Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

HUMAN ORAL MICROBIOME: ROLE IN HEALTH AND DISEASE. A SYSTEMATIZED REVIEW.

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RESUMEN

Introducción El microbioma oral humano es un ecosistema complejo y diverso que participa en el mantenimiento de la salud oral y sistémica. Su desequilibrio se ha asociado cada vez más a enfermedades orales comunes como la caries y la periodontitis, así como a afecciones sistémicas como trastornos cardiovasculares, metabólicos y neurodegenerativos. **Objetivos** Describir la composición y función del microbioma oral humano, comprender sus funciones beneficiosas para la salud y explorar los mecanismos a través de los cuales su disbiosis puede contribuir a la enfermedad. **Métodos** Se realizó una revisión sistematizada utilizando la base de datos PubMed para identificar estudios en inglés de los últimos 10 años centrados en la investigación basada en humanos que demuestre el papel del microbioma oral en la salud o la enfermedad. **Resultados** Un microbioma oral equilibrado contribuye a la defensa del huésped a través de mecanismos como la producción de amoníaco, nitrito y moléculas antiinflamatorias. Sin embargo, la disbiosis está estrechamente relacionada con la aparición y progresión de la caries, la periodontitis y el cáncer oral. Además, determinados cambios microbianos y factores de virulencia podrían estar implicados en enfermedades sistémicas como la aterosclerosis, la diabetes de tipo 2 y la enfermedad de Alzheimer. **Conclusiones** El microbioma bucal humano desempeña un papel fundamental en la salud al favorecer la modulación inmunitaria, la defensa frente a patógenos y la regulación metabólica. La disbiosis microbiana puede promover afecciones tanto locales como sistémicas. Estos hallazgos sugieren que las futuras estrategias preventivas y terapéuticas dirigidas al microbioma oral pueden mejorar la salud.

PALABRAS CLAVES

Odontología, Microbioma Oral, Simbiosis, Disbiosis, Probióticos.

ABSTRACT

Introduction The human oral microbiome is a complex and diverse ecosystem that plays a crucial role in maintaining both oral and systemic health. Dysbiosis, or imbalance, has been increasingly associated with common oral diseases such as caries and periodontitis, as well as systemic conditions including cardiovascular, metabolic, and neurodegenerative disorders. **Objectives** To describe the composition and function of the human oral microbiome, understand its beneficial roles in health, and explore mechanisms through which its dysbiosis may contribute to disease. **Methods** A systematized review was conducted using the PubMed database to identify English-language studies from the last 10 years focused on human-based research proving the oral microbiome role in health or disease. **Results** A balanced oral microbiome contributes to host defense through mechanisms such as ammonia, nitrite, and anti-inflammatory molecules production. Dysbiosis, however, is strongly linked to the onset and progression of caries, periodontitis, and oral cancer. Moreover, specific microbial shifts and virulence factors might be implicated in systemic diseases such as atherosclerosis, type 2 diabetes, and Alzheimer's disease. **Conclusions** Human oral microbiome plays a fundamental role in health by supporting immune modulation, pathogen defense, and metabolic regulation. Microbial dysbiosis can promote both local and systemic conditions. These findings suggest that future preventive and therapeutic strategies targeting the oral microbiome may improve health.

KEYWORDS

Dentistry, Oral Microbiome, Symbiosis, Dysbiosis, Probiotics.

ÍNDICE

1. INTRODUCTION

The human oral microbiome is a diverse ecosystem of microorganisms with viruses, mycoplasmas, bacteria, archaea, fungi, and protozoa that interact with the body (1).

Trillions of microorganisms make up the oral cavity, after the gut, being the second most important human microbial environment (2).

In microbiology, organisms are classified into distinct domains with the oral microbiome primarily consisting of three: Bacteria, Archaea, and Eukaryota. Regarding bacteria (the predominant domain of the oral microbiome), Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, and Actinobacteria are the most common phyla of the 12 presents, then forming 185 genera. These genera are further subdivided into species. Regarding to Eukaryota we find fungi, such as Candida albicans (3,4). An explanation of these scales is shown in the figure 1.

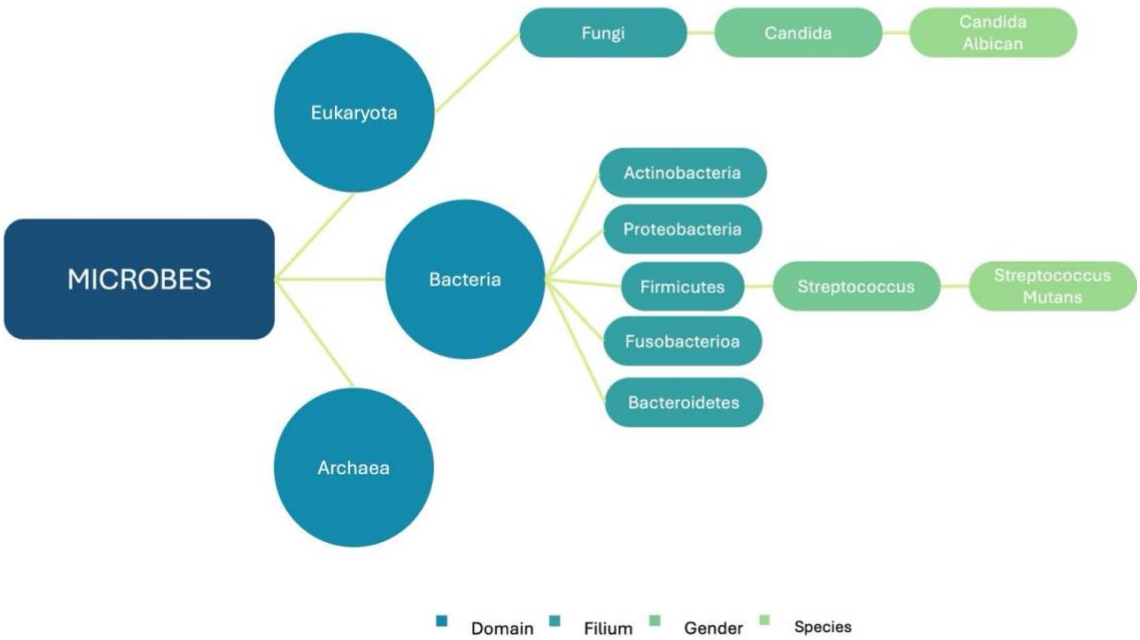


Figure 1: Simplified taxonomic classification of the oral microbiome.

In a healthy state, these microbes do not cause damage and play an important role, stimulating the immune system and help to avoid infections. However, changes in the microbiome composition (dysbiosis) increase the risk of diseases such as caries, periodontal diseases and systemic conditions (5), as dysbiosis breaks the homeostasis of the host, producing abnormal mucosal immune responses (6).

Systemic conditions associated with dysbiosis include metabolic disorders, autoimmune diseases, and gastrointestinal conditions (2,6). Indeed, as the oral cavity makes up the entrance of the respiratory and digestive systems, while also being highly vascularized, microorganisms can use it to reach other parts of the body. The main diseases associated to dysbiosis and their causes are shown in figure 2.

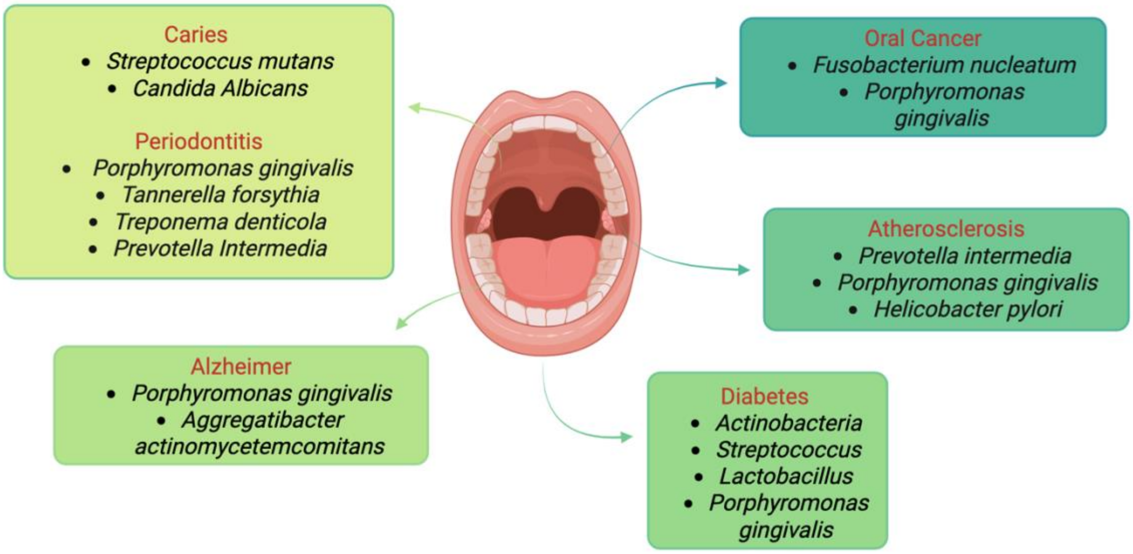


Figure 2: Oral and systemic diseases associated with human oral microbiome. Image created with Bio render.

In the case of the gastrointestinal tract, the gut microbiome is highly related with the oral one, and both are influenced by the diet, lifestyle, exposure to environmental stimuli, and genetic factors (2). Due to their actions and their close relationships with the host and between each other, the oral and gut microbiomes are considered the major actors in human health and disease (2).

The stability of the oral microbiome is influenced by the diet. By the disproportionate accumulation of microorganisms, the biofilm affects the equilibrium of the oral cavity and can increase the risk of disease (dysbiosis). The presence of fermentable carbohydrates like starches and sugars will increase the development of bacteria, particularly Streptococcus mutans, responsible for the production of acids and leading to the formation of caries (7). With the increased intake of sugar, the buffering capacity of saliva is lost and oral bacteria ferment dietary carbohydrates. The pH will constantly decrease and the oral microbiota will change, starting with the development of lactobacilli and Streptococcus mutans, being the principal cariogenic species leading to the erosion of enamel first, then dentin and pulp. Other microorganisms, part of the genera Bifidobacterium, Scardovia and Propionibacterium, also play a role in negative evolution of caries. Nevertheless, the microbiome can have beneficial capacity, for example,

Streptococcus salivarius activate urease gene when the pH decreases, avoiding excessive acid buildup, being a major alkali producers in the oral microbiome (8).
Moreover, variations in aliments consumed such as an increase in nitrate-rich aliments will increase the amount of nitrate reducing bacteria. Indeed, Veillonella and Prevotella populations will decline and Neisseria and Rothia populations increase (9). These changes will then have a systemic effect on the body by increasing the nitric oxide levels and the blood pressure. (10)
The lifestyle could also influence the oral human microbiome, especially the tobacco consumption. Nicotine, enhances the pathogenic effect of oral microorganisms by increasing the virulence factors or the amount of plaque formed. It influences the human cells through nicotine acetylcholine receptors (11). These changes will create a more favorable environment for proliferation of beneficial microbes but also dangerous ones, associated with oral disease. Smokers are more susceptible to develop infections, oral diseases, have a diminution of Proteobacteria, and an increase of Actinobacteria and Firmicutes (12). E-cigarettes might also influence the microbiome indirectly as in vitro e-cigarette exposure increases the production of proinflammatory cytokines in saliva by premalignant and malignant cell lines and promotes bacterial infection (12).
In addition, alcohol consumption decreases Lactobacillus levels in heavy drinkers (13), with lower production of lactic acid, decreasing the capacity to maintain oral pH, while increasing the proliferation of species suited for more alkaline environments, such as Neisseria (13).

Microbiota (the microbial taxa associated with humans) and microbiome (the expression of the genes of theses microbes), are often used interchangeably (14). Next generation sequencing technologies have revolutionized microbiota research, as entire genomes or targeted regions of DNA or RNA can now be detected quickly (15). These new techniques are particularly important as more than 90% of microbial species cannot be easily cultured using current laboratory culture techniques (16). Some examples of these new techniques include the whole metagenome shotgun sequencing, the 16S ribosomal RNA amplicon sequencing, and microarray-based technologies. The whole genome shotgun sequencing will define the bacteria in a more accurate and precise way. However, it is more expensive and requires more complex data analysis (16). The 16S ribosomal RNA amplicon sequencing, amplifies RNA sequences (16). This technique lacks precision because it analyze the microbes as taxa instead of particular species (16).
Microarrays, are cheaper and provide more range but a certain quantity of DNA is necessary to detect an organism (8).
In the mouth, we can find several ecosystems called niches, colonized by different microorganisms. The saliva is the most important niche and the planktonic phase (free-floating stage) of the oral microbiota, containing up to 10^9 microorganisms per milliliter, transported

when swallowed (17). The saliva plays a role in the (re)colonization of the hard and soft tissues of the oral cavity. Some of the microbes will settle to shedding surfaces (mucosal surface) such as tongue, lips, cheeks or palate, while the others to non-shedding surfaces such as natural teeth or foreign materials like orthodontic appliances, sealants, or implants. For example, Candida species can be found in denture plaque, which may cause denture stomatitis and Staphylococcus aureus, common on implants, as they are attracted by titanium surfaces, may cause peri-implantitis (17). When placing foreign bodies in the mouth, the microbiome might be influenced, depending on the structural and chemical characteristics of the object. For example, the microbiome around dental implants presents different characteristics compared to the one surrounding natural tooth, under healthy conditions and during disease states. The shape of tissues around an implant is not the same that around a tooth, making it more vulnerable to microbial infection or colonization. Other factors such as the surface energy, the texture, wettability, and electrochemical properties of the implant surface influence the adhesion and development of the peri-implant biofilm (18). Oral microorganisms can also attach to surfaces to persist in the mouth and avoid being lost by swallowing. By this action, they take part in the biofilm present around teeth and, if they are not removed by mechanical brushing, they will keep on developing (Figure 3).

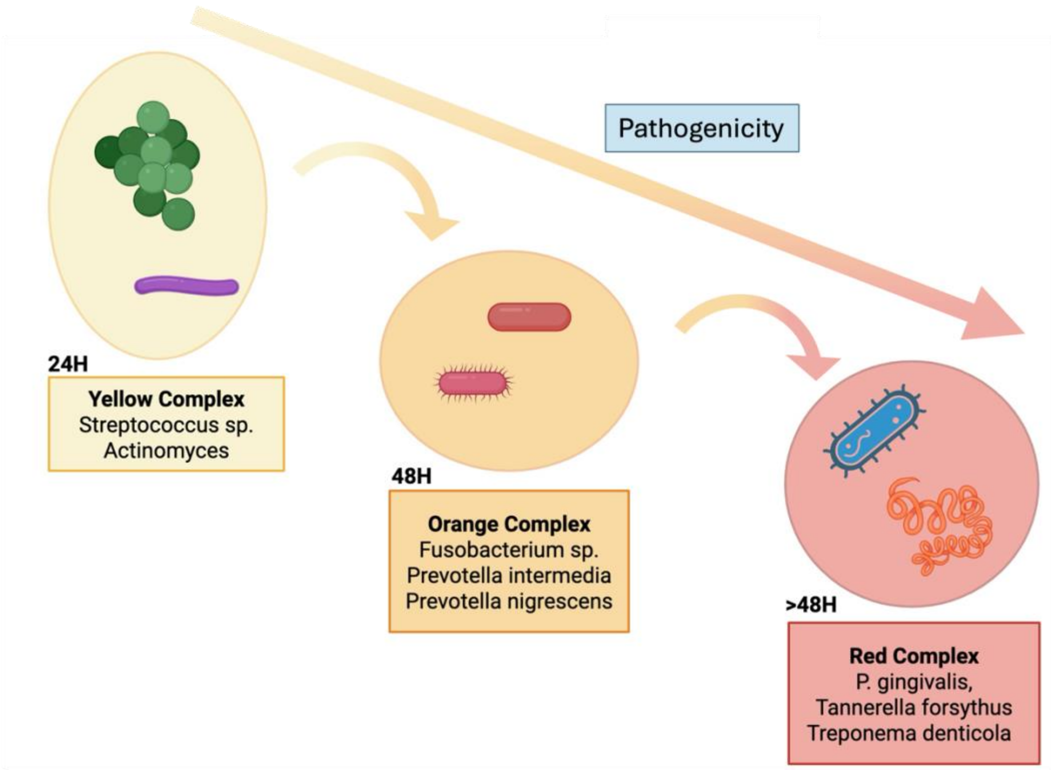


Figure 3: Evolution of Biofilm colonizers depending on the time. Image created with Bio render.

The earliest colonizers are present in a first yellow complex composed mainly of streptococci. Then, the orange complex groups different species, with in majority, Fusobacterium nucleatum. These species play a major role by congregating with other bacteria, acting like a link between the earlier yellow and the late red complex.

The last red complex composed of Tannerella fosythus, Treponema, and P. gingivalis, is closely related to the progression and aggravation of periodontitis (inflammation of the periodontium) (17).

Thanks to their anchorage, and their physical proximity, microbes start interacting with relevant partner species. Candida albicans form synergistic partnership in which they promote streptococcal biofilm formation while streptococci enhance the invasive property of Candida (1). These facilitating nutritional co-operations and antagonist interactions are both listed in Table 1.

Synergic interactions	Antagonist interactions
Enzyme sharing	Bacteriocin production
Food chains (food webs)	Hydrogen peroxide production
Co-adhesion	Organic acid production
Cell-Cell signaling	Bacteriophage release
Gene transfer	Competition for essential nutrients
Environmental modifications	Predation

Table 1: Types of synergistic and antagonistic microbial interactions that occur among oral microorganisms growing in dental plaque biofilms. Adapted from (1).

Justification and Hypothesis

1- Justification:

Several factors influence our microbiome, including sugar foods, population aging and lack of correct oral hygiene. Understanding changes of the oral human microbiome might help to prevent periodontitis and caries avoiding periodontal pockets and hard tissue loss. In addition, as dysbiosis is associated with systemic diseases, its treatment might improve atherosclerosis, diabetes, Alzheimer disease, and other conditions.

Our systematized review will provide information that could be useful for dental professionals, to improve patient care and well-being.

2- Hypothesis:

The human oral microbiome is a major actor of health. Maintaining a healthy oral microbiome could benefit overall health. Dysbiosis could be associated with local and systemic diseases.

2. OBJETIVE

The objective of this systematized review is to describe the oral human microbiome and its influence in health and disease.

3. MATERIAL AND METHODS

PubMed was used to find scientific articles published from 2014 to January 2025 that focused on the role of the human oral microbiome in health and disease.

3.1 Identification of the PICO question

In order to formulate this research question, we answered to the following questions:

(P) Patient. Patients in health or with oral/systemic diseases.

((I) Intervention. Dysbiotic oral microbiome)

(C) Comparation. Healthy oral microbiome

(O) Outcome. Health maintenance or development of disease (oral or systemic).

In healthy patient or with oral or systemic diseases, how does a dysbiotic microbiome compared to a healthy microbiome affect the evolution of oral and systemic diseases.

3.2 Inclusion Criteria

- Languages: English

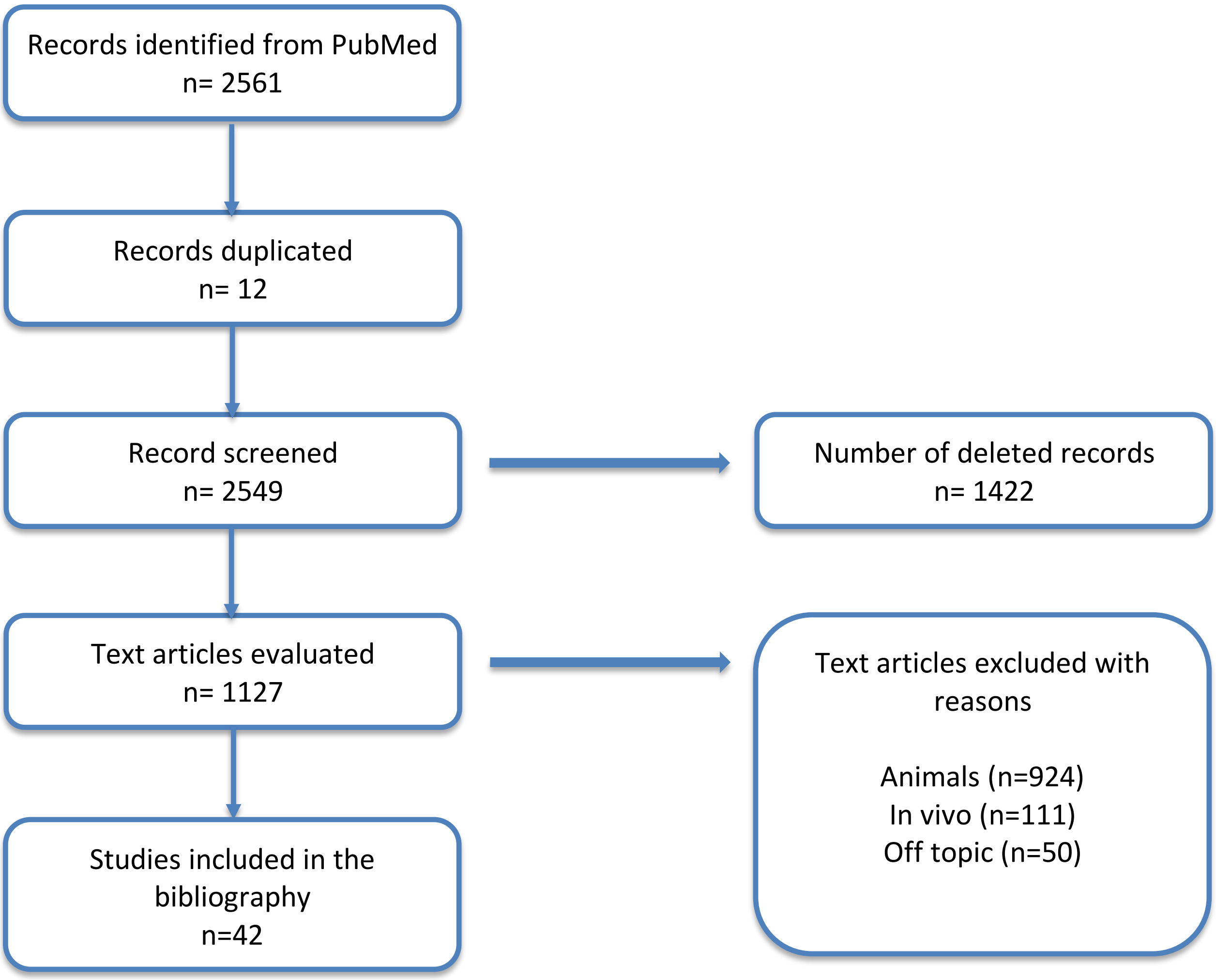
3.3 Exclusion Criteria

- Studies on animals
- Languages: Other than English
- Studies focusing on non-oral microbiomes

3.4 Keywords

The automatized search was performed. The keywords used were the following: (((((((microbiome[MeSH Terms]) OR (human microbiome[MeSH Terms])) OR (human microbiomes[MeSH Terms])) OR (microbiome, human[MeSH Terms])) OR (microbiomes[MeSH Terms])) AND (health)) AND (disease)) AND (oral))

4. RESULTS AND DISCUSSION



The PubMed database screening provided 2561 records, of which 12 remained after duplicates where eliminated. After reading the title then abstract, this number was decreased to 1127; 1062 of them were eliminated because they didn't meet the inclusion criteria. Also, the references mentioned at the end of each article helped build the primary research and provided more information to support this thesis.

Oral microbiome is obtained by maternal transmission and by the environment using specific patterns. Immediately after birth, the oral microbiome will obtain its original composition that will vary depending on the type of birth, natural or cesarean. Indeed, newborn obtained by vaginal delivery are directly exposed to vaginal and rectal microbes when the ones delivered by Cesarian obtain their microbes from the maternal skin and hospital environment. It has been shown that within the 6 first months after birth, lower prevalence of selected oral taxa such as Lactobacillus salivarius, Rothia dentocariosa and Streptococcus sanguis is present in saliva of Cesarian delivered infants (19,20). This disproportion has been confirmed by the fact that female vagina is rich in many probiotics, especially Lactobacillus, and newborns delivered via vagina have them in higher quantity (21). However, this disproportion could be partially reversed by exposing neonates delivered by Cesarian to maternal vaginal microbiota with gauze. After this the oral microbiome of these children resemble to the one of vaginally delivered (22). The original composition of the oral microbiome is also defined by early-life nutrition (natural or artificial). Breastfeed brings stability to the oral microbial composition by supporting the growth of commensal bacteria observed in healthy infants microbiome which are Streptococcus, and Lactobacillus (20). This is due to the fact that breast milk contains a high amount of human milk oligosaccharides, which are non-digestible carbohydrates that are degraded by these bacteria, using them as food source. This fact will favorize the development of these commensal bacteria and reduce potentially harmful ones such as Staphylococcus epidermidis, contributing to a healthier and more stable oral microbiome in breastfed infants (23).

Disease	Pathogens involved	Niche	Virulence factors	Consequences
Dental caries	Streptococcus mutans, Candida Albicans	Supragingival plaque, saliva	Acid production, Lactate, biofilm, synergy	Enamel/Dentin degradation
Periodontal disease	Porphyromonas gingivalis, Treponema Denticola, Tannerella forsythia, Fusobacterium Nucleatum	Subgingival plaque, periodontal pocket	Enzymes production, immune evasion, synergy	Bone loss, inflammation
Oral Cancer	Porphyromonas gingivalis, Fusobacterium Nucleatum	Tumor surrounding	Immune suppression, tumor feeding, Lactate	Tumor progression, metastasis
Atherosclerosis	Porphyromonas gingivalis, Prevotella Intermedia, Helicobacter Pylori	Blood, atherosclerotic plaque	Cytokine stimulation, Foam cell formation	Vascular plaque formation
Type 2 Diabetes	Actinobacteria, Streptococcus spp., Lactobacillus spp., Porphyromonas gingivalis	Dental plaque, saliva	Insulin receptor degradation, amylase inhibitor loss	Hyperglycemia, Insulin resistance
Alzheimer disease	Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans	Brain tissue, subgingival plaque	Gingipains, cytokines release, BBB crossing	Neuroinflammation, Amyloid accumulation

Table 2: Oral microbiome and disease.

4.1. Oral Microbiome in Health

• 4.1.1. Biochemical role

Oral human microbiome protects the host by different mechanisms. Indeed, an important factor is the production of beneficial substances by oral bacteria such as Streptococcus gordonii or Streptococcus sanguinis that metabolize Arginine, a molecule presents in the saliva or obtained from the diet. This way, they will produce ammonia that is responsible to increase local pH, limiting acidification of the oral cavity and protecting against caries (24). The production of beneficial substances can also be related to the capacity of certain oral bacteria, such as Veillonella to transform dietary nitrates into nitrites, a precursor of nitric oxide, known for its vasodilatory and cardiovascular protective effect (25). In addition, Streptococcus salivarius, another predominant commensal bacterium of the oral cavity, has been shown to release low-molecular-weight metabolites capable of inhibiting the NF-κB inflammatory pathway in human epithelial cells. This anti-inflammatory activity, which depends on the bacterium's metabolic activity, suggests a potential role for S. salivarius in maintaining immune homeostasis and preventing diseases such as inflammatory bowel disease (26). These findings highlight the diversity of beneficial substances produced by the oral microbiome making it play an active biochemical role in maintaining oral and even systemic health.

• 4.1.2. Probiotics

It has been suggested that microorganisms naturally present in the oral cavity can be isolated, cultured and then reintroduced into the body as probiotics to restore microbial balance, prevent dysbiosis and promote oral and systemic health. Lactobacillus strains (including Lactobacillus salivarius and Lactobacillus reuteri) significantly inhibit the growth of Streptococcus mutans, leading to the reduction of the formation of cariogenic biofilm, slight increase of pH and suppressing the expression of virulence genes produced by this bacteria, helping to limit the progression of dental caries (27,28). Moreover, in a periodontal context, a combination of probiotics and scaling resulted in a significant reduction in Tannerella forsythia and clinical improvement (pocket depth, bleeding on probing), illustrating the role of probiotics in preventing periodontal dysbiosis. The effects of probiotics in health are not limited to the oral cavity and can be used at a systemic level. Indeed, probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis significantly improves the LDL/HDL ratio in patients with type 2 diabetes, suggesting a potentially beneficial lowering of cholesterol levels (29). This is supported by the capacity of a daily intake of Lactobacillus gasseri that has proven to improved gastric emptying and reduced salivary amylase, a biomarker of stress, suggesting an effect on autonomic nervous system regulation, and by extension, on digestive comfort and overall body homeostasis (30). Thus, recent investigations strongly support the idea that oral probiotics derived from natural strains can modulate pathogenic oral flora, but also contribute to the improvement of systemic health.

4.2. Oral Diseases

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Dental caries, resulting from an imbalance of the oral microbiome is one of the most prevalent infectious diseases in humans (31). The progression of caries is linked with a change in the human oral microbiome, with an increase in cariogenic bacteria (Streptococcus) and a reduction of species responsible for the maintain of health (Neisseria or Fusobacterium) (31). Recent investigations have proven the major role of Streptococcus mutans in the development of dental caries, particularly due to its capacity of fermenting sucrose to produce organic acids, resulting in a decreasing the oral pH and promoting the formation of cariogenic biofilms on human enamel. This metabolic activity, is associated with expression of genes responsible for adhesion and synthesis of exopolysaccharide, confirming the major pathogenic role of S. mutans in the development of caries (32). In addition, the role of this bacteria in producing caries has been seen in its interactions with Candida albicans and their ability to influence the formation of cariogenic biofilms. These robust biofilms contribute to local acidification and an increased caries risk. This suggests that Candida albicans are not simple opportunistic commensals, but active players in the etiology of caries (33). Additionally, the predominance of Candida albicans in the dental plaque of children with severe early childhood caries shows that this fungal species is significantly more abundant in ecological niches where caries is present, particularly in supragingival plaque and carious lesions. The presence of Candida albicans promotes the production of extracellular polysaccharides, thereby strengthening biofilm cohesion and increasing caries severity. However, some researchers believe that Candida albicans is a normal commensal of the oral cavity and that its presence in cariogenic biofilms could be a consequence rather than a cause of the disease which represent a scientific debate (34). In addition, Streptococcus Mutans membrane vesicles have a role in increasing Candida Albicans virulence by facilitating the growth and adhesion of Candida Albicans on the dental surface and increase its capacity for demineralization (35). The cohabitation of the two microorganisms leads to an increase in the production of organic acids, notably lactate and acetate, inducing prolonged acidification of the oral environment and accelerated dissolution of hydroxyapatite from dental enamel (36). This highlights a synergy mechanism where extracellular components of S. mutans

act as modulators of fungal virulence, enhancing biofilm robustness and accelerating the progression of carious lesions. These complex interactions confer to biofilms an increased protection and resilience against antimicrobial treatments and host immune defenses, making early childhood caries particularly difficult to treat (35,36). However, it can also be seen that fungi and bacteria occupy distinct spatial niches within the dentin tubules, with a predominance of Candida albicans within the carious lesions. Fungi and bacteria rarely co-colonize the same dentin tubules due to the competition for nutrients and space, underlining a more complex interaction between them having an importance in the way to treat deep carious lesions (37). In order to target these microbes, an enzymatic approach can be used to reduce this bacterial biofilm formation, leading to a weakening of the biofilm structure and a decrease in tooth enamel demineralization (38).
All of this suggests that targeting Streptococcus mutans and Candida albicans could be a promising strategy for caries prevention and treatment (31).

- ### 4.2.2. Periodontal Diseases

Periodontal disease is a multifactorial infectious condition involving multiple pathogens. A disruption in the ecological balance of the oral microbiome happen where not only pathogenic species rise in abundance, but where beneficial ones disappear, weakening the system's natural resilience. This shift begins early, usually when the condition is still reversible, during the gingivitis stage. Recent investigations marked reduction in Actinobacteria and Firmicutes, taxa typically dominant in oral health, while Bacteroidetes and Fusobacteria increase. This compositional shift was accompanied by a rise in functional genes linked to motility, particularly those involved in flagellar biosynthesis, suggesting that the microbiome doesn't just change in composition, but becomes more aggressive and mobile (39,40). From this imbalance, disease can progress toward irreversible damage as periodontitis and here, the microbial players shift again. A central role is played by the red complex presented before, composed of Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia. These species are not only highly responsible for producing periodontal pockets and bone loss but interact in oreder to amplify their impact. Within this group, Porphyromonas gingivalis present the biggest association with disease. Even in low abundance, it significantly raises the risk of periodontitis, unlike Treponema denticola, and Prevotella intermedia that require high levels to have a comparable effect. Its mechanisms include immune evasion, the production of proteolytic enzymes like gingipains, and its ability to disrupt host-microbe homeostasis, traits that allow it to alter the microbial environment and promote the growth of other pathogens (40,41). Even if the single virulence of Porphyromonas gingivalis has been proven, pathogens present in the mouth have been seen to collaborate. In the presence of Tannerella forsythia or Treponema denticola, it participates in cooperative behaviors that enhance virulence. For example, Treponema denticola shows broad transcriptional changes when exposed to its red complex partners. Genes involved in metabolism, transport, outer membrane proteins, and motility are differentially regulated, to optimize survival and immune evasion. This response is not limited to red complex species. Indeed, similar gene regulation occurs when Treponema denticola interacts with Prevotella intermedia, a member of the orange complex. These findings underscore that the oral biofilm is a dynamic system where collaboration between microbes will enhance their virulence (39,41,42). This cross-complex cooperation becomes even more significant when considering Fusobacterium nucleatum. This bacteria from the orange complex links early colonizers (like streptococci) with late, more virulent species such as Porphyromonas gingivalis. Moreover, Fusobacterium nucleatum changes its gene expression in biofilm compared to planktonic form, increasing the production of genes leading to carbohydrate and amino acid metabolism, while reducing those related to oxidative stress and cell growth. These shifts enhance its ability to survive in hostile environments and protect more fragile partners. Moreover, by reducing oxygen levels, Fusobacterium nucleatum creates a niche favorable for anaerobic pathogens like Porphyromonas gingivalis, further helping in progression of the periodontal disease (43,44).

Periodontal disease is a result of dysbiosis, where health-associated bacteria decline, and pathogens like red complex ones change their gene expression in order to protect each other and increase inflammation and tissue damage. Understanding these collaborations offers not only a more accurate model of disease progression but also opens the door to new therapeutic approaches focusing on specific pathogens of the human oral microbiome.

- ### 4.2.3. Oral Cancer

Oral squamous cell carcinoma is the most common type of cancer of the oral cavity. Its treatment is mainly done by surgery but results in important damages in the functional and aesthetic level in the region of the head and neck (45). Patients with oral squamous cell carcinoma have a reduction in bacterial diversity and an increase in pathogenic bacteria such as Fusobacterium nucleatum and Porphyromonas gingivalis. Indeed, metabolic processes related to sugar metabolism and lipopolysaccharide biosynthesis promote cancer development. For example, researchers have shown that Fusobacterium nucleatum alters the tumor environment by accumulating at their edges. It enables the tumor to absorb more glucose, consequently generating more lactate, which results in an acidic environment that impairs immunity. Consequently, this bacteria aids in the growth and spread of oral cancer like oral squamous cell carcinoma. Targeting Fusobacterium nucleatum may be a viable new treatment option for oral cancer. In the case of Porphyromonas gingivalis, there are pathogenic effects as it creates a resistance to the chemotherapeutic Taxol drug. Its pathogenic activity is shown in the Figure 3. This shows that its prevention is of the outmost importance (45–48).

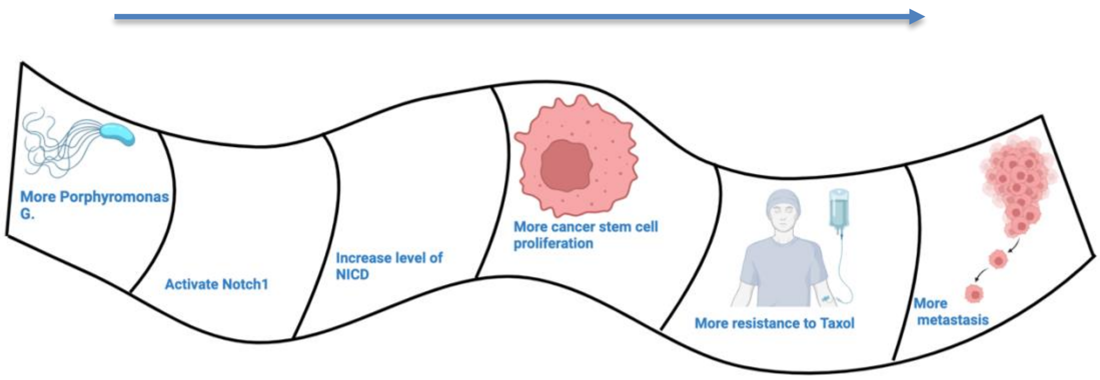

Figure 3: Influence of Porphyromonas gingivalis in resistance to Taxol and higher metastatic potential of cancerous cells.

While the functional microbial complexity increases with cancer progression, beneficial bacteria such as Neisseria, Streptococcus and Rothia decrease. Indeed this bacteria are associated to less invasive and more stable tumor microenvironment leading to lower tumor aggressiveness (46,48,49). The microbial diversity can also be affected by chemoradiotherapy by decreasing pathogenic bacteria like Porphyromonas gingivalis and Prevotellaceae, while maintaining protective bacteria like Lactobacillus spp. and Gemella spp. That is why chemotherapy creates an adaptive response, balancing out the oral microbiome, becoming a post-therapy biomarker for cancer virulence (45,50).

It highlights that microbial dysbiosis plays a key role in the initiation and progression of oral cancer, suggesting that the microbiome could be used as a diagnostic and prognostic biomarker. The identification of Fusobacterium nucleatum and Porphyromonas gingivalis as predictive markers of oral squamous cell carcinoma opens perspectives for targeted therapeutic strategies, including microbiome modulation by probiotics or specific antimicrobial interventions. Moreover, the close correlation between microbiome alterations and treatment response suggests that restoring microbial balance could improve therapeutic efficacy and prevent recurrence. By integrating this knowledge, personalized approaches based on patients' microbial profile could be developed to optimize oral cancer prevention and treatment, by reducing the presence of pro-inflammatory bacteria and promoting a more balanced oral microbiota.

4.3. Systemic conditions

- ### 4.3.1. Atherosclerosis

Atherosclerosis is a chronic inflammatory disorder of arterial walls due to the accumulation of lipids and immune cells, leading to the formation of plaque, reducing blood flow and increasing the risk of cardiovascular events such as heart attacks, strokes, and peripheral artery disease. Recent investigations are suggesting that the oral human microbiome is a contributing factor to the development of atherosclerosis. Indeed, high numbers of oral pathogens have been found within atherosclerotic plaques, presenting possible translocation from the oral cavity into vascular tissues of these microbes. Among the bacterial species implicated, Porphyromonas gingivalis and Prevotella intermedia are frequently detected in coronary and carotid plaques of patients with cardiovascular disease. The presence of 23 oral commensals bacteria within atherosclerotic lesions have been shown, with five species exclusively found in vascular plaques, reinforce the hypothesis of bacteremia leading to direct plaque colonization (51,52). The penetration of oral bacteria in the blood is notably due to chronic and low level of inflammation caused by periodontitis as presented before. However, the prevalence of severe periodontitis in patients with carotid atherosclerosis has been proven to be significantly higher than in healthy patients. Periodontitis being significantly associated with myocardial infarction and stroke, suggests that the persistent inflammatory environment caused by oral dysbiosis contributes independently to worsening of atherosclerosis (53,54). These bacteremias allow pathogens like Porphyromonas gingivalis or Helicobacter pylori. to interact with the vascular endothelium, triggering immune system activation. Once in circulation, they will induce endothelial dysfunction by stimulating cytokines such as IL-6, IL-1β, and TNF-α. These pro-inflammatory mediators recruit monocytes, enhance oxidative stress, and promote the transformation of macrophages into foam cells, accelerating plaque formation and arterial wall thickening (51,52). In addition to the stimulation of the immune system, oral dysbiosis has been related to elevated levels of trimethylamine N-oxide in plasma, a liver produced metabolite that is known to promote atherosclerosis by increasing plaque buildup in arteries. These elevated plasma levels have been linked with higher abundances of Porphyromonas and Peptidiphaga in dental plaque, even in patients without traditional cardiovascular risk factors. This supports the concept of an oral–gut–liver axis in which oral microbes influence systemic metabolite levels that drive cardiovascular pathology. Trimethylamine N-oxide increases platelet activity and damages the inner part of blood vessels which prove that oral microbiome imbalance contribute to the development of atherosclerosis (54,55).

These evidences definitely support the notion that the human oral microbiome plays a significant role in atherosclerosis. The identification of oral pathogens in vascular plaques, their capacity to modulate immune and metabolic pathways, and their correlation with disease severity all suggest that oral health is intricately linked to cardiovascular risk. Future work exploring targeted antimicrobial therapies and oral hygiene interventions may reveal new strategies to reduce cardiovascular disease by managing the oral microbiome.

- ### 4.3.2. Diabetes Mellitus

Diabetes mellitus is due to a range of metabolic disorders related to carbohydrates metabolism where glucose is underutilized and overproduced, resulting in hyperglycemia. The main forms include type 1 diabetes (autoimmune in origin), type 2 diabetes (linked to insulin resistance and environmental factors), and gestational diabetes, which occurs during pregnancy (56). Diabetes is one of the different systemic diseases associated with dysbiosis of the human oral microbiome. Recent evidences supposed that changes in the bacterial composition of the oral microbiome have an active contribution in the apparency of the disease. A notable reduction of certain strains of Actinobacteria (Actinomyces and Atopobium), known to produce amylase inhibitors, the enzymes responsible for the hydrolysis of dietary starch into simple sugars, have been shown in diabetic patients. This suggests that their reduction could therefore promote excessive carbohydrate degradation and contribute to glycemic dysregulation, contributing to the pathogenesis of type 2 diabetes (57). In addition, other changes in bacterial composition have been recently found, with significantly higher levels of Streptococcus and Lactobacillus in dental plaque and saliva of diabetic patients. This increased bacterial amount was linked with HbA1c and fasting blood glucose levels, two markers of the glucose amount in the blood, indicating a clear link between poor glycemic control and alteration of the oral microbiome (56). Furthermore, Porphyromonas gingivalis has been shown to be capable of directly degrading insulin receptors via its gingipain protease, thus altering their insulin binding capacity. This mechanism contributes to insulin resistance, particularly in target tissues such as liver, muscle and adipocytes. These data confirm a direct role for Porphyromonas gingivalis in systemic metabolic disruption, and suggest the importance of prevention strategies targeting oral pathogens in diabetes (58). In this context, strategies have been tried by doing regular periodontal care in diabetic patients, leading to an important reduction in HbA1c, particularly in patients with poor glycemic control at baseline. This suggests that managing oral dysbiosis via periodontal treatment can positively influence the course of diabetes, confirming the interconnection between oral and metabolic health (59).

These studies showed a difference of composition of the oral microbiome of diabetic patients and non-diabetic patients. They collectively demonstrate that the human oral microbiome is playing a role in its development and progression. By identifying specific bacterial markers, molecular mechanisms and therapeutic benefits linked to treatment of the oral cavity, these studies demonstrate that the oral microbiome represents a promising target in the prevention and management of type 2 diabetes.

- ### 4.3.3. Alzheimer disease

Alzheimer disease is a neurodegenerative condition, due to a chronic neuroinflammation, gradually increasing, creating a memory decline. Increasing evidences present the human oral microbiome as a contributing factor in Alzheimer disease by being responsible of this inflammation (60). Among the bacterial species implicated, Porphyromonas gingivalis, has been detected in the brains of patients with Alzheimer disease. Toxic proteases from this bacterium, the gingipains, already seen before for their pathogenicity, have been identified in brain tissue, where they correlate with tau and ubiquitin pathology, two proteins which normally have beneficial roles in the brain, supporting neuronal stability and clearing damaged proteins, but whose functions are disrupted by gingipains, thereby accelerating Alzheimer's disease progression. When orally introduced in experimental models, Porphyromonas gingivalis is capable of colonizing the brain, increasing amyloid-beta production, and promoting neurodegeneration. Blocking these gingipains with specific inhibitors support the notion that targeting Porphyromonas gingivalis could be a viable therapeutic approach. In addition, Aggregatibacter actinomycetemcomitans has also been implicated in Alzheimer disease due to its capacity to induce strong inflammation similar to the one triggered by Porphyromonas gingivalis, suggesting that multiple oral pathogens contribute to neurodegeneration through overlapping mechanisms (61–63). The connection between oral bacteria and Alzheimer disease is further supported by evidence of elevated Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans levels in the oral cavities of individuals with neurodegenerative diseases. A significant difference in abundance of these bacteria is observed when comparing neurodegenerative patients to healthy controls. Higher circulating antibodies against these two bacteria, indicate a systemic immune response. This inflammation will lead to the presence of inflammatory cytokines, such as IL-6, IL-1β, and TNF-α. These molecules have been implicated in the dysfunction of the blood-brain barrier where they lead to neuroinflmmation and neuronal damage. Porphyromonas gingivalis, its components, and Aggregatibacter actinomycetemcomitans can so cross the blood-brain barrier and further driving neurodegeneration (62–64). This capacity of crossing the blood brain barrier has been proven in recent investigations showing that Porphyromonas gingivalis and its virulence factors, including lipopolysaccharides and outer membrane vesicles, have been detected in both circulating blood and cerebrospinal fluid, reinforcing the idea that the bacterium can breach the blood-brain barrier. The extracellular RNA in the outer membrane vesicle of this bacteria has been shown to cross the blood-brain barrier and induce inflammation, further supporting the idea that oral pathogens do not just influence Alzheimer disease through immune activation but may also be directly involved in neurotoxicity (63–65). An explanation of these phenomenon is presented in the figure 4.

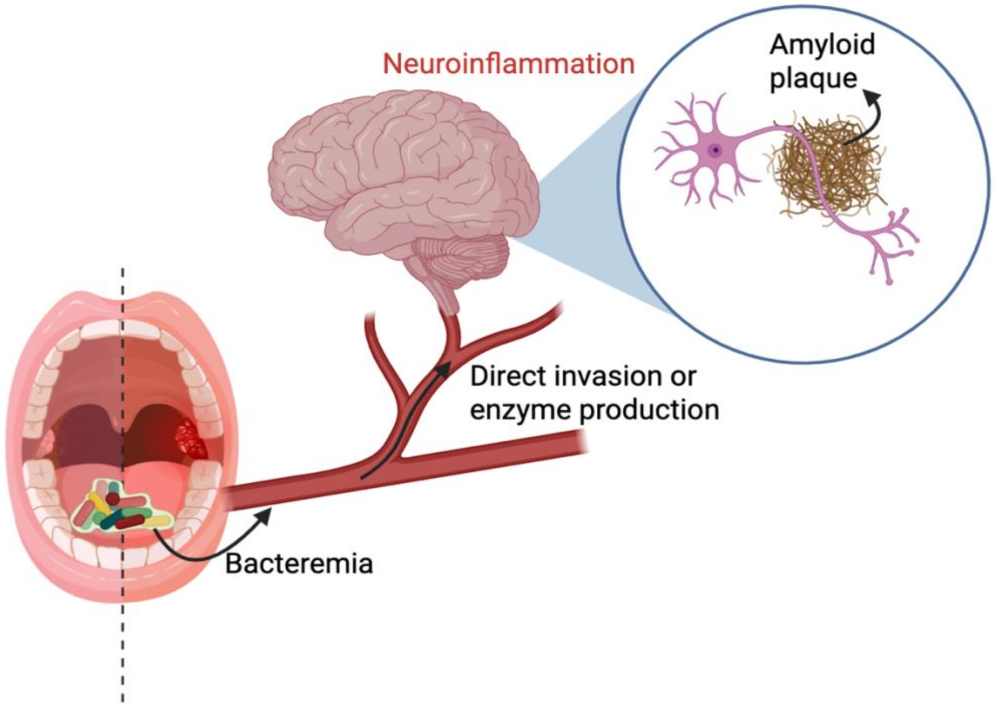

Figure 4: Impact of Oral Pathogens on Amyloid Plaque Formation

The oral microbiome composition in Alzheimer diseased patients exhibits notable differences compared to healthy individuals, with increase in Firmicutes and decrease in Bacteroidetes suggesting a microbial imbalance that may contribute to chronic inflammation and metabolic changes linked to neurodegeneration. However, other reports indicate that certain periodontitis-associated bacteria are reduced, leading to conflicting interpretations. The variation in results may stem from differences in sample collection, as some analyses focus on salivary microbiomes, while others examine subgingival plaque, which is a more precise indicator of periodontal disease. This highlights the complexity of the oral-brain axis, where different pathogens and sampling techniques may lead to different conclusions, but ultimately point to a dysbiotic microbiome as a risk factor for Alzheimer disease (60,63). The link between oral bacteria and amyloid-beta production provides further evidence that the microbiome may be influencing Alzheimer disease pathology. Amyloid-beta, typically associated with the disease progression, also acts as an antimicrobial peptide, suggesting that its overproduction in Alzheimer disease brains could be a defense mechanism against bacterial invasion. This aligns with findings that show higher Amyloid-beta accumulation following Porphyromonas gingivalis infection, reinforcing the idea that the brain reacts to bacterial presence by producing more amyloid plaques, which later become neurotoxic (61,64). The combined evidence strongly supports the notion that the human oral microbiome plays a role in Alzheimer's disease. The presence of Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans in Alzheimer diseased brains, their ability to trigger systemic inflammation, and their link to amyloid-beta pathology all suggest that oral health may be a contributing factor to neurodegeneration. Future research focusing on longitudinal clinical trials and targeted antimicrobial interventions will be essential in determining whether oral health management could play a role in preventing or slowing the progression of Alzheimer's disease.

4.4. Implications for Future Research

Recent investigations have been possible thanks to advances in capacity of detections of microorganisms leaving in the human oral microbiome as describe before. However, an important part of these microbes is hard to cultivate or even remains undiscovered. Future investigations to fully know the human oral microbiome and being able to analyze it better are needed. In addition, recent discoveries are based on small samples or can be biased due to secondary factors such as age or sex. Large-scale longitudinal studies on large time course, including all patients' characteristics need to be done. Although, archaea, viruses and microeukaryotes are less important in quantity in the oral microbiome even if they proved to have importance in human health and disease and for this, should be more studied. Finally, as explained before, future treatments options are suggested since recent years such as the use of probiotics in human health. More investigations should be done in order to find safer and more effective treatments.

5. CONCLUSIONS

This systematized review confirms that the human oral microbiome is a fundamental complex of microorganisms having a decisive impact in maintaining oral and systemic health. In balanced condition, oral microbes influence the immune defense, regulate the inflammation and produce metabolites, having a protective role in human health. Moreover, new strategies such as the use of probiotics obtained from species of the oral microbiome have shown their ability to inhibit pathogenic species, reduce inflammation and promote healthier microbial environment. However, in imbalanced conditions, the oral microbiome might be a key factor in the progression of oral diseases such as dental caries, periodontal diseases and oral cancer. In addition, emerging evidence links oral microbial imbalance with systemic conditions such as atherosclerosis, diabetes, and Alzheimer's disease. These findings suggest that continuing to discover the entirety of oral human microbiome and produce treatments focusing on pathogens composing it could help for disease prevention and treatment in dentistry and beyond.

6. SUSTAINABILITY

This work has been done in order to respect modern academic and professional standards that promote environment respect. The entirety of the work was conducted digitally, using online databases such as PubMed for literature review and analysis. This approach significantly minimized the consumption of paper and printing materials, helping to reduce the project's carbon footprint. Furthermore, all data collection, note-taking, drafting, and editing processes were performed electronically, allowing a long-term accessibility, without the need to print any paper and security.

Beyond the methods of research and presentation, the topic itself addresses aspects of sustainability in public health. By avoiding oral and systemic diseases through microbiome balance, this study indirectly supports a reduction in the use of invasive medical treatments, pharmaceuticals, and non-recyclable clinical materials. Moreover, the promotion of healthier diets especially those low in refined sugars and processed foods in polluting factories not only contributes to better oral health but also encourages more sustainable agricultural and food production practices.

Finally, future implementations of oral microbiome-based therapies, including the use of natural probiotics, could also align with environmentally conscious medical practices by reducing reliance on synthetic drugs and promoting biocompatible alternatives. In this way, oral microbiome research not only contributes to health and wellness but also supports a more ecological way of living and of treating patients.

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8. APPENDIXES