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Oral Microbiota Dysbiosis: Significance in Coexistence of Rheumatoid Arthritis and Oral Lichen Planus

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Abstract

The oral cavity and gastrointestinal (GI) tract contain a complex and diverse micro-biome composition community that is important for both health and disease. Major oral infections like oral lichen planus (OLP) and periodontitis, which are aggravated by oral microbiota dysbiosis, are heavily influenced by it. Similar to the oral microbiota more than 100 trillion bacteria, or the largest variety of microorganisms, reside in the GI system (1,500 distinct species). Chronic systemic diseases can either be caused by or made worse by oral as well as GI tract microbial dysbiosis. The oral and gut microflora axis is a novel target in the detection, monitoring, and treatment of systemic diseases. According to the recent research, oral and GI microbiomes have a significant influence on musculoskeletal health such as rheumatoid arthritis (RA). The genus Haemophilus is a cylindrical, gram-negative, facultative-anaerobic microorganism naturally occurring in the oral cavity that needs the coenzymes (V-factor), such as nicotinamide adenine dinucleotide (NAD), hemin, and/or other porphyrins (X-factor). Dysbiosis in the many species of this genus causes a variety of chronic systemic illnesses. The role of oral-gut microbial contact in disease hasn't received enough attention, though. We will emphasize the significance of oral and gut microflora interaction and its consequences in the etiology of RA and OLP in this article. A thorough knowledge of the involvement of the oral-gut microbiome axis in disease pathogenesis would assist in accurate diagnosis, prognosis, and successful therapy.

Keywords: *Oral and gut microflora; Dysbiosis; Rheumatoid arthritis (RA); Oral lichen planus (OLP); Haemophilus; Chronic systemic diseases.*

Introduction

There are at least 10 times more microorganisms on and in the human body than there are human cells. Since bacteria "lay" in the interior mucosae like reproductive organs, respiratory tract, and gastrointestinal (GI) tract as well as externally in the body such as skin and hair, humans are more prokaryotic than eukaryotic. Even among healthy people, the microbial community is extremely diversified. The pattern of microbial communities in each microorganism's environment varies from one individual to another.[1–3] The human microbiome is made up of a wide range of microorganisms, such as viruses, bacteria, archaea, protozoan, and fungi. The equilibrium between homeostatic health and pathology is governed by such a varied and multifarious population of microorganisms, which also plays a role in the etiopathogenesis of dysbiotic infection and offers the host significant functional and immunologic advantages during eubiosis.[4] The two main microbial habitats, the oral passage, and the gut are important in diseases linked to the microflora. The oral and gut barrier keeps both microbiome profiles separate, irrespective of the fact that the intestine and oral region are one continuous area linked by the GI tract. Notably, pathological situations in the GI tract have shown characteristic oral-resident species.[5] These microorganisms provide their host with important physiological benefits including immunologic homeostasis and pathogen invasion tolerance **(**Table 1**)**. Dysregulation of the microbial communities in the mouth and gut is a precursor of many oral diseases (e.g., chronic periodontitis) and systemic illnesses, including diabetes, cancer, autoimmune disorders, and inflammatory diseases. It is known that bacteria-driven chronic periodontitis is characterized by the breakdown of gingival tissue, the periodontal ligament, and alveolar bone, and ultimately leads to tooth loss. Previously, Alim et al. also reported that the protein pleckstrin is highly upregulated in human saliva samples and gingival tissue of patients with chronic periodontitis and this is the only gene/protein concurrently upregulated in other inflammatory diseases including rheumatoid arthritis (RA) and cardiovascular diseases.[6,7] Inherent barrier failure, immunological dysfunction, pro-inflammatory signaling pathways, and biochemical imitation can all contribute to this dysregulation.[8,9] Instead of using an integrated approach, the majority of studies on dental and intestinal microbiomes have been done in isolation and have focused on individual systems. Recent investigations have demonstrated the role of microbiota composition in inter-organ networks. It has been observed that fecal-oral transmission and intestinal colonization of oral microbiota can influence pathological events in humans.[2,10]

In the majority of investigations on the microflora of different areas of the human oral cavity, Haemophilus and other facultative gram-negative rods have gotten special attention. This bacterial group is sometimes regarded as a minor component of the oral bacteria ecology.[11] The genera

Haemophilus has a variety of pathogens that cause a range of illnesses but share a similar morphological structure and required blood-derived nutrients for growth, which gives the genus its name.[12]

Organ surface	**Genera**	**Reference**
Tooth Surfaces	*Actinomyces, Fusobacterium, and Veillonella*	Caselli et al., 2020 [13]
Soft Tissue Surfaces	*Veillonella, Prevotella, Streptococcus, Haemophilus, Porphyromonas, Leptotrichia, Neisseria,* and *Actinomyces,*	Ren et al., 2017; Zhang et al., 2021 [14,15]
Saliva	*Veillonella Actinobacteria and Porphyromonas, Fusobacteria, Haemophilus, Neisseria, Prevotella, Streptococcus,* and *Gemella*	Murugesan et al., 2020 [16]
Intestinal flora	*Bacteroides* and *Prevotella Actinobacteria, Proteobacteria*	D'Argenio & Salvatore, 2015; Song et al., 2021 [17,18]
Urogenital tract	*Firmicutes, Bacteroidetes, Actinobacteria*	D'Argenio & Salvatore, 2015 [17]

Table 1: Normal microbiota in human oral cavity and gut

Based on the antigenic nature of the envelope glycoproteins, the major pathogenic species, *Haemophilus influenzae* is classified into enteric-coated or typable strains, of which there are seven subspecies **(**a, b, c, d, e, and f plus e'**)**. The most virulent agent in this group, type b *H. influenzae,* frequently injures infants under 2 years old by invading their bloodstream and causing meningitis. Newborns, toddlers, and adults who have respiratory tract infections frequently get them from non-typable strains.[19,20] *H. influenzae* is a common cause of meningococcal disease **(**meningitis**)**, pyogenic pneumonia, and blood poisoning in kids, but it can also cause chronic inflammatory disease, erysipelas, infectious arthritis, and bone infection. According to estimates, it has a fatality rate of 5% and 15–30 % chances of neurological disability.[21]

To remove pathogenic microbes as well as accept symbiotic microorganisms, unique anti-inflammatory mechanisms have been established by the buccal cavity immune system **(**oral as well as mucosal tolerance**)**. However, the mucosal inflammatory response also needs to provide localized responses against environmental risks **(**e.g., invading pathogenic microorganisms**)**.[22] Pathogenic

microorganisms and their toxins, as well as poorly performing mucosal immune response systems, can alter intestinal mucosal homeostasis. On the other hand, a manifestation of pathologically elevated immune activity may cause a variety of inflammatory diseases. Therefore, alterations in the processes governing mucosal immunity or abnormalities of mucosal barrier functionality might lead to a variety of chronic illnesses. This might encompass autoimmune disorders beginning on mucosal surfaces or progressing there during their entire course, as well as viral diseases, immunological disorders **(**allergies**)**, and multi-organ dysfunction.[23,24]

A persistent inflammatory condition of the oral mucosa known as oral lichen planus **(**OLP**)**, usually affects women during their 40s.[25] Six clinical subtypes of OLP have been identified: erosive, plaque, papular, atrophic, reticular, and bulbous. Erosive and reticular variants, which have white lines and lesions, are the most prevalent.[26] Speaking, swallowing, and eating can all be painful for persons with OLP. In contrast to reticular lesions, which are often asymptomatic, atrophic and erosive plaques are frequently agonizing. Even though a T cell-mediated immune response has been associated with the onset of OLP, the pathophysiology and etiology of OLP are still unknown.[27]

Recent scientific studies have also emphasized how the gut microbiota affects various pathologic disorders that frequently affect far-off anatomical areas including the liver, brain, heart, and skeleton system. These studies have called attention to the gut microbiota's immunomodulatory impact on these organs.[28] The involvement of bacteria in the health of bones and joints has been explained by several processes and variables. Many essential vitamins, including folate, pyridoxal 5-phosphate, Vit-B12, Vit-B7, thiamine **(**B1**)**, Vit-B5, Vit-B3, phylloquinone, and tetrahydrofolate **(**THF**)**, which are existent in the GI microbiota and are essential for the health of the musculoskeletal system.[29] It has been noted that rheumatic diseases, particularly juvenile RA, RA, dermatitis, and associated pelvospondylitis ossificans, such as ankylosing spondylitis **(**AS**)** and Reiter's disease might affect the gut microflora. It has been proposed that gut bacteria play a vital role in the etiopathogenesis of the aforementioned illnesses.[30,31] The autoimmune disorder RA is a persistent, inflammatory infection that causes systemic complications and premature mortality. The primary features of RA include collagenous hyperplasia, rheumatoid factor **(**RF**)** as well as anti-citrullinated-protein-antibody **(**ACPA**)** secretion, articular cartilage-bone, as well as systemic symptoms such as heart, lung, psychiatric, skin, and skeletal diseases.[32]

Targeting molecular biomarkers and inflammatory mediators have been proven to be an efficient strategy in the developing field of precision medicine for modifying host immune responses. Although links among the human immune system, microbiota, and systemic diseases are becoming increasingly

clear, additional study and interdisciplinary cooperation will be needed to fully understand the complex interaction and potential future advancements in treatment methods. In this review, we have mainly focused on the role of the oral microorganism, *Haemophilus*, its interaction, and its effects on the progression of RA and OLP. A comprehensive understanding of the involvement of Haemophilus species in the pathophysiology of both diseases would aid in accurate diagnosis, prognosis, and efficient treatment.

Oral-Gut Microbiota: Cross-talk and Exclusion

The buccal cavity is one of the body's major reservoirs of microbes, and it has been the subject of extensive investigation in recent times. The mouth microbiota, a complex microbial population that is habitat in the buccal cavity, is mostly made up of bacteria but also comprises viral, protozoa, fungus, archaea, bacteriophage, and extremely tiny bacteria from the candidate phylum radiation group.[33] More than 500 distinct bacterial species make up the oral microbiota, which began to grow within the first few minutes of a newborn existence. The specific composition of microflora varies from individual to individual depending on a number of variables including age, diet, and lifestyle decisions like smoking and physical exercise.[34] In a healthy anatomical condition, these bacteria coexist with the human body in a symbiotic relationship **(**Table 2**)**. There are two equilibrium states: the one between the propagation of the various species and the host immunological defense system, and another between the various species of microorganism itself. When this balance is disrupted by dysbiosis, one or more species of bacteria grow and, at least briefly, seize control of the immune system.[35]

The intestinal microbiome plays a critical responsibility in preserving human health and contains over 10-100 trillion microbial cells, the majority of which are varied bacterial symbiotic organisms, colonized opportunist pathogens **(**COPs**)**, and simple opportunist pathogens **(**SOPs**)** in a homeostatic ratio.[36] The beneficial bacteria and the latent opportunist pathobionts **(**COPs and SOPs**)** cohabit in the gut cooperative way as a "good gut" and regularly invade, colonize, and remain there without causing symptoms. Nonetheless, any disruption in the proportionate cohabitation of COPs or SOPs dwelling alongside the symbiotic organisms results in dysregulation, sometimes known as a "leaky gut," and when these opportunistic bacteria reach a certain threshold, they can cause serious severe, prolonged, or underlying human illnesses. Health conditions, environmental variables, genetics, and even lifestyle can change the human gut microbiota patterns.[37,38] According to metagenomic research, the bacterial population that lives in the human gut controls metabolic processes such as

amino acid synthesis and carbon metabolism.[39] Microbial-associated molecular patterns **(**MAMPs**)** and pathogen-associated molecular patterns **(**PAMPs**)** are conserved molecular motifs shown by microorganisms that may be identified by the host through pattern recognition receptors **(**PRRs**)**, such as Toll-like receptors **(**TLRs**)**.[40]

The Human Microbiome Project **(**HMP**)** and the Human Oral Microbiome Database **(**HOMD**)** are two significant oral microbiome datasets that emerged in previous decades. The goal of HMP is to describe the ecosystem of human microbial populations and to investigate various ways microbes can affect human health and illness. The mouth canal, nasal passages, vagina, intestines, and epidermis are the five main areas of the human body where it maps the metagenomics of microorganisms **(**"The Integrative Human Microbiome Project," 2019**)**.

Core oral microbiota	**Types of microbial population**	**Reference**
Healthy individual	**Firmicutes** ***(****genus Granulicatella* and *Streptococcus****)****, Treponema,* **Actino-bacteria** ***(***genus *Corynebacterium Actinomyces* and *Rothia****)*** *Veillonella* **Fuso-bacteria** ***(****genus Fusobacterium****)****,* **Bacteroidetes** ***(****genus Prevotella, Capnocytophaga, Prevotella,* and *Porphyromonas****)****,* ***Proteo-bacteria*** ***(****genus Haemophilus and Neisseria****)****, Porphyromonas,*	Zaura et al., 2015 [41]
Microflora in females during the menstrual cycle	*Campylobacter, Haemophilus, Oribacterium, and Prevotella,*	Bostanci et al., 2021 [42]
Pregnant women	*Neisseria, Porphyromonas, and Treponema*	Saadaoui et al., 2021 [43]

Table 2: Oral microbiota in a healthy person under various situations

Physio-pathologic significance of oral microbiota in systemic inflammation

Recent published research suggests a linkage between the presence of an imbalance in the oral flora and the development and/or worsening of several systemic illnesses.[44] These illnesses share a pathogenic pathway based on the presence of a low-grade systemic inflammatory state, which cannot

be resolved or stabilized in the presence of oral microbiota dysbiosis. Additionally, other researchers suggested that microbes can induce dysbiosis in the oral microbiota, which can circulate throughout the body or release some of its components into circulation, creating difficulties far from where they first began to proliferate.[45] The term "bacterial meta factors" refers to all bacterial components **[**such as lipopolysaccharide (LPS), flagellin, and teichoic acid**]** that are the potential for pathogenicity or immune system activation throughout physiology and physiopathology.[46]

Bacteria or their parts, such as the endotoxin LPS, found on the outer membrane of gram-negative bacteria, are a constant resource of infection and inflammation that pass through the epithelial barrier, enter the circulation, and affect several different organs in the body. Dysbiosis of the oral microbiota is the primary cause of this bacterial translocation. The disruption of the salivary bacterial composition causes an overabundance of gram-negative as well as gram-positive bacteria or its disease-causing factors. PAMPs**,** which are identified by PRRs of innate immunity cells, are used by oral microorganisms or meta-factors to stimulate intrinsic immunological responses.

Various surface molecules, such as teichoic acid **(**unique to gram-positive bacteria**)** or LPS, serve as PAMPs **(**gram-negative specific**)**. Similarly, TLRs are a class of receptors that are also included in PRRs.[47] When oral microbiota dysbiosis causes systemic disorders, there are two main reasonable mechanisms **(**through bacterial translocation in the blood**)** that might be responsible for an increase in pro-inflammatory cytokines. The other is a sequence of protein kinase-catalyzed phosphorylation chain events required for the transmission of an inflammatory signal to the cell nucleus. Several pathways, including MAPK **(**Mitogen-Activated Protein Kinases**)**, and JAK/STAT, IKKs **(**Inhibitor of Kappa-B-Kinases**)**, are employed to activate the inflammasome such as Janus-Kinase **(**Signal Transducers and Activators of Transcription**)**.[34]

Rheumatoid arthritis (RA) co-morbid with oral lichen planus (OLP)

OLP is a skin and mucous membrane inflammatory condition. It causes white lesions that resemble plaques or reticulated patterns.[48] It is a chronic inflammatory condition related to T-cells that affects more women than males, especially those who are over fifty. Although it's unclear if oral microbes affect OLP disease status, certain research has supported the link between OLP and oral microbes.[49] In recent decades, considerable emphasis has been placed on the pathophysiology of OLP caused by microbial infection. For example, one of the major causes of OLP is thought hepatitis C virus **(**HCV**)** infection.[50] Research carried out by Li et al. in 2019 elaborated that oral bacterial composition alterations might impact the immunological responses of the host and contribute to the progression of

the OLP. Dysregulation of the salivary microbiome **(**i.e., lower salivary mycobiome bio-diversity and higher bacterial bio-diversity**)** contributes to OLP.[51] Antimicrobial peptides such as histatins, defensins **(**both α and β**)**, and precursors of cathelicidin hCAP-18 **(**identified as LL-37**)** are considered to be involved in OLP. According to Davidopoulou et al. **(**2014**)**, LL-37 can protect from dangerous microorganisms and hasten the healing of wounds, since people with this condition were shown to have higher amounts of cathelicidin than the general population. There was a distinct correlation between the degree of the disease progression and the quantity of the peptide produced.[52] The pathogenetic processes of OLP production suggest an autoimmune response in which T-cells infiltrate basal keratinocytes that have undergone antigen modification. In OLP, macrophages and a modest number of lymphocytes make up the inflammatory infiltrate. T-lymphocytes predominate over B-lymphocytes, and CD4+T-helper lymphocytes are more prevalent than CD8+T **(**cytotoxic/suppressor**)** lymphocytes. Research also suggests that various autoimmune processes are the cause of the pathological condition known as autoimmunity disease **(**AID**)**, and it could be multifactorial.[53]

OLP frequently co-occurs with other pathological conditions, including various autoimmune disorders such as diabetes mellitus **(** Type 1**)**, thyroid problems, and RA.[54] Inflammation and swelling of the synovial membrane are hallmarks of an immune-system mediated, chronic inflammatory disease known as RA. The major clinical symptoms of RA are extra-articular lesions and persistent, symmetric and polysynovial arthritis.[55] In 2013, Lopez-Jornet conducted research on the relationship between autoimmune disorder and OLP, comparing OLP patients with a control group. His findings revealed that the coexistence of RA and OLP may be responsible for the onset and development of OLP. However, it is challenging to determine the degree of relationship between the two disorders because there is so little research that addresses this cohabitation.[56] The correlation between OLP and other autoimmune conditions raises the potential that individuals with OLP may be developing an autoimmune condition that makes them more likely to engage in auto-aggression against various targets. The research published in this area has found a link between RA **(**prevalence value = 2.40%**)** and OLP. However, the information that is now available is based on a few studies and patients, making the abovementioned findings weak and lacking in support.[54]

The Possible significance of Haemophilus species dysbiosis in RA and OLP comorbidity

Haemophilus is a poorly differentiated coccobacillus in the Pasteurellaceae family. Haemophilus bacteria are multinucleated bacteria due to the vast diversity of forms they occasionally acquire, even though they are normally tiny coccobacilli.[57] No matter what the niche location in the oral cavity is,

a healthy person carries the Haemophilus genus throughout all oral locations.[58] Remarkably, pathological scenarios have resulted in the detection of typical oral-resident species throughout the GI tract.[59] Haemophilus bacteria have proteins known as auto-transporters, which are present on the outer membrane and perform several significant functions such as adhesion, invasion, proteolytic activity, and cytotoxic activity. Respiratory tract illnesses in newborns, children, and adults are frequently caused by *Haemophilus influenzae*.[20,60] Other Haemophilus species are less common pathogenic. Sometimes, pneumonia or bacterial endocarditis is carried on by *Haemophilus parainfluenzae*. Additionally, chancroid is caused by *Haemophilus ducreyi*. The bacteria *Haemophilus aphrophilus*, which occasionally results in bacterial endocarditis, are a natural component of oral flora. Both *Haemophilus haemolyticus* and *Haemophilus aegyptius*, which produce Brazilian purpuric fever and conjunctivitis, were formerly classified as non typable *H. influenzae* strains based on their proteolysis ability or agglutinate red blood cells, respectively.[12]

An article published on bacterial populations found within OLP lesions **(**2020**)** revealed that even though the relative abundance of *Haemophilus parainfluenzae* was substantially lower than it was on the surface of normal control. However, *H. parainfluenzae* was still the dominant species in the OLP intra-tissue community.[61] Contrarily, there were considerably more Haemophilus, Cellulosimicrobium, Corynebacterium, and Campylobacter in the healthy than in the OLP group. Few species, meanwhile, showed significantly differing abundance levels amongst the three groups. *Prevotella melaninogenica* exhibited considerably greater levels of reticular OLP compared to *Haemophilus parainfluenzae*, and *Streptococcus parasanguinis*, which were less prevalent in erosive OLP.[62]

A research article published in a scientific report journal accomplished that bacteria have a unique role in the progression of OLP by damaging epithelial barriers, internalizing into epithelial cells and T-cells, and inducing T-cell-mediated chemokines.[63] In line with the study by Deng et al., the comparative density of gram-negative bacteria, such as *Derxia, Haemophilus, and Pseudomonas*, reduced in the OLP patients, and the levels of TLR4, NF-B p65, IL-6, and TNF- were all enhanced, suggesting that the LPS of *Haemophilus, Pseudomonas, as well as Derxia* potentially adhere to the immunological cellular membranes surface receptor **(**TLR4**)** to conduct cellular responses. TLR4 activates the NF-B signaling route as well as other associated pathways such as the TNF-α-tumor-necrosis-factor-receptor-1 related signaling system and the JAK/STAT mediated signaling pathway, which is connected to IL-6; and the TGF signaling pathway, which can influence T-lymphocyte cell immunity.[50] This indicates that the alteration in the flora's ratio disturbed the delicate balance of the original flora, disrupting the physical barrier provided by the epithelium.[50]

It's noteworthy that autoimmune disorders typically affect tissues other than those where the microbiome is anticipated to play a pathogenic function. Beginning in the twentieth century, when it was established that treating periodontal infections helped RA patients with their symptoms, dysbiosis in the oral microbiota provided significant hints for relevant causes of the disease.[64] Lately, it has been abundantly evident that RA development is greatly influenced by dental health, particularly oral flora.[65,66] Various results are supporting the association of RA with *H. influenza*.[67] Similarly, other species such as *H. paraphrohaemolyticus*, and *H. parainfluenzae* are also involved in the pathogenesis of RA.[68] We used the mBodyMap data source, a curated database, on human body microorganisms and their relationships to health and diseased conditions. The findings revealed an association between RA and various species of Haemophilus, such as *H. haemolyticus*, *H. influenza*, *H. parahaemolyticus*, *H. parainfluenzae*, *H. paraphrohaemolyticus*, and *H. sputorum* **(**Table 3**)**.[69] Sabrina Weber also reported that *H. haemolyticus* has been seen in immune-compromised patients with septic knee arthritis.[70]

Name	**relative_ abundance_avg**	**relative_ abundance_med**	**relative_ abundance_std**	**relative_ abundance_sum**
Haemophilus haemolyticus	0.11452	0.05326	0.1528	2.86292
Haemophilus influenza	0.25065	0.03523	0.51182	6.51695
Haemophilus parahaemolyticus	0.10894	0.02908	0.16015	2.2878
Haemophilus parainfluenzae	2.82519	1.86541	3.12644	76.28007
Haemophilus paraphrohaemolyticus	0.15793	0.0226	0.46067	3.79038
Haemophilus sputorum	0.0586	0.01733	0.10176	1.28911

Table 3: Association of Haemophilus species with Rheumatoid Arthritis (data procured from mBodyMap; https://mbodymap.microbiome.cloud)

According to many authors, it was hypothesized that OLP and RA are related. Nevertheless, on the particular abnormal immunological pathways, nothing is known. With this review, we theoretically hypothesized that OLP pathogenesis results in epithelial barrier cells being damaged and Haemophilus species bacterial LPS entangling to the immune cell membrane to start various signal transduction.[50] The infection and inflammation that led to this attachment crossed the epithelial barrier, entered the bloodstream, and activated several signaling pathways including MAPK, IKKs, and JAK/STAT.[34] As a result, the Janus kinase/STAT pathways are activated, which is a crucial stage in the pathogenesis and progression of RA **(**Figure 1**)**.[71]

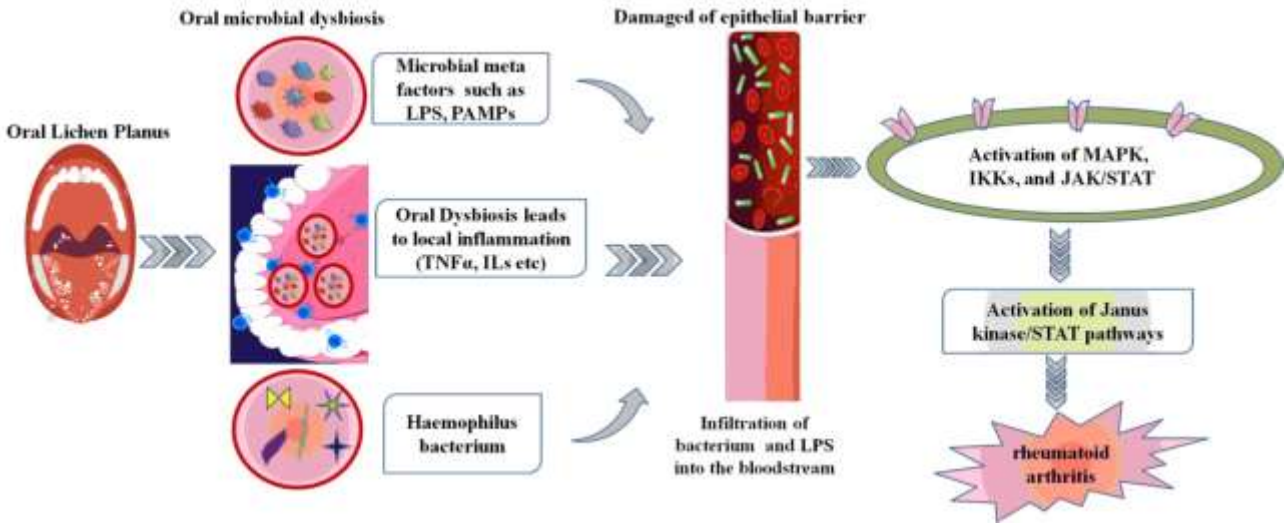

Figure 1: Potential role of Haemophilus species in the progression of the disease from Oral Lichen Planus to Rheumatoid arthritis

Conclusion

Microbes are a significant risk factor for both oral and systemic chronic diseases. Even if the function of microorganisms and the microbiota is still not fully understood, any alteration in dental health should be taken into consideration as a warning sign in the fight against the onset of systemic disorders. We have outlined the potential contribution of Haemophilus species in the coexistence of OLP and RA disease in this review. However, there is no direct connection between Haemophilus, RA, and OLP. It was abundantly obvious that microbial-host interactions might activate inflammatory and immunological responses in patients. This means that the oral microbiota can affect the body's metabolism, immunology, and central biological processes, resulting in dysbiosis, which is linked to

a variety of human disorders, from OLP to RA. The potential link between OLP and RA caused by the dysbiosis of Haemophilus species requires more research with bigger sample numbers from various geographical locations.

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