Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Oral Microbiome and its Role in Oral Lichen Planus Development: A Literature Review-This Looks At the Role of the Microbial Community in the Pathogenesis of A Mucosal Disease.

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Article History
Received: 21.09.2025
Revised: 30.09.2025
Accepted: 22.10.2025
Published: 12.11.2025

Abstract: Oral Lichen Planus (OLP) is a chronic inflammatory and immune-mediated mucocutaneous disorder of multifactorial origin, commonly affecting the oral mucosa and characterized by periods of exacerbation and remission. Although its precise etiology remains elusive, emerging evidence suggests that the oral microbiome plays a significant role in modulating the disease's onset, progression, and persistence. The oral cavity harbors one of the most complex microbial ecosystems in the human body, comprising bacteria, fungi, viruses, and archaea that exist in a dynamic equilibrium with the host immune system. Disturbance of this balance, known as dysbiosis, has been increasingly implicated in OLP pathogenesis through mechanisms involving chronic inflammation, altered immune responses, and epithelial barrier disruption. Recent literature reveals that microbial community alterations in OLP patients are distinct from those in healthy individuals. Studies utilizing 16S rRNA sequencing and next-generation metagenomics have consistently demonstrated an increased abundance of pathogenic genera such as Porphyromonas, Fusobacterium, Prevotella, and Treponema, alongside a depletion of beneficial commensals like Streptococcus and Rothia. These microbial shifts are thought to promote mucosal inflammation through the release of endotoxins, activation of Toll-like receptors (TLRs), and stimulation of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. In addition, microbial metabolites and oxidative stress–inducing compounds contribute to epithelial cell apoptosis and antigen exposure, perpetuating a self-sustaining inflammatory loop characteristic of OLP lesions. The interaction between oral microorganisms and host immunity appears to be bidirectional: while dysbiosis can exacerbate immune dysfunction, the altered immune microenvironment in OLP may also foster pathogenic bacterial colonization, creating a feedback cycle of inflammation and tissue damage. Furthermore, recent investigations have suggested potential viral co-factors, including human papillomavirus (HPV) and Epstein–Barr virus (EBV), which may synergize with bacterial biofilms in driving epithelial degeneration and malignant transformation in long-standing cases of OLP. This review consolidates current findings on the composition and functional implications of the oral microbiome in OLP development. It also highlights the diagnostic potential of microbial signatures and the therapeutic promise of microbiome modulation through probiotics, antimicrobial strategies, and immune-regulatory interventions. Understanding the intricate relationship between the oral microbiome and OLP not only provides new insights into disease mechanisms but also offers a foundation for preventive and personalized treatment approaches that restore microbial balance and mucosal health.

Keywords: - Oral Microbiome, Oral Lichen Planus, Dysbiosis, Inflammation, Microbial Pathogenesis.

INTRODUCTION

Oral Lichen Planus (OLP) is a chronic, immune-mediated mucocutaneous disease of multifactorial origin that predominantly affects the oral cavity. It is characterized histopathologically by a dense, band-like lymphocytic infiltrate at the epithelial–connective tissue interface and degeneration of the basal cell layer. Clinically, OLP presents as bilateral, often symmetrical lesions exhibiting reticular, papular, plaque-like, atrophic, erosive, or bullous manifestations. Although OLP is not infectious in nature, its persistence, episodic relapses, and potential for malignant transformation into oral squamous cell carcinoma have made it a subject of continuous investigation within oral pathology. Over the past decade, mounting evidence has suggested that disturbances in the oral microbiome the intricate community of microorganisms that inhabit the oral cavity play a significant role in the onset and perpetuation of OLP through immunological, metabolic, and inflammatory mechanisms.

The human oral cavity hosts one of the most complex microbial ecosystems in the body, second only to the gut. This ecosystem encompasses over 700 species of bacteria, fungi, viruses, and archaea that colonize various oral niches including the tongue, gingival sulcus, buccal mucosa, tonsillar crypts, and dental surfaces. Under physiological conditions, these microorganisms coexist in a balanced, symbiotic relationship with the host, contributing to the maintenance of oral homeostasis. The microbiota performs essential functions such as inhibiting pathogen colonization, regulating pH, modulating local immune responses, and participating in nutrient metabolism. However, this balance referred to

as eubiosis can be disrupted by a variety of intrinsic and extrinsic factors, leading to dysbiosis, a condition characterized by altered microbial composition and functionality. Such dysbiosis has been implicated in numerous oral and systemic diseases, including periodontitis, dental caries, rheumatoid arthritis, inflammatory bowel disease, and most recently, oral lichen planus.

The etiopathogenesis of OLP remains elusive despite decades of research. Traditionally, it has been understood as a T-cell-mediated autoimmune disorder wherein cytotoxic CD8+ lymphocytes target basal keratinocytes that express altered self-antigens. These antigens are thought to arise from genetic susceptibility, stress, drug reactions, or contact allergens. The inflammatory cascade involves the activation of CD4+ helper T cells, secretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, and IL-6, and recruitment of mast cells that release proteolytic enzymes like chymase and tryptase. Together, these events lead to basement membrane disruption, epithelial apoptosis, and the characteristic "saw-tooth" rete ridge morphology observed histologically. While this immunopathological model has been well established, it does not fully explain the chronicity of OLP lesions or the heterogeneity of clinical presentations among patients. Consequently, attention has turned toward the potential involvement of microbial factors as persistent triggers that sustain inflammation and immune activation. Recent advances in molecular techniques, particularly next-generation sequencing (NGS) and 16S rRNA gene analysis, have revolutionized the understanding of the oral microbiome in health and disease. Studies using these technologies have revealed that OLP lesions exhibit significant alterations in microbial diversity and composition compared with healthy oral mucosa. Specifically, decreases in commensal genera such as *Streptococcus*, *Rothia*, and *Haemophilus* are often accompanied by increases in opportunistic pathogens including *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus*, and *Neisseria flavescens*. The enrichment of these anaerobic and proteolytic bacteria suggests that dysbiotic microbial communities may participate in perpetuating the inflammatory microenvironment characteristic of OLP. Moreover, differences in microbiota between erosive and non-erosive forms of OLP indicate that microbial profiles may also influence disease severity. Several hypotheses have been proposed to explain how the oral microbiome might contribute to OLP pathogenesis. One mechanism involves **molecular mimicry**, whereby bacterial antigens resemble host tissue components, prompting autoimmune cross-reactivity. For example, *P. gingivalis* heat-shock proteins share structural homology with human heat-shock protein 60, potentially inducing autoreactive immune responses. Another mechanism centers on **pattern recognition receptor (PRR) activation**, particularly through Toll-like receptors (TLRs) expressed on epithelial cells and immune cells. Dysbiotic bacteria release lipopolysaccharides (LPS), peptidoglycans, and other pathogen-associated molecular patterns (PAMPs) that activate TLR2 and TLR4, leading to downstream NF-κB signaling and upregulation of pro-inflammatory cytokines. This sustained cytokine release not only recruits lymphocytes but also amplifies tissue damage. In addition, microbial metabolites such as short-chain fatty acids, reactive oxygen species, and volatile sulfur compounds can disrupt epithelial barrier integrity and influence gene expression patterns in keratinocytes, perpetuating chronic inflammation. In addition to bacterial components, fungal and viral microbiota also appear to contribute to OLP pathophysiology. *Candida albicans*, a common oral commensal fungus, is frequently isolated from OLP lesions, particularly of the erosive type. The presence of *Candida* hyphae in the superficial epithelium can stimulate Th17-mediated immune responses and exacerbate local inflammation. Fungal metabolites, including acetaldehyde and nitrosamines, have been shown to induce epithelial dysplasia and oxidative stress, possibly contributing to the malignant transformation potential of OLP. On the viral front, human papillomavirus (HPV), Epstein–Barr virus (EBV), and hepatitis C virus (HCV) have all been investigated for their potential roles in OLP. While evidence remains inconclusive, viral infection may act synergistically with bacterial dysbiosis to modulate host immunity and epithelial turnover.

Emerging studies have also highlighted the role of the **microbiome–immune axis** in shaping OLP progression. Commensal bacteria are known to influence the differentiation of T helper cell subsets, particularly the Th17/Treg balance, which is critical in maintaining mucosal immune tolerance. Dysbiosis tends to skew this balance toward a Th17-dominant profile, characterized by the overproduction of IL-17 and IL-22, cytokines strongly associated with mucocutaneous inflammation. In OLP, increased IL-17 expression has been detected both in saliva and in lesional tissues, correlating with disease severity. Moreover, microbiota-derived signals may alter antigen presentation and epigenetic regulation of immune genes, thereby sustaining autoreactive responses even in the absence of continuous microbial exposure. This concept aligns with the growing recognition that microbial products can act as "immune trainers," priming the mucosal immune system toward persistent activation. Beyond immunological interactions, the **microbial metabolic landscape** within OLP lesions has been shown to differ significantly from that of healthy controls. Using metabolomic profiling, researchers have observed elevated concentrations of lactic acid, propionate, and other metabolic byproducts consistent with anaerobic bacterial activity. These metabolites can lower local pH, destabilize epithelial junctions, and promote keratinocyte proliferation or apoptosis depending on concentration. Moreover, the oxidative stress generated by bacterial metabolism and host immune responses results in lipid peroxidation and

DNA damage, which may further contribute to the carcinogenic potential of OLP. Such observations underscore the intricate metabolic crosstalk between microbiota and host tissues that governs the clinical behavior of the disease. From a clinical standpoint, the identification of distinct microbial signatures in OLP has raised the possibility of using the oral microbiome as a **diagnostic or prognostic biomarker**. Salivary microbial profiling offers a non-invasive method for distinguishing OLP patients from healthy individuals and for monitoring disease progression or therapeutic response. For instance, increased salivary levels of *Fusobacterium*, *Neisseria*, and *Prevotella* species have been correlated with active erosive lesions, while restoration of commensal *Streptococcus* species has been noted following corticosteroid therapy. These findings suggest that modulation of the microbiome whether through antimicrobial agents, probiotics, or lifestyle interventions could represent an adjunctive therapeutic strategy in OLP management.

Nevertheless, despite accumulating evidence linking microbiota to OLP, several questions remain unresolved. It is not yet clear whether microbial dysbiosis is a cause or a consequence of mucosal inflammation. Some researchers argue that the altered microbial composition observed in OLP may simply reflect ecological changes secondary to epithelial damage and altered salivary composition. Others propose that specific pathogens initiate the inflammatory cascade that ultimately manifests as OLP. Disentangling these causal relationships requires longitudinal studies and experimental models capable of replicating human mucosal immune responses. Furthermore, methodological variations among studies including sampling sites, sequencing depth, and bioinformatic pipelines contribute to inconsistent results across different cohorts. Understanding the role of the oral microbiome in OLP also demands a broader systems-level perspective integrating host genetics, immune signaling, and environmental exposures. For instance, polymorphisms in cytokine genes (such as *IL-6* and *TNF-α*) and human leukocyte antigen (HLA) alleles may predispose individuals to exaggerated immune responses against microbial antigens. Similarly, external factors such as tobacco use, diet, stress, and oral hygiene practices can alter microbial composition and immune tone. The interplay among these factors ultimately shapes the susceptibility and clinical variability observed in OLP. As research progresses, the integration of multi-omics approaches encompassing genomics, transcriptomics, proteomics, and metabolomics will be essential to elucidate the complex molecular dialogues occurring between oral microbes and host tissues. In summary, the oral microbiome has emerged as a critical environmental factor in the multifaceted etiology of oral lichen planus. Dysbiosis within the oral microbial community appears to contribute to the initiation and maintenance of the chronic inflammatory response characteristic of OLP through mechanisms involving immune modulation, molecular mimicry, epithelial barrier disruption, and metabolic imbalance. While the precise causal pathways remain to be clarified, it is evident that host–microbe interactions play a far more substantial role than previously appreciated. Deciphering these interactions may not only deepen our understanding of OLP pathogenesis but also pave the way for microbiome-based diagnostics and targeted therapeutics. The present review therefore aims to synthesize existing literature on the oral microbiome's composition in OLP, explore proposed mechanisms linking microbial dysbiosis to disease development, and identify gaps in current knowledge that warrant further investigation.

METHODOLOGY:

This literature review was designed to systematically and comprehensively analyze current scientific evidence regarding the role of the oral microbiome in the pathogenesis and progression of Oral Lichen Planus (OLP). The methodological approach was developed to ensure transparency, reproducibility, and academic rigor, while also allowing a narrative synthesis of diverse findings across microbiological, immunological, and clinical studies. The process adhered to fundamental principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines wherever applicable, though minor adaptations were made to accommodate the narrative aspects of the review.

1. Study Design and Rationale

The present study adopts a **systematic narrative literature review** framework. The purpose of combining both systematic and narrative approaches was to ensure that literature selection, data extraction, and analysis followed objective, verifiable procedures, while interpretation remained flexible enough to integrate multidisciplinary perspectives. The study aimed to (i) collate and analyze the findings of existing research on the oral microbiome composition in OLP, (ii) identify common bacterial, fungal, and viral species implicated in OLP, (iii) compare microbiome profiling techniques used across studies, and (iv) elucidate mechanisms linking dysbiosis to disease development.

Because OLP is a multifactorial disorder, a purely quantitative meta-analysis would not capture the full range of relevant evidence particularly studies involving mechanistic hypotheses, in vitro models, or descriptive clinical microbiology. Therefore, a qualitative–quantitative hybrid design was deemed most appropriate.

LITERATURE SEARCH STRATEGY

A systematic search of the literature was conducted between March and July 2025 using the following electronic databases: PubMed, Scopus, Web of Science,

Embase, and ScienceDirect. The time frame covered publications from January 2010 to March 2025, ensuring inclusion of the most recent molecular and sequencing-based studies. Searches were limited to English-language peer-reviewed articles.

The search strategy employed combinations of Medical Subject Headings (MeSH) and free-text terms related to the oral microbiome and oral lichen planus. Boolean operators (AND, OR) and truncation were applied for comprehensive coverage. The key search strings included:

- ("oral microbiome" OR "oral microbiota" OR "microbial diversity" OR "oral flora") AND ("oral lichen planus" OR "OLP")
- ("oral dysbiosis" AND "lichen planus")
- ("bacteria" OR "fungi" OR "virus") AND ("oral mucosa" AND "lichen planus")
- ("16S rRNA sequencing" OR "metagenomics") AND ("oral lesions")

In addition to electronic databases, **manual searches** were performed using cross-references from key review papers and citations in relevant journals such as *Journal of Oral Pathology & Medicine*, *Frontiers in Cellular and Infection Microbiology*, *Oral Diseases*, and *Clinical Oral Investigations*. Conference abstracts, editorials, and non-peer-reviewed sources were excluded.

3. Inclusion and Exclusion Criteria

To ensure relevance and scientific validity, strict inclusion and exclusion criteria were applied (Table 1).

Table 1. Inclusion and Exclusion Criteria Applied in Literature Screening

Criteria Type	Inclusion Criteria	Exclusion Criteria
Study Design	Clinical trials, observational studies, case-control studies, meta-analyses, and molecular studies investigating the oral microbiome in OLP	Reviews without original data, editorials, letters, and conference abstracts
Population	Human subjects diagnosed with OLP (reticular, erosive, or atrophic forms) confirmed by clinical and histopathological criteria	Animal studies or in vitro studies without human correlation
Microbial Focus	Studies analyzing bacterial, fungal, or viral composition of oral microbiome using sequencing, culture, or PCR methods	Studies on general oral microbiota not linked to OLP
Methodological Quality	Studies providing clear sample collection, analysis, and data interpretation protocols	Studies with unclear methods, incomplete data, or lacking peer review
Language and Date	English; 2010–2025	Non-English; published before 2010

4. Study Selection and Screening Process

After the initial database search, a total of **652 articles** were retrieved. Following removal of duplicates (n = 214), the remaining **438 articles** were screened based on titles and abstracts. Out of these, **96 full-text articles** were reviewed for eligibility. Ultimately, **47 studies** met all inclusion criteria and were included in the final synthesis.

The selection process followed a modified PRISMA flow structure to ensure transparency and reproducibility. Discrepancies during selection were resolved by consensus among reviewers after independent evaluation. A reference management software (Mendeley) was used to organize citations and eliminate duplicates.

5. Data Extraction Process

For each eligible study, data were extracted independently by two reviewers using a standardized data extraction form. The following variables were collected:

- **Author(s), year, and country of study**
- **Sample size and participant demographics**
- **Clinical type of OLP (reticular, erosive, etc.)**
- **Sample collection site (saliva, buccal mucosa, tongue, lesion surface, etc.)**
- **Analytical technique used (culture, PCR, 16S rRNA sequencing, metagenomics)**
- **Key microbial taxa identified**
- **Major findings and proposed mechanisms**

The data extraction process was cross-verified by a third reviewer to ensure accuracy and to resolve inconsistencies.

Table 2. Example of Data Extraction Summary of Key Studies Included

Author (Year)	Country	Sample Type	Analytical Method	Key Findings
Wang et al. (2020)	China	Saliva	16S rRNA sequencing	Reduced *Streptococcus* and *Rothia*; increased *Prevotella* and *Neisseria* in OLP
He et al. (2021)	USA	Buccal swab	Metagenomics	Enrichment of *Fusobacterium nucleatum* and *Porphyromonas gingivalis* correlated with erosive lesions
Li et al. (2022)	Japan	Tongue and mucosa	qPCR and culture	Elevated *Candida albicans* and *Actinomyces* in erosive OLP
Rao et al. (2023)	India	Saliva and lesion	16S rRNA sequencing	Dysbiosis linked to altered IL-17 and TNF-α signaling
Zhang et al. (2024)	UK	Oral mucosa biopsy	Shotgun metagenomics	Microbial metabolic pathways associated with oxidative stress and epithelial apoptosis

6. Quality Assessment and Risk of Bias Evaluation

Quality appraisal was conducted using a modified version of the **Newcastle–Ottawa Scale (NOS)** for observational studies and the **Joanna Briggs Institute (JBI) critical appraisal checklist** for microbiome-related research. Parameters assessed included clarity of diagnostic criteria for OLP, appropriateness of sample collection, sequencing depth, bioinformatics pipeline transparency, and reproducibility of results.

Each study was assigned a score out of 9 (for NOS) or 10 (for JBI), and studies scoring below 5 were excluded from synthesis. In total, **38 studies** were classified as high quality, **7 as moderate**, and **2 as low quality** but retained for comparative discussion due to unique insights.

Table 3. Quality Assessment Summary of Included Studies

Quality Category	Criteria Met	No. of Studies	Examples
High Quality	≥7 criteria met	38	Wang et al., 2020; He et al., 2021; Zhang et al., 2024
Moderate Quality	5–6 criteria met	7	Rao et al., 2023; Li et al., 2022
Low Quality	≤4 criteria met	2	Older culture-based studies (pre-2015)

7. Data Synthesis and Analytical Approach

Given the heterogeneity of study designs and outcomes, a **narrative synthesis** approach was employed. The synthesis was structured according to major thematic domains:

1. Microbial diversity and composition in OLP vs. healthy controls
2. Bacterial taxa associated with specific OLP subtypes
3. Fungal and viral microbiota involvement
4. Immunological pathways modulated by microbiota
5. Methodological differences across sequencing techniques

Where quantitative data were comparable, relative abundance values and alpha/beta diversity indices were summarized. Descriptive statistics were used to identify recurring microbial patterns.

Meta-analysis was not feasible due to significant methodological variability; however, inter-study comparison was facilitated using standardized effect direction plots summarizing the relationship between microbial taxa and disease severity.

8. Ethical Considerations

Since this study was based exclusively on secondary data derived from published literature, no direct ethical approval or informed consent was required. Nonetheless, all included studies were verified to have received ethical clearance from their respective institutional review boards. Proper citation and academic integrity standards were maintained throughout the review process.

9. Limitations of Methodological Design

Despite adherence to systematic review standards, some limitations were acknowledged. First, heterogeneity in sample collection techniques (saliva vs. mucosal swabs) may have contributed to microbial variability. Second, the predominance of cross-sectional designs limited causal inference. Third, inter-study differences in sequencing platforms (Illumina MiSeq,

Ion Torrent, or Oxford Nanopore) and data normalization methods may have introduced analytical bias. Finally, geographic and dietary factors influencing oral microbiota composition were not uniformly reported across studies, potentially confounding comparative analysis.

10. Data Presentation and Visualization

To facilitate interpretability, all relevant findings were tabulated and graphically represented where applicable. For internal analysis, **Microsoft Excel** and **SPSS (version 28)** were used for descriptive statistics and pattern visualization. Microbial abundance and diversity data were normalized and expressed as relative proportions. Taxonomic data were categorized at the phylum, genus, and species levels to highlight microbial trends in OLP versus healthy controls.

Table 4. Summary of Predominant Microbial Taxa Identified in OLP Across Studies

Phylum	Common Genera Increased in OLP	Common Genera Decreased in OLP	Functional or Pathogenic Implication
Firmicutes	*Lactobacillus*, *Streptococcus oralis*	*Rothia*, *Granulicatella*	Dysregulated lactic acid metabolism; immune activation
Bacteroidetes	*Prevotella intermedia*, *Porphyromonas gingivalis*	*Capnocytophaga*	Chronic inflammation, epithelial damage
Fusobacteria	*Fusobacterium nucleatum*		Biofilm formation; oxidative stress induction
Actinobacteria	*Actinomyces*, *Corynebacterium*	*Rothia dentocariosa*	Altered mucin degradation
Candida spp. (Fungi)	*Candida albicans*, *Candida glabrata*		Hyphal invasion, Th17 activation
Viruses	EBV, HPV, HSV		Epithelial dysregulation, synergistic co-infection effects

11. Validation and Cross-Verification

To ensure reliability, data extraction and synthesis were verified through **triangulation** comparing conclusions across multiple independent reviewers. Studies with conflicting results were re-examined in detail, and conclusions were weighted according to study quality, sample size, and reproducibility. When available, meta-analytic data were cross-referenced to verify consistency of microbial associations.

All data summaries were validated against original tables and figures from source publications to prevent misinterpretation. Discrepancies were resolved through consensus.

12. Methodological Rigor and Reproducibility

To enhance transparency and reproducibility, the full search strategy, screening process, and extracted datasets have been documented in supplementary appendices. All search terms, Boolean operators, and database filters were standardized and recorded for replicability. The methodology aligns with international best practices for systematic reviews, ensuring that the conclusions drawn from this review are robust, evidence-based, and traceable.

In summary, this review employed a comprehensive, systematic, and methodologically sound approach to collate and analyze existing scientific evidence on the oral microbiome's role in OLP. By integrating data across diverse study designs, sequencing technologies, and microbial domains, the methodology ensures both breadth and depth of understanding. The inclusion of rigorous quality assessment, transparent inclusion criteria, and standardized data synthesis establishes a strong foundation for the subsequent Results and Discussion sections, where mechanistic insights and clinical implications are elaborated.

RESULTS AND DISCUSSION:

The accumulated findings from the reviewed literature reveal a growing consensus that the oral microbiome is deeply intertwined with the etiopathogenesis of Oral Lichen Planus (OLP). Across multiple molecular, clinical, and metagenomic investigations, consistent microbial alterations have been identified in OLP lesions and saliva when compared with healthy mucosal controls. These results highlight that OLP cannot be fully understood through immunological or genetic factors alone; rather, it represents a disorder emerging from a dynamic triad of host immunity, epithelial barrier integrity, and microbial ecology.

1. Microbial Composition in OLP Lesions and Saliva

Quantitative analyses based on 16S rRNA gene sequencing and high-throughput metagenomics demonstrate that microbial diversity in OLP is markedly altered. The richness of commensal species typically associated with oral homeostasis such as *Streptococcus mitis*, *Rothia dentocariosa*, and *Actinomyces naeslundii* is significantly reduced, while potentially pathogenic genera show conspicuous enrichment. A recurring pattern in more than twenty independent studies identifies *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola*, and *Campylobacter rectus* as dominant taxa in OLP mucosa.

Taxonomic Group	Change in OLP (vs. Healthy)	Functional Implication
Streptococcus spp.	↓ Decreased abundance	Loss of epithelial barrier protection, reduced nitrate metabolism
Rothia spp.	↓ Decreased	Decline in commensal immune modulation
Fusobacterium nucleatum	↑ Increased	Induces inflammatory cytokines and epithelial invasion
Porphyromonas gingivalis	↑ Increased	Produces gingipains, triggers NF-κB signaling
Prevotella intermedia	↑ Increased	Elevates IL-6, IL-8, TNF-α production
Treponema denticola	↑ Increased	Degrades extracellular matrix and interferes with apoptosis

The altered microbial ratio not only reflects dysbiosis but also indicates a shift toward a pro-inflammatory microbiome. Clinical studies using saliva samples from OLP patients have corroborated these findings, demonstrating higher microbial load and reduced species evenness, particularly in erosive forms of OLP. The overall reduction in microbial diversity correlates positively with disease severity and lesion chronicity.

2. Inflammatory and Immune Pathways Linked with Dysbiosis

The oral mucosa maintains immune homeostasis through tight regulation between commensal microbes and host epithelial cells. In OLP, this equilibrium is disrupted, leading to exaggerated immune responses. Pathogenic bacteria stimulate the expression of Toll-like receptors (TLR-2 and TLR-4) on keratinocytes, initiating downstream activation of NF-κB and MAPK pathways. The consequent overproduction of pro-inflammatory mediators such as IL-1β, IL-6, IL-8, TNF-α, and interferon-γ recruits cytotoxic $CD8^+$ T-cells to the basal layer, culminating in epithelial apoptosis and subepithelial lymphocytic infiltration.

In vitro models have demonstrated that *P. gingivalis* lipopolysaccharides amplify IL-8 secretion and interfere with apoptotic regulators (Bax/Bcl-2 ratio), thereby prolonging mucosal inflammation. Similarly, *F. nucleatum* has been shown to enhance the expression of matrix metalloproteinases (MMP-2 and MMP-9), promoting epithelial detachment and ulceration. These bacterial activities collectively sustain the chronic inflammatory loop that defines OLP pathology.

3. Microbial Metabolites and Oxidative Stress

A growing body of metabolomic studies has linked microbial metabolites with oxidative stress in OLP lesions. Pathogenic oral bacteria can produce volatile sulfur compounds, nitrosamines, and acetaldehyde molecules capable of inducing DNA damage and lipid peroxidation. Increased reactive oxygen species (ROS) and decreased antioxidant enzyme activity (catalase, glutathione peroxidase) have been repeatedly detected in OLP tissues.

This oxidative imbalance serves a dual purpose: it aggravates local inflammation and creates an environment conducive to epithelial dysplasia. In chronic erosive OLP, oxidative DNA damage markers such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) are markedly elevated, suggesting a plausible microbial-driven precursor pathway to malignant transformation. The interplay between microbial metabolites and host oxidative stress therefore represents a crucial pathogenic mechanism bridging benign inflammation with oncogenic potential.

4. Viral and Fungal Components of the OLP Microbiome

Although bacterial dysbiosis has dominated the literature, recent metagenomic analyses reveal that the oral virome and mycobiome also participate in OLP pathogenesis. Human papillomavirus (HPV) and Epstein–Barr virus (EBV) have been detected at higher frequencies in OLP lesions than in normal mucosa, suggesting synergistic microbial-viral interactions. Viral infection may up-regulate pro-inflammatory cytokines or weaken epithelial defense, permitting secondary bacterial colonization.

The fungal microbiome, particularly *Candida albicans*, is also enriched in erosive OLP and may exacerbate mucosal damage by releasing hydrolytic enzymes and promoting antigenic mimicry. The coexistence of bacterial and fungal pathogens creates a complex biofilm network that sustains mucosal irritation and delays healing. Collectively, these findings broaden the traditional bacterial paradigm to a multi-kingdom microbial model in OLP development.

5. Correlation Between Microbial Changes and Clinical Manifestations

Several clinical studies have attempted to correlate microbial abundance with disease subtype and severity. Erosive and atrophic variants consistently show higher pathogenic bacterial counts and stronger inflammatory profiles than reticular or plaque-like types. Salivary cytokine levels, especially IL-6 and TNF-α, correlate positively with *F. nucleatum* and *P. gingivalis* loads, suggesting that microbial quantification could serve as a biomarker of disease activity.

OLP Clinical Type	Predominant Microbial Pattern	Observed Cytokine Elevation
Reticular	Moderate dysbiosis; *Streptococcus* dominance retained	Mild IL-6, TNF-α elevation
Erosive	High *Fusobacterium* and *Prevotella* abundance	Strong IL-8, IFN-γ up-regulation
Atrophic	Elevated *P. gingivalis*, decreased commensals	Sustained IL-1β, IL-6 expression

Such associations reinforce the concept that microbial imbalance is not merely a secondary phenomenon but may actively influence disease phenotype and persistence. Longitudinal analyses also indicate that microbial composition fluctuates in parallel with clinical improvement following anti-inflammatory or antimicrobial therapy, further supporting a causal link.

6. Therapeutic and Diagnostic Implications

The recognition of the oral microbiome's contribution to OLP pathogenesis introduces new diagnostic and therapeutic possibilities. Non-invasive microbial profiling through saliva sampling could allow early detection, monitoring of treatment response, and differentiation between benign and potentially malignant lesions.

Therapeutically, modulation of the oral microbiota through probiotics, prebiotics, or selective antimicrobial agents has shown encouraging preliminary outcomes. Administration of *Lactobacillus rhamnosus* and *Bifidobacterium longum* has been reported to restore microbial balance, reduce inflammatory cytokines, and accelerate mucosal healing in small clinical trials. Adjunctive antimicrobial mouth rinses containing chlorhexidine or essential oils have demonstrated transient symptom relief, although excessive use may further disrupt the commensal flora.

Emerging research advocates the concept of personalized microbiome-based interventions, integrating genomic sequencing data with clinical evaluation. Such precision approaches could enable the selection of tailored probiotic strains or immunomodulatory regimens to re-establish ecological equilibrium in OLP patients. Moreover, the identification of microbial metabolic markers such as short-chain fatty acid profiles or nitrosamine levels could aid in distinguishing high-risk lesions prone to malignant transformation.

7. Comparative Analysis with Other Chronic Oral Diseases

Comparison of OLP-associated dysbiosis with other chronic oral conditions, such as periodontitis and leukoplakia, reveals overlapping microbial signatures. *P. gingivalis* and *F. nucleatum* emerge as common denominators across these disorders, both capable of inducing chronic low-grade inflammation and modulating epithelial signaling. However, OLP differs in its autoimmune component: microbial triggers appear to act as amplifiers rather than sole initiators of disease. The resemblance of microbial profiles in OLP and early oral squamous cell carcinoma (OSCC) supports the hypothesis that prolonged dysbiosis could constitute a transitional step toward malignancy.

8. Integration of Host–Microbe Interactions

Central to OLP pathogenesis is the reciprocal relationship between microbial communities and host immunity. Cytotoxic T-cells in OLP lesions exhibit elevated expression of perforin and granzyme B, mediating keratinocyte apoptosis. Concurrently, microbial antigens perpetuate this immune activation through molecular mimicry and sustained cytokine signaling. Transcriptomic studies have demonstrated that keratinocytes exposed to pathogenic oral bacteria show up-regulation of genes related to antigen processing, apoptosis, and oxidative stress.

The host genetic background further influences these interactions. Polymorphisms in cytokine genes (IL-6, IL-10, TNF-α) and TLR pathways modulate susceptibility to OLP and its response to microbial stimuli. This intricate interplay implies that therapeutic success may require simultaneous correction of immune dysregulation and microbial imbalance rather than focusing exclusively on one aspect.

9. Emerging Technologies and Future Perspectives

Recent technological advances, including shotgun metagenomics, metatranscriptomics, and metabolomics, are refining our understanding of the oral microbiome's functional dynamics in OLP. These methods go beyond taxonomic identification

to reveal gene expression patterns and metabolic interactions within microbial communities. Integrating these omics datasets with clinical parameters will enable a systems-biology view of OLP.

Machine-learning algorithms applied to microbiome data have already demonstrated high accuracy in distinguishing OLP patients from healthy controls, suggesting potential clinical applicability. Such predictive models, if validated across populations, could form the basis of chair-side diagnostic tools capable of identifying disease risk through salivary microbial signatures.

Nevertheless, the heterogeneity of study designs, limited sample sizes, and geographic variability of microbial communities remain obstacles. Standardization of sampling sites, sequencing platforms, and bioinformatics pipelines is essential for achieving reproducible results across cohorts.

10. Synthesis of Evidence and Conceptual Model

The collective findings from current literature converge on a conceptual model in which oral microbial dysbiosis acts as both a trigger and perpetuator of OLP (Figure 1 – conceptual model not included). The sequence begins with environmental or immune perturbation leading to the disruption of commensal balance. Opportunistic pathogens proliferate, releasing virulence factors that provoke epithelial inflammation. The ensuing immune response causes keratinocyte apoptosis and antigen presentation, sustaining a chronic cycle of inflammation and tissue damage. Over time, oxidative and genotoxic stress induced by microbial metabolites increases the risk of malignant transformation.

This integrated model supports the notion that OLP exists along a biological continuum between chronic mucosal inflammation and epithelial neoplasia, with the microbiome serving as a critical modulator at every stage. Recognizing and targeting these microbial mechanisms may therefore represent a turning point in preventing disease progression.

Summary of Key Findings

Domain	Core Observation	Implication for OLP Pathogenesis
Bacterial Dysbiosis	Decrease in commensals, rise in *Fusobacterium*, *Porphyromonas*	Drives inflammation and apoptosis
Cytokine Profile	Elevated IL-6, IL-8, TNF-α	Sustains chronic immune activation
Oxidative Stress	High ROS and 8-OHdG levels	DNA damage, potential malignant change
Viral/Fungal Interplay	Presence of HPV, EBV, *Candida*	Synergistic mucosal injury
Therapeutic Potential	Microbiome modulation and probiotics	Restores homeostasis, symptom relief

Interpretative Discussion

The cumulative evidence establishes that OLP is not merely an immune-driven condition but a complex immuno-microbial disease. The observed dysbiosis is both a cause and a consequence of immune dysfunction, creating a self-propelling pathological cycle. The presence of overlapping microbial species between OLP and oral malignancies strengthens the argument that microbial surveillance could serve as an early warning system for cancer risk.

Despite these insights, substantial gaps persist in defining causality. Most available data are cross-sectional, offering associative rather than mechanistic conclusions. Future research should emphasize longitudinal cohort studies to determine whether microbiome alterations precede clinical onset or arise secondary to mucosal inflammation. Moreover, functional experiments using organoid models or gnotobiotic animals could clarify the specific molecular pathways through which individual microbes influence epithelial and immune responses.

Ultimately, the oral microbiome represents both a challenge and an opportunity in understanding OLP. Harnessing its diagnostic value and therapeutic potential will require a coordinated interdisciplinary approach involving microbiologists, immunologists, and oral pathologists. As evidence continues to accumulate, microbiome-guided precision medicine may redefine current paradigms in the prevention and management of chronic oral mucosal diseases.

CONCLUSION:

The collective evidence from current literature establishes that the oral microbiome plays a critical and previously underappreciated role in the initiation and persistence of Oral Lichen Planus (OLP). Once considered solely an autoimmune mucocutaneous disorder, OLP is now recognized as a multifactorial disease in which microbial dysbiosis interacts intricately with host immunity, epithelial barrier function, and inflammatory signaling pathways. The reviewed studies

consistently demonstrate that patients with OLP exhibit marked alterations in their oral microbial communities, characterized by reduced species diversity, depletion of beneficial commensals such as *Streptococcus* and *Rothia*, and enrichment of pathogenic genera including *Fusobacterium*, *Porphyromonas*, *Prevotella*, and *Treponema*. These microbial changes are not random but correlate closely with disease severity and histopathological findings, suggesting a direct biological link between microbial imbalance and mucosal pathology. Mechanistically, the altered microbiota in OLP contributes to disease development through multiple interrelated pathways. Pathogenic bacteria release virulence factors, endotoxins, and volatile metabolites that activate Toll-like receptors on keratinocytes and immune cells, leading to the persistent activation of NF-κB and STAT3 signaling cascades. This promotes excessive cytokine production particularly IL-6, IL-8, TNF-α, and IFN-γ and recruits cytotoxic T lymphocytes to the basal cell layer of the oral epithelium. The resulting epithelial apoptosis, basement membrane disruption, and chronic inflammatory infiltration create a self-sustaining cycle of immune activation and tissue injury. Concurrently, microbial metabolites such as nitrosamines and acetaldehyde induce oxidative stress and DNA damage, thereby linking chronic inflammation with a potential risk for malignant transformation in long-standing OLP lesions.

In addition to bacterial dysbiosis, the contribution of viral and fungal communities, notably human papillomavirus, Epstein–Barr virus, and *Candida albicans*, further amplifies epithelial stress and immune dysregulation. This highlights that OLP pathogenesis should be viewed as a polymicrobial phenomenon rather than the consequence of a single pathogen. The reciprocal relationship between the microbiome and the host immune response is central to this process: immune dysfunction favors the overgrowth of opportunistic microorganisms, and dysbiosis, in turn, perpetuates immune imbalance. From a clinical standpoint, these insights open promising diagnostic and therapeutic horizons. Salivary microbiome profiling may serve as a non-invasive biomarker for early disease detection, risk assessment, and treatment monitoring. Interventions aimed at restoring microbial homeostasis such as probiotics, prebiotics, or selective antimicrobial therapies have demonstrated preliminary benefits in symptom reduction and lesion healing. However, translating these findings into standardized clinical practice demands robust longitudinal and mechanistic studies to clarify causality and to determine the most effective strategies for microbiome modulation. In conclusion, the oral microbiome represents a pivotal factor in the complex pathobiology of Oral Lichen Planus. Understanding its composition, functional dynamics, and interactions with host immunity not only enriches our conceptual framework of the disease but also provides a foundation for innovative diagnostic tools and targeted therapies. Future interdisciplinary research integrating microbiology, immunology, genomics, and clinical science is essential to transform microbiome knowledge into practical solutions for the prevention and management of OLP.

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