zhang, S. (2025). Type I interferon protects against bone loss in periodontitis by mitigating an interleukin (IL)-17-neutrophil axis. *Life Sciences, 371*, 123559. https://doi.org/10.1016/j.lfs.2025.123559
12. Papathanasiou, E., Conti, P., Carinci, F., Lauritano, D., & Theoharides, T. C. (2020). IL-1 superfamily members and periodontal diseases. *Journal of Dental Research, 99*(13), 1425–1434. https://doi.org/10.1177/0022034520945209
13. Alarcón-Sánchez, M. A., Rodríguez-Montaño, R., Mosaddad, S. A., & Heboyan, A. (2025). Levels of IL-1β, MMP-8, and MMP-9 in the saliva of subjects with periodontitis: A systematic review and meta-analysis. *Journal of Clinical Laboratory Analysis, 39*(10), e70040. https://doi.org/10.1002/jcla.70040
14. Marchesan, J. T. (2020). Inflammasomes as contributors to periodontal disease. *Journal of Periodontology, 91*(Suppl. 1), S6–S11. https://doi.org/10.1002/JPER.20-0157
15. Karrabi, M., Baghani, Z., & Atarbashi-Moghadam, F. (2024). Effect of adjunctive photodynamic therapy on gingival crevicular fluid interleukin-1β in stage III and IV periodontitis: A systematic review and meta-analysis. *Journal of Indian Society of Periodontology, 28*(2), 156–175. https://doi.org/10.4103/jisp.jisp_494_23
16. Gomes, P.-R., Rocha, M.-D., Lira, J.-A., Coelho, F.-A., Alves, E.-H., Nascimento, H.-M., Oliveira, S.-M., Carmo, R.-R., Araújo, H.-T., Silva, F.-R., & Vasconcelos, D.-F. (2023). Salivary biomarkers present in patients with periodontitis without clinical distinction: Findings from a meta-analysis. *Medicina Oral, Patología Oral y Cirugía Bucal, 28*(5), e457–e466. https://doi.org/10.4317/medoral.25876
17. Mazurek-Mochol, M., Bonsmann, T., Mochol, M., Poniewierska-Baran, A., & Pawlik, A. (2024). The role of interleukin 6 in periodontitis and its complications. *International Journal of Molecular Sciences, 25*(4), 2146. https://doi.org/10.3390/ijms25042146
18. Martins, A. A., Lima, M. L. S., Vieira, G. H. A., Costa, H. E. S., Leitão, R. F. C., Ribeiro, S. B., Medeiros, C. A. C. X., Silva, D. N. A., Suksakulchai, R., Pirih, F. Q., Brito, G. A. C., Garcia, V. B., Araújo Júnior, R. F., Lins, R. D. A. U., & Araújo, A. A. (2025). Effectiveness of local tocilizumab administration in mitigating alveolar bone loss and inflammation in experimental periodontitis. *Scientific Reports, 16*(1), 1004. https://doi.org/10.1038/s41598-025-30737-4

19. Rodríguez-Montaño, R., Alarcón-Sánchez, M. A., Lomelí-Martínez, S. M., Martínez-Bugarin, C. H., & Heboyan, A. (2025). Genetic variants of the IL-23/IL-17 axis and its association with periodontal disease: A systematic review. *Immunity, Inflammation and Disease, 13*(2), e70147. https://doi.org/10.1002/iid3.70147
20. Liukkonen, J., Gürsoy, U. K., Pussinen, P. J., Suominen, A. L., & Könönen, E. (2016). Salivary concentrations of interleukin (IL)-1β, IL-17A, and IL-23 vary in relation to periodontal status. *Journal of Periodontology, 87*(12), 1484–1491. https://doi.org/10.1902/jop.2016.160146
21. Sasikumar, P. K., Varghese, S. S., Kumaran, T., & Devi, S. S. (2020). Meta-analysis of risk association between interleukin-17A gene polymorphism and chronic periodontitis. *Contemporary Clinical Dentistry, 11*(1), 3–9. https://doi.org/10.4103/ccd.ccd_448_19
22. Alarcón-Sánchez, M. A., Romero-Castro, N. S., Becerra-Ruiz, J. S., Romero-Servin, S., & Heboyan, A. (2024). Increased of IL-18 levels are associated with periodontitis: A systematic review and meta-analysis. *BMC Oral Health, 24*, 981. https://doi.org/10.1186/s12903-024-04747-z
23. Alarcón-Sánchez, M. A., Romero-Castro, N. S., Reyes-Fernández, S., Sánchez-Tecolapa, E. U., & Heboyan, A. (2024). Expression of IL-33 in subjects with periodontitis: A systematic review and meta-analysis. *European Journal of Medical Research, 29*, 440. https://doi.org/10.1186/s40001-024-02039-4
24. Liu, A., Hayashi, M., Ohsugi, Y., Katagiri, S., Akira, S., Iwata, T., & Nakashima, T. (2024). The IL-33/ST2 axis is protective against acute inflammation during the course of periodontitis. *Nature Communications, 15*, 2707. https://doi.org/10.1038/s41467-024-46746-2
25. Yang, S.-L., & Huang, S.-J. (2019). Interleukin-10 polymorphisms (rs1800871, rs1800872 and rs1800896) and periodontitis risk: A meta-analysis. *Archives of Oral Biology, 97*, 59–66. https://doi.org/10.1016/j.archoralbio.2018.10.012
26. Skrypnyk, M., Spahr, A., Berkovsky, S., Yatsenko, T., Xu, C., Zuieva, O., Osada, T., Takahashi, S., Hattori, N., Takahashi, K., Hattori, K., & Heissig, B. (2025). Chronic stress and the IL-10-mediated immunoregulatory loop in the pathogenesis of periodontitis. *Clinical Science, 139*(22), 1469–1487. https://doi.org/10.1042/CS20256843
27. Yue, G., Qian, J., Weng, B., Mao, J., Zhang, M., Wang, S., & Huang, W. (2025). Effect of scaling and root planing on TNF-α, IL-1β, and IL-10 levels in periodontitis patients with and without diabetes: A cross-sectional study. *BMC Oral Health, 25*, 1481. https://doi.org/10.1186/s12903-025-06894-3
28. Chen, D., Zhang, T.-L., & Wang, X. (2016). Association between polymorphisms in interleukins 4 and 13 genes and chronic periodontitis in a Han Chinese population. *BioMed Research International, 2016*, 8389020. https://doi.org/10.1155/2016/8389020
29. Schmidlin, P. R., Dehghannejad, M., & Fakheran, O. (2021). Interleukin-35 pathobiology in periodontal disease: A systematic scoping review. *BMC Oral Health, 21*, 139. https://doi.org/10.1186/s12903-021-01515-1
30. Pashova-Tasseva, Z., Mlachkova, A., Kotsilkov, K., & Maynalovska, H. (2025). The multifaceted role of IL-35 in periodontal disease and beyond: From genetic polymorphisms to biomarker potential. *Genes, 16*(8), 891. https://doi.org/10.3390/genes16080891
31. Toraman, A., Sağlam, E., Savran, L., & Köseoğlu, S. (2025). Evaluation of salivary IL-38 levels in periodontitis: A cross-sectional study. *Journal of Interferon & Cytokine Research, 45*(2), 76–82. https://doi.org/10.1089/jir.2023.0233
32. Jaedicke, K. M., Preshaw, P. M., & Taylor, J. J. (2016). Salivary cytokines as biomarkers of periodontal diseases. *Periodontology 2000, 70*(1), 164–183. https://doi.org/10.1111/prd.12117
33. Suvan, J., Leira, Y., Moreno Sancho, F. M., Graziani, F., Derks, J., & Tomasi, C. (2020). Subgingival instrumentation for treatment of periodontitis: A systematic review. *Journal of Clinical Periodontology, 47*(Suppl. 22), 155–175. https://doi.org/10.1111/jcpe.13245
34. Ho, S. N., Acharya, A., Sidharthan, S., Li, K. Y., Leung, W. K., McGrath, C., & Pelekos, G. (2020). A systematic review and meta-analysis of clinical, immunological, and microbiological shift in periodontitis after nonsurgical periodontal therapy with adjunctive use of probiotics. *Journal of Evidence-Based Dental Practice, 20*(1), 101397. https://doi.org/10.1016/j.jebdp.2020.101397
35. Kruse, A. B., Kowalski, C. D., Leuthold, S., Vach, K., Ratka-Krüger, P., & Woelber, J. P. (2020). What is the impact of the adjunctive use of omega-3 fatty acids in the treatment of periodontitis? A systematic review and meta-analysis. *Lipids in Health and Disease, 19*, 100. https://doi.org/10.1186/s12944-020-01267-x