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Review Article

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A comprehensive literature review on the oral microbiota: key concepts and implications for dental and systemic health

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Abstract

The oral microbiota plays a crucial role in maintaining oral health by forming a dynamic ecosystem across the buccal components. It contributes to oral homeostasis through pathogen defense, pH regulation, local immune support, biofilm formation, nutrient metabolism, and microbial balance preservation. Dental biofilms influence oral health by maintaining balance or contributing to conditions such as dental caries and periodontal diseases. Advancements in studying the oral microbiota have evolved from culture-dependent to culture-independent methods. Next-generation sequencing technologies such as Illumina platforms, have revolutionized the human understanding by revealing comprehensive microbial composition and functional insights. These methods collectively deepen our understanding of oral microbial communities, which are pivotal for maintaining both oral and systemic health. This review aims to explore dental caries, periodontal diseases, and other oral infections, detailing their symptoms, progression, and treatments. Dental caries manifests several symptoms from toothache to abscesses, managed through oral hygiene and restorative procedures. Periodontal diseases cause gum inflammation, necessitating plaque control, deep cleaning, and/ or surgery for resolution. Other infections, including canker sores, oral candidiasis, and herpes are discussed alongside their treatments such as topical agents, antifungals, and antivirals. Conventional treatments encompass antibiotics, antifungals, chlorhexidine, and invasive procedures, thus effectively eliminate pathogens and restore oral health.

Keywords: Oral microbiota, Dental biofilms, Dysbiosis, Dental caries, Periodontal diseases

1. Introduction

The human body is a complex and dynamic ecosystem, hosting trillions of microorganisms that form the human microbiota. These microorganisms, which include bacteria, fungi, viruses, and archaea, inhabit various body sites such as the skin, gut, respiratory tract, and urogenital tract (Shibly and Ningthoujam, 2023). The microbiota plays an essential role in maintaining human health by aiding in digestion, producing vitamins, protecting against pathogens, and modulating the immune system (Afzaal *et al*., 2022). Among these diverse microbial communities, the oral microbiota is particularly significant, due to its unique environment and critical role in both oral and systemic health (Li *et al*., 2022).

The term "microbiota" refers to collection of microorganisms living in a specific environment, including bacteria, viruses, fungi, and protozoa. In the oral context, the oral microbiota includes all microorganisms residing in the oral cavity, contributing to the health or disease of the mouth (Marchesi and Ravel, 2015). The "microbiome" on the other hand, refers to the complex and dynamic set of microorganisms present in the oral cavity, their genetic material, and specific environmental conditions (Marchesi and Ravel, 2015). The term "microbiome" was coined by Nobel Prize laureate Joshua Lederberg to signify the relationship between microorganisms and their hosts, including the symbiotic relationships of commensalism, mutualism, and pathogenicity. The oral microbiota is characterized using culture-independent molecular methods such as 16S rRNA gene-based cloning studies (Sudhakara *et al*., 2018).

The oral cavity is a home to a wide variety of microorganisms that colonize the different surfaces, including the teeth, tongue, cheeks, and gums (Deo and Deshmukh, 2019). This complex community is crucial for maintaining oral health by preventing colonization of harmful pathogens and participating in various physiological processes (Sedghi *et al*., 2021). However, imbalances in the oral microbiota or oral dysbiosis, can lead to common oral diseases such as dental caries, periodontal disease, and several other oral infections, including aphthae, candidiasis, and herpes. These diseases highlight the range of microorganisms involved in oral health and have been linked to broader systemic conditions, underscoring the importance of understanding and maintaining a healthy oral microbiota (Kozak and Pawlik, 2023).

Effective management of these infections often requires a combination of good oral hygiene, antimicrobial treatments, and in some cases invasive dental procedures (Jiao *et al*., 2019). The objective of this review is to provide a descriptive and comprehensive overview of oral microbiology, encompassing fundamental concepts and intricate relationships among dysbiosis, oral diseases, and systemic health conditions. This knowledge is vital for developing innovative diagnostic tools, preventive measures, and personalized treatments, ultimately enhancing oral and overall health.

2. Concepts in oral microbiology

2.1. Anatomical and functional description of the oral cavity

2.1.1. Morphology of the oral cavity

The oral cavity is a gateway to the digestive system, located in the cephalic region below the nasal fossae. It is bounded at the front by the upper and lower lips, on the sides by the cheeks, at the bottom by the tongue and the sublingual area, and at the top by the palate, which is divided into a bony section called the hard palate and a fleshy part known as the soft palate (Fig.1). This cavity, lined by mucous membrane, is divided into two parts by the presence of the alveolar dental arches and contains salivary and gustatory glands (Netter and Scott, 2019).

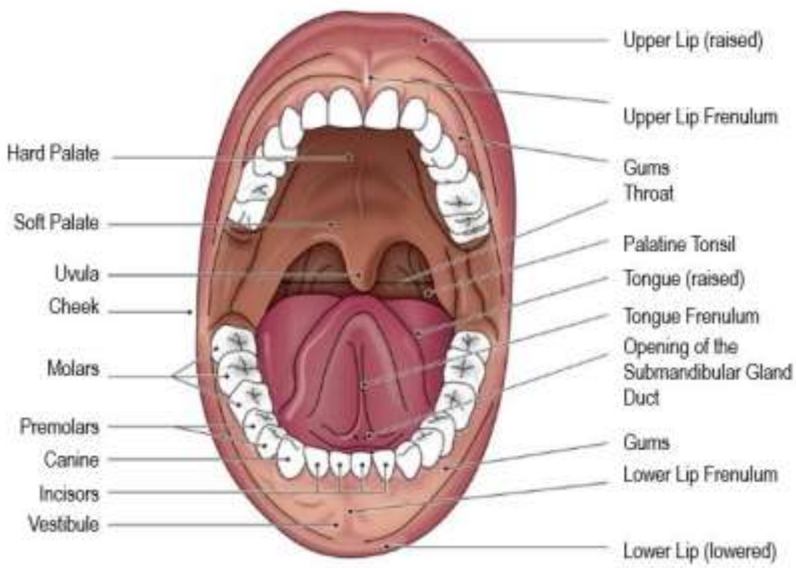

Fig.1. Anterior view of the oral cavity adopted by Netter and Scott, (2019)

2.1.2. Anatomy of the teeth and periodontal tissues

The tooth is a living organ composed of a visible crown within the oral cavity and a root embedded in the alveolar bone (Fig. 2). Its vitality is maintained by the pulp, which is a connective tissue containing nerves, venules, and arterioles. This tissue is protected by two calcified layers: in the crown; these are the dentin and enamel, while in the root, they are the dentin and cementum. The periodontal tissues are divided into the superficial periodontium, represented by the gingiva, which is an epithelial-connective tissue, and the deep periodontium, composed of alveolar-dental ligaments, alveolar bone, and cementum (Tilotta *et al*., 2018).

2.2. Functions of the oral cavity

The oral cavity serves as a multitude of interconnected functions that are integral to our daily lives and overall well-being. Beyond its primary role in digestion through chewing and swallowing, the oral cavity plays critical roles in sensory perception, speech articulation, facial aesthetics, and gustatory experience of the taste (Table 1). These functions highlight its importance not only in physiological processes but also in social interactions and aesthetic appearances. Damage or loss of teeth can significantly impair these functions, emphasizing the necessity of dental care and prosthetic solutions to maintain oral health and overall quality of life. These interconnected functions make the oral cavity a central element in digestion, communication, and aesthetics, underscoring its crucial importance to our physical and social well-being (Tilotta *et al*., 2018).

2.3. Oral microbiota and microbiome

2.3.1. Acquisition

During birth, the mother transmits microorganisms to the child, and the mode of delivery (*i.e*., vaginal or cesarean) is a determining factor for the type of microorganisms to which the child is initially exposed. The mode of delivery also influences the diversity of the oral microbiota later in the infant's life; with

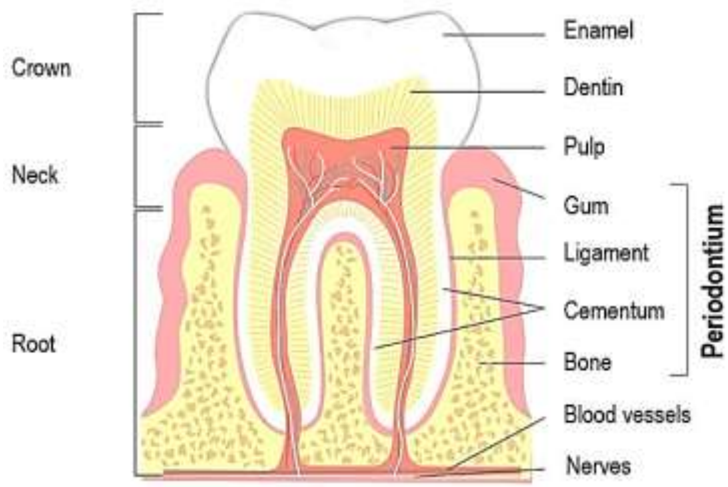

Fig. 2. Longitudinal section view of the tooth and its supporting tissues adopted by Tilotta *et al*., (2018)

Table 1. Essential functions of the oral cavity (Tilotta *et al*., 2018)

Functions	Description
Sensory perception	Perception of pain, sensitivity, temperature, and taste, connecting us with our sensory environment.
Chewing of food	Essential for nutrition and development, disrupted by tooth damage or loss, necessitating dental prostheses in extreme cases.
Phonation	Teeth aid in speech articulation, absence can cause pronunciation disorders such as lisping.
Facial aesthetics	Teeth contribute to facial aesthetics during smiling, supporting cheek and lip volume, edentulous individuals may appear aged with sunken cheeks and thinned lips.
Taste	Oral taste buds perceive flavors, crucial for the gustatory experience during eating.
Salivation of food	Saliva from oral glands moistens and aids in chewing and swallowing food.
Swallowing	Starting point of swallowing, involving coordinated actions of the tongue, throat muscles, and pharynx to propel food to the stomach.

children born vaginally exhibiting a greater number of taxa three months after birth compared to those born by cesarean section (Manos, 2022). Feeding method also has an effect, as 3-month-old infants who are breastfed show a higher colonization of oral lactobacilli than those fed with formula. The eruption of teeth provides new surfaces for microbial colonization and constitutes a major ecological event in the child's mouth. By the age of three, children's oral microbiota is already complex and becomes increasingly so with age. Replacement of the primary teeth with an adult dentition significantly alters the oral microbial habitat once again (Kilian *et al*., 2016).

2.3.2. Composition

The oral microbiota, also known as the oral microbial flora, refers to the diverse community of microorganisms that inhabit an individual's oral cavity. This complex community encompasses a wide range of microorganisms that coexist and interact within a dynamic ecosystem (Lu *et al*., 2019). This oral microbiota comprises a diverse array of microorganisms, including bacteria, viruses, fungi, archaea, and eukaryotes. Bacteria are among the most abundant occupants, existing in thousands of different species. Each bacterium plays a specific role in the oral ecosystem, some being beneficial for microbial balance and others are potentially pathogenic (Meuric, 2016). It has been discovered that more than 700 bacterial species can inhabit the human mouth, with over 30 % being unknown. Other authors have reported that more than 300 different bacterial species can colonize the oral cavity of a healthy individual (Patini, 2020). Viruses are also present, notably bacteriophages that specifically target the bacteria, thereby regulating bacterial populations and influencing dynamics of the oral microbiota (Lu *et al*., 2019). Moreover, eighty-five fungal species; mainly yeasts, reside in the oral cavity. Some yeasts are normally present, but their imbalances can lead to oral fungal infections such as candidiasis (Lu *et al*., 2019). Archaea, a distinct form of microorganisms from bacteria, also play a role in the oral microbiota. They are methanogens that use hydrogen to reduce carbon dioxide, acetate, and various methyl compounds to methane. Although less studied, archaea contribute to complexity of this ecosystem (Kaan *et al*., 2021). Eukaryotes, including unicellular protists, add to the diversity of the oral microbiota. Although less well-known than bacteria and viruses, eukaryotes also participate in the complex microbial balance.

Precise composition of the oral microbiota is influenced by various factors, including an individual's genetic characteristics, age, diet, oral hygiene practices, and overall health. Maintaining a balance among these different microorganisms is essential for optimal oral health. Imbalances or changes in the composition of the oral microbiota can contribute to developing oral health problems; mainly cavity and periodontal diseases (Arweiler and Netuschil, 2016).

2.3.3. Localization

The oral microbiota occupies a complex and diverse space within the oral cavity, where its localization varies depending on the anatomical structures and surfaces present in this area. The surfaces of the teeth, including the crown, root, and the surrounding gums are major sites for colonization by the oral microbiota. Dental plaque, a biofilm layer composed of bacteria, salivary proteins, and other components, is formed on the teeth surfaces and provides a prime habitat for numerous microorganisms. Two different microbial communities are detected there; mainly supragingival plaque and subgingival plaque. The supragingival plaque is associated with dental caries on the occlusal and proximal surfaces of the tooth. Microorganisms residing in these niches tend to produce acids and are resistant to an acidic environment. The subgingival plaque, which extends along the root at the gingival sulcus, contains more serum and less saliva. This environment becomes more anaerobic and the pH and temperature become extreme. The tongue, particularly its rough dorsal surface, is another significant site of colonization by the oral microbiota. The fissures and papillae of the tongue offer niches where microorganisms; mainly anaerobes, can adhere and grow (Zhang *et al*., 2018). Moreover, the mucous membranes lining the oral cavity, including the cheeks, lips, soft palate, and sublingual areas, also serve as surfaces for microbial colonization. Microorganisms can attach to epithelial cells of these mucous membranes (Li *et al*., 2022). The salivary glands, including the parotid and submandibular glands, contribute to composition of the oral microbiota by producing saliva. The saliva contains enzymes and proteins that can influence growth and activity of the microorganisms (Zhang *et al*., 2018). Other structures like the tonsils, taste buds, and additional components within the oral cavity can also harbor microorganisms, although the density and composition of this microbiota may vary (Zhang *et al*., 2018). Distribution of the oral microbiota depends on many factors, including differences in pH, partial oxygen pressure, salinity, humidity, temperature, redox potential, surface texture, nutrient availability, and interactions with the host cells. This distribution plays a crucial role in maintaining microbial balance and preventing imbalances that could lead to oral health problems (Barboza-Solís and Acuña-Amador, 2020).

2.3.4. Role in oral health balance

The oral microbiota plays an essential role in maintaining oral balance, contributing to overall health of the oral cavity and preventing the development of dental problems. Beneficial microorganisms of the oral microbiota occupy ecological niches and prevent pathogenic bacteria from establishing themselves. This competition for resources limits growth of the pathogens and reduces their potential to cause infections or diseases (Kilian *et al*., 2016). The oral microbiota also helps to maintaining homeostasis by regulating the acid-base balance of the oral cavity. It regulates pH by producing acids and bases, which is crucial for preventing conditions favorable for excessive growth of the acidogenic bacteria responsible for dental caries (Langella, 2017). Furthermore, it stimulates the local immune system by activating the immune cells present in the mucous membranes, enhancing the oral cavity's ability to defend against infections and maintains an appropriate inflammatory response (Langella, 2017). Formation of protective biofilm is another vital function, where dental plaque, a biofilm made up of bacteria and salivary secretions, protects the teeth by forming a physical barrier against the pathogens. A balanced microbiota helps to maintaining this protective biofilm without allowing the harmful bacteria to predominate (Bertolini *et al*., 2022). Some microorganisms metabolize compounds present in the saliva or food, helping to maintain nutritional balance and an environment conducive to oral health (Deo and Deshmukh, 2019). By limiting growth of the potentially harmful bacteria, a balanced oral microbiota helps prevent several issues, including caries, gum diseases (*i.e*., periodontal diseases), and fungal infections (Jia *et al*., 2018). Moreover, some microorganisms help break down food and initiate digestion, facilitating nutrient absorption (Deo and Deshmukh, 2019).

It is important to note that an imbalance of the oral microbiota, also known as oral dysbiosis, can lead to oral health problems and overall health issues. Disruptions in the composition of the microbiota can promote overgrowth of the pathogenic bacteria, contributing to deleterious conditions such as caries, periodontal diseases, and fungal infections. Therefore, maintaining a healthy balance of the oral microbiota is fundamental for preserving long-term oral health (Maier, 2023).

2.4. Methods of studying the oral microbiota

Studying the oral microbiota has evolved significantly over time, transitioning from traditional culture-dependent methods to more advanced culture-independent techniques (Table 2). This study requires

Table 2. Overview of key methods used in studying the oral microbiota (Deo and Deshmukh, 2019)

Methods	Description	Limitations
Culture and microscopy	Identifies bacteria through traditional culture methods and microscopy.	Limited in revealing the full diversity of the oral microbiota.
Gel-based techniques	Techniques such as Denaturing Gradient Gel Electrophoresis (DGGE) and Restriction Fragment Length Polymorphism (RFLP) have allowed for in-depth analysis of microbial communities.	Cannot detect low-abundance species, labor-intensive, and less comprehensive compared to sequencing methods.
Polymerase chain reaction (PCR)	Identifies microbes using PCR methods, including real-time quantitative PCR and PCR-DGGE.	Limited to detecting known species, does not provide full genome data, thus missing functional gene analysis.
DNA microarrays	Facilitate systematic and quantitative analysis of bacterial communities in the oral microbiota.	Limited to pre-designed probes, so they can't detect unknown species or genes outside of the array's scope.
16S rRNA sequencing	Targets the conserved 16S rRNA gene to study uncultured microbial communities.	Provides limited resolution at the species level and lacks insights into the functional potential of the microbial community.
Metagenomic techniques	Detect non-cultivable bacteria and analyze microbial genomic diversity, revealing species and their functional potential.	High cost and complexity; require advanced bioinformatics for data interpretation.
Shotgun metagenomic sequencing	Sequences entire DNA of a sample, providing insights into microbial species and metabolic pathways.	Data analysis is computationally intensive, high costs compared to 16S rRNA sequencing.
Next-generation sequencing (NGS)	Platforms like 454 pyrosequencing and Illumina enable comprehensive analysis of microbial diversity and metagenomes.	Expensive and generates large datasets that require complex computational resources for analysis, potential for sequencing bias.

a combination of advanced techniques, both culture-dependent and culture-independent, for a comprehensive understanding of their complexity and diversity. These methods, ranging from 16S rRNA sequencing to metagenomics and Next-Generation Sequencing (NGS) platforms, offer detailed insights into the microbial communities present in the oral cavity and their functions (Deo and Deshmukh, 2019).

3. Dental plaque or biofilm

3.1. Formation

In the adhesion stage, formation of a dental biofilm is greatly influenced by the acquired exogenous pellicle or salivary pellicle (Fig. 3). Rich in glycoproteins, this pellicle facilitates initial anchoring of bacteria (Jakubovics *et al*., 2021). Transitioning from a fluid medium where they move freely, the bacteria gradually aggregate to form a complex structure (Jin and Sengupta, 2024). Several forces are involved in this initial attachment; mainly hydrodynamic forces, which guide the random movement of bacteria towards the dental surface, and chemotaxis that promotes targeted movement through the various receptors present on the bacterial membranes (Jeong *et al*., 2024). Electrostatic and Van der Waals forces also play a role, influencing the attraction and repulsion between the bacteria and the surface (Müller-renno and Ziegler, 2024).

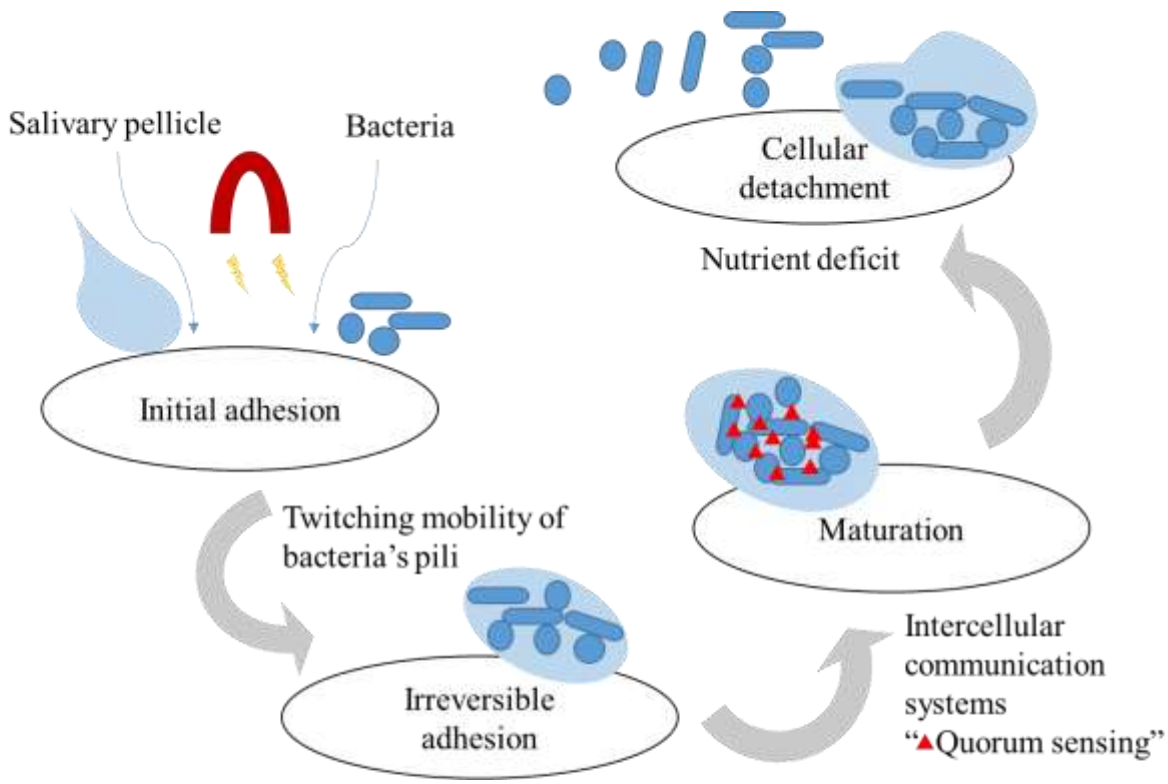

Fig. 3. The formation process of a dental biofilm

When adhesion becomes irreversible, the bacterial structures such as flagella, curli, and pili take over. The characteristic movements, known as "twitching motility" are manifested by the retraction of pili, strengthening their attachment to the surface. Flagella, in particular, facilitate movement of bacteria toward this surface. At this stage, increased production of exopolymers is observed, further reinforcing the bacterial cohesion (Jeong *et al*., 2024). During maturation, biofilm structure undergoes a significant transformation due to intensive proliferation of bacteria, resulting in an increase in the overall size (Fig. 3). The extracellular matrix thickens, leading to variations in oxygen, substrate, and even pH gradients. Intercellular communication systems emerge, allowing bacteria to perceive cell density and surrounding interactions. Some bacteria, such as *Pseudomonas aeruginosa*, produce molecules such as homoserine lactones (HSL) and numerous peptides. These elements, often described in the context of "quorum sensing" diffuse through the bacterial membrane. When these molecules reach a threshold concentration, they activate a specific set of genes, thereby enhancing the biofilm's nature (Jakubovics, 2015). In the stage of cellular detachment, bacterial growth and enzymatic degradation cause a notable nutritional shortage within the biofilm, leading to cycles of growth and cell detachment known as the "sloughing" phenomenon (Muhammad *et al*., 2020). This nutrient deficit promotes detachment of some bacteria or even fragments of biofilms. Many bacteria then detach from this three-dimensional structure. Under the effect of shear forces, the detached bacteria disperse, colonizing other regions and acting as sources of infection. These bacteria under certain circumstances can revert to a planktonic state and aggregate at a distance to form new biofilms (Abebe, 2021).

3.2. Composition

The oral cavity is a true reservoir of microbial diversity, with dental biofilm being a major ecosystem. This complex biological structure is dominated by bacteria, with an estimated hundred million to a billion bacteria per milligram of acquired pellicle.

In addition to bacteria, dental biofilm also harbors protozoa such as *Entamoeba gingivalis* and *Trichomonas tenax*, and fungi, highlighting the diversity of organisms in this environment. The biofilm matrix, representing about 30 % of dental plaque mass, is mainly composed of polysaccharides, lipids, nucleic acids, and other molecular components. It plays a crucial role in the structure and function of the biofilm, with 80 % of its composition being water and 20 % solid matter, including proteins, lipids, trace elements, minerals, and polysaccharides such as glucans and fructans (Jakubovics *et al*., 2021). These are essential for bacterial adhesion and cohesion within the biofilm. Composition of the biofilm is dynamic, evolving over time and influencing its pathogenic potential. Bacteria such as streptococci, actinomycetes, and lactobacilli have a high cariogenic potential because they produce acids in the absence of oxygen and can thrive in acidic environments. These acidogenic and aciduric bacteria are central to the development of dental caries (Abebe, 2021). Fungi play a significant role in colonizing the mouth. Although oral biofilms are traditionally known to host three to four fungal varieties; notably *Candida albicans*, recent studies based on pyrosequencing have revealed much greater diversities. By examining the oral microbiota of 20 healthy individuals, 85 fungal genera have been identified, among which 75 are non-culturable and 10 are culturable. *Candida* is the most commonly found genus (in 75 % of subjects), followed by *Cladosporium* (65 %), *Aureobasidium* and Saccharomycetales (50 % each), and *Aspergillus* (35 %). It is essential to note that some fungal genera, including *Candida*, *Aspergillus*, *Cryptococcus*, and *Fusarium*, are pathogenic to humans and may cause systemic or nosocomial infections (Milho *et al*., 2021).

4. Oral dysbiosis

The balance between different species of microorganisms in the oral cavity is crucial for maintaining a healthy (symbiotic) state. Imbalance in the normal microbial community of the mouth refers to bucco-dental dysbiosis (Maier, 2023). Loss of benefits of the healthy oral microbiota can decrease the host's immune response and increases its susceptibility to internal and external diseases, and opportunistic infections, which occur when commensal microorganisms turn into pathogenic ones (Georges *et al*., 2022).

4.1. Causes of oral dysbiosis

A visual summary of the various factors that contribute to oral dysbiosis is illustrated in Fig. (4). Dysbiosis can lead to oral and systemic health issues. The factors highlighted in the figure, based on previous findings reported by Kilian *et al*., (2016); Wu *et al*., (2016); Lamont *et al*., (2018), include dietary habits, lifestyle influences, certain medical conditions, and specific oral hygiene practices. Each factor plays a role in disrupting the microbial balance, promoting the growth of pathogenic bacteria, and diminishing the beneficial microbial populations. This illustration underscores the complexity and multifactorial nature of oral dysbiosis, emphasizing the importance of a balanced approach to diet, lifestyle, and healthcare to maintain an oral and systemic health.

4.2. Consequences of dysbiosis on oral health

Oral dysbiosis leads to various oral health problems, which include dental caries resulting from increased proliferation of the acidogenic and aciduric bacteria (Inchingolo *et al*., 2022). Periodontal diseases such as gingivitis and periodontitis are associated with inflammation and destruction of tissues supporting the teeth (Hajishengallis, 2015). Oral candidiasis is a fungal infection caused by overgrowth of *Candida albicans* (Patel, 2022). Halitosis, or bad breath, results from bacterial breakdown of food particles and dead cells (Dey *et al*., 2024). Other oral infections such as dental abscesses result from bacterial proliferation (Ahmadi *et al*., 2021). As for oral cancers, dysbiosis is suspected to play a role in the development of some of these cancers (Rosa *et al*., 2020).

4.3. Oral dysbiosis and systemic diseases

Oral dysbiosis, an imbalance in the normal oral microbiota, can contribute to a variety of systemic conditions and diseases, impacting not only the oral health but also the overall health of the individual (Table 3). The interactions between oral dysbiosis and systemic diseases may be multifactorial, and understanding that these relationships can aid in developing new therapeutic and preventive strategies for the associated systemic diseases (Sudhakara *et al*., 2018).

5. Oral diseases and roles of the microorganisms

5.1. Dental caries

5.1.1. Formation process

Dental caries begins with demineralization of the enamel; the outermost layer of the tooth, which is attributed to attack by acids produced by the bacteria that metabolize the sugars present in our diet, leading to loss of minerals. The oral microbiota plays a crucial role in the formation of caries, where the interaction between consumed sugars and the bacteria creates an acidic environment conducive to enamel degradation (Gao *et al*., 2024).

5.1.2. Pathogenic agents involved

Streptococcus mutans is the primary bacterium responsible for caries, along with *Streptococcus sobrinus*. These bacteria produce acids that dissolve dental enamel. Other acidogenic bacteria such as *Lactobacillus* spp. also play a secondary role in the development of caries (Chismirina *et al*., 2021).

5.1.3. Symptoms

Caries can be asymptomatic at first. However, as it progresses to the dentin, it causes toothache, increased sensitivity to hot; cold, or sweet foods, white or brown spots on the enamel and visible holes in the teeth (Cheng *et al*., 2022).

Fig. 4. Factors leading to oral dysbiosis adopted by Lamont *et al*., (2018)

Table 3. Systemic diseases linked to oral dysbiosis

Systemic disease	Link with oral dysbiosis	References
Cardiovascular diseases	Oral dysbiosis may contribute to systemic inflammation and atherosclerosis, potentially leading to heart diseases.	(Pietiainen *et al*., 2018)
Diabetes	Oral dysbiosis can exacerbate diabetes by affecting blood sugar management and increasing insulin resistance.	(Sudhakara *et al*., 2018)
Respiratory diseases	Dysbiosis may be linked to respiratory infections such as pneumonia, especially in vulnerable populations.	(Dong *et al*., 2022)
Inflammatory and rheumatic diseases	It may play a role in the development and progression of inflammatory diseases such as rheumatoid arthritis.	(Leech and Bartold, 2015)
Pregnancy complications	Studies have associated oral dysbiosis with complications during pregnancy, including preterm birth.	(Sampaio-Maia *et al*., 2016)
Cancers	Several researches suggest a connection between oral dysbiosis and the development of certain cancers, including pancreatic cancer.	(Mohammed *et al*., 2018; Koliarakis *et al*., 2019)
Neurodegenerative diseases	There are indications of links between oral dysbiosis and diseases such as Alzheimer's disease.	(Kamer *et al*., 2019)
Gastrointestinal disorders	Oral dysbiosis can also influence the health and balance of the intestinal microbiota, potentially affecting gastrointestinal diseases.	(Contaldo *et al*., 2021)

5.1.4. Progression

When untreated caries extends beyond the dentin, it can reach the pulp, leading to pulpitis (*i.e*., inflammation of the pulp). This pulpal involvement may cause acute and persistent pain that often exacerbates at night (Botirovna *et al*., 2021). If the infection spreads further, it affects the tooth root and surrounding tissues, leading to a dental abscess, characterized by pus accumulation. This condition is polymicrobial, involving several facultative anaerobes, including *viridans* group streptococci and the strict anaerobes; particularly anaerobic cocci, *Prevotella* spp. and *Fusobacterium* spp. This type of infection is manifested with severe pain, swelling, bad breath, and sometimes fever (Nautiyal *et al*., 2022). In rare untreated cases, several systemic complications such as facial cellulitis, sepsis, or endocarditis, may develop due to spread of the infection (Tomar *et al*., 2024).

5.1.5. Prevention and treatment

Oral hygiene is crucial, including regular brushing, flossing, reducing sugar intake, and regular dental visits. Caries can be treated by dental restoration (*i.e*., fillings). If they are deep, a root canal may be necessary. However, in severe cases, the tooth may need to be extracted (Dominika *et al*., 2023).

5.2. Periodontal diseases

5.2.1. Gingivitis

Gingivitis is a non-destructive inflammation of the gums, caused by the accumulation of the dental plaque, a bacterial adhesive matrix that is formed on the surface of teeth. The gums become red, swollen, and may bleed during brushing or chewing. Dental plaque; primarily composed of bacteria like *Streptococcus mutans*, is the main culprit. Regular plaque removal through professional cleaning and good oral hygiene is essential to prevent gingivitis (Wirata *et al*., 2023).

5.2.2. Periodontitis

Periodontitis is a chronic inflammation of the periodontal tissues that is unlike gingivitis, leads to destruction of the tissues and bones supporting the tooth. While many bacteria are involved, *Porphyromonas gingivalis* is often considered as one of the main pathogenic bacteria. Periodontitis is manifested through the formation of periodontal pockets (spaces between the tooth and gum), increased tooth mobility, gum recession, and eventually tooth loss. Deep cleaning, sometimes accompanied by periodontal surgery, is necessary. Antibiotics may also be prescribed in some cases (Martínez *et al*., 2023).

5.3. Other oral infections

5.3.1. Aphthae

Aphthae are painful ulcers formed inside the mouth, usually are round or oval, and are surrounded by a red inflammatory area (Sekar, 2023). They may be triggered by stress, injuries in the mouth, acidic or spicy foods, and other factors. Alterations in the normal balance of bacteria in the mouth and immune responses to certain bacteria normally present in the mouth, or even an autoimmune response, have been suggested as possible triggers for aphthae in some individuals (Ślebioda *et al*., 2014). These lesions cause discomfort during chewing or speaking. Topical treatments such as medicated mouthwashes or ointments can help to reduce the pain and speed the healing process (Sekar, 2023).

5.3.2. Candidiasis

Oral candidiasis is a fungal infection of the mouth, manifested as creamy white patches on the surface of the mouth, redness, a burning sensation, and difficulty swallowing in advanced stages. The primary pathogen involved is *Candida albicans*. Antifungals in the form of lozenges, gels, or liquids are commonly used (Lu, 2021).

5.3.3. Herpes

Oral herpes is a viral infection that typically appears on the lips or around the mouth. The Herpes simplex virus; mainly HSV-1, is the main pathogenic agent involved. Oral herpes is characterized by the appearance of fluid-filled blisters that can burst and leave painful ulcers. Antivirals, such as acyclovir, may reduce the duration and severity of symptoms (Bandara and Samaranayake, 2019).

6. Conventional approaches to combat the oral microorganisms

6.1. Antibiotics and antifungals

Antibiotics such as amoxicillin are commonly used to treat oral bacterial infections like dental abscesses, often followed by a combination of amoxicillin and metronidazole (Favier *et al*., 2019). Antifungals such as Fluconazole or Nystatin are used to treat yeast infections such as oral candidiasis (Pamoukdjian *et al*., 2016). Meanwhile, overuse and misuse of antibiotics may lead to bacterial resistance, making some oral infections more difficult to treat (Thualfakar and Al-Harmoosh, 2020). Antibiotics can cause side effects, including diarrhea, skin rashes, and, more rarely, severe allergic reactions (Dilley and Geng, 2022). Antifungals may cause nausea, abdominal pain, and skin rashes (Shirsat *et al*., 2021). Indications for antibiotics and antifungals use include severe dental infections, oral surgical interventions in high-risk patients, etc. Contraindications may include known allergies, certain medical conditions, and/ or the use of other incompatible medications (Segura-Egea *et al*., 2017).

6.2. Antiseptics and disinfectants

Several oral hygiene products have been formulated and marketed to manage oral biofilms. The chemical agents in mouthwashes must be effective in selectively eliminating the pathogens without disrupting the normal microbial flora. Oral antiseptics include a mixture of different substances in a solution. The different families of oral antiseptics include cationic surfactants derived from bisbiguanides, bispyridinamines, quaternary ammonium derivatives, iodinated compounds, phenolic agents, alcohols, and various mixtures of organic compounds. Chlorhexidine (CHX) is the oral antiseptic of choice that is often used in the form of a mouthwash, which works by disrupting integrity of the cell membrane of microorganisms. Chlorhexidine may cause tooth staining with prolonged use, taste alteration, and mouth irritation (Garrido *et al*., 2023).

6.3. Invasive treatments

Invasive treatments in dentistry are primarily aimed at treating structural and functional conditions of the mouth (Table 4); however, they also have a direct or indirect impact on the pathogenic oral microorganisms (Alyahya, 2024).

Conclusion

In conclusion, the intricate balance of the oral microbiota plays a fundamental role in maintaining oral health and influencing systemic well-being. The dynamic processes within this microbial community, ranging from biofilm formation to pathogen defense, highlight the significance of a healthy oral environment. However, disturbances in this balance can lead to dysbiosis, thus increasing the risk of oral diseases such as dental caries and periodontal conditions. The advancement of research methodologies, including metagenomics and next-generation sequencing, has greatly enhanced our understanding of these microbial communities, offering promising avenues for the development of novel therapeutic and preventive strategies. Effective management of oral infections requires a comprehensive approach, integrating preventive practices, including proper oral hygiene, dietary considerations, and early detection. Recognition of bacterial culprits such as *Streptococcus mutans* in dental caries and progression of the periodontal diseases, underscores the importance of timely interventions. Conventional treatments, from antibiotics to surgical procedures, remain essential for managing severe infections and preserving long-term oral health. Overall, maintaining a balanced oral microbiota through holistic approaches combined with modern research and targeted treatments, offers the best potential for promoting both oral and systemic health.

Table 4. Overview of invasive dental treatments

Treatment	Target Bacteria	Description	References
Endodontics or root canal treatment	Target bacteria inside the dental pulp or root canal such as *Enterococcus faecalis*.	Involve cleaning and disinfecting the canal to remove the bacteria causing the infection, and then sealing it to prevent new contamination.	(Siqueira and Rôças, 2013)
Periodontal surgery	Targets anaerobic bacteria and others responsible for periodontal disease, *Porphyromonas gingivalis*, *Tannerella forsythia*, and other anaerobic bacteria.	Removes subgingival plaque and calculus where these bacteria reside. Reduces periodontal pockets, which are habitats for pathogenic bacteria responsible for periodontal disease.	(Fischer *et al.*, 2020)
Tooth extraction	Bacteria causing abscesses or infections around a tooth.	Eliminates infected teeth along with the associated bacteria causing abscesses or other infections.	(Siqueira and Rôças, 2013)
Apicoectomy	Bacteria in the apical region (end of the root) of a tooth.	Removes the apex of the tooth to eliminate bacteria responsible for apical infections.	(Tsesis *et al.*, 2013)
Scaling and root planning	General oral bacteria present in plaque and tartar.	Mechanically removes plaque and tartar to reduce the number of bacteria present in the mouth.	(Fischer *et al.*, 2020)

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Conflict of interests

The authors hereby declare that they have no conflicts or competing interests.

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Authors' Contributions

Conceptualization: A.B., M.A. and S.B.; Methodology: A.B., M.A. and K.H.; Roles/Writing - original draft: A.B.; Supervision, M.A., Z.L. and S.B.; Reviewing and editing: K.H. and S.B.; Writing - review & editing: A.B. and K.H.

7. References

Abebe, G.M. (2021). Oral Biofilm and Its Impact on Oral Health, Psychological and Social Interaction. International Journal of Oral and Dental Health. 7(1): 1-11. https://doi.org/10.23937/2469-5734/1510127.

Afzaal, M.; Saeed, F.; Shah, Y.A.; Hussain, M.; Rabail, R.; Socol, C.T. et al. (2022). Human gut microbiota in health and disease: Unveiling the relationship. Frontiers in Microbiology. 13: 1-14. https://doi.org/10.3389/fmicb.2022.999001.

Ahmadi, H.; Ebrahimi, A. and Ahmadi, F. (2021). Antibiotic Therapy in Dentistry. International Journal of Dentistry. 2021: 1-10. https://doi.org/10.1155/2021/6667624.

Alyahya, Y. (2024). A narrative review of minimally invasive techniques in restorative dentistry. The Saudi Dental Journal. 36(2): 228–233. https://doi.org/10.1016/j.sdentj.2023.11.005.

Arweiler, N.B. and Netuschil, L. (2016). The Oral Microbiota. Microbiota of the Human Body, Advances in Experimental Medicine and Biology. Springer International Publishing Switzerland. 902: 45-60. https://doi.org/10.1007/978-3-319-31248-4_4.

Bandara, H.M.H.N. and Samaranayake, L.P. (2019). Viral, bacterial and fungal infections of the oral mucosa. Types: Incidence; predisposing factors; diagnostic algorithms; management. Periodontology. 80(1): 148–176. https://doi.org/10.1111/prd.12273.

Barboza-Solís, C. and Acuña-Amador, L.A. (2020). The Oral Microbiota: A Literature Review for Updating Professionals in Dentistry. Odovtos International Journal of Dental Sciences. 22(3): 59-68. https://doi.org/10.15517/IJDS.2020.39178.

Bertolini, M.; Costa, R.C.; Barão, V.A.R.; Cunha Villar, C.; Retamal-Valdes, B. et al. (2022). Oral Microorganisms and Biofilms: New Insights to Defeat the Main Etiologic Factor of Oral Diseases. Microorganisms. 10(12): 1-9. https://doi.org/10.3390/microorganisms10122413.

Botirovna, S.J.; Shuhratovna, R.Z. and Rustambekovna, S.A. (2021). Tooth pulpitis. Texas Journal of Medical Science. 3: 40-41.

Cheng, L.; Zhang, L.; Yue, L.; Ling, J.; Fan, M.; Yang, D. et al. (2022). Expert consensus on dental caries management. International Journal of Oral Science. 14: 1-8. https://doi.org/10.1038/s41368-022-00167-3.

Chismirina, S.; Sungkar, S.; Andayani, R.; Rezeki, S. and Darmawi. (2021). Existence of *Streptococcus mutans* and *Streptococcus sobrinus* in Oral Cavity as Main Cariogenc Bacteria of Dental Caries. Advances in Health Sciences Research: 90–92. https://doi.org/10.2991/ahsr.k.210201.020.

Contaldo, M.; Lucchese, A.; Lajolo, C.; Rupe, C.; Stasio, D.D.; Romano, A. et al. (2021). The Oral Microbiota Changes in Orthodontic Patients and Effects on Oral Health : An Overview. Journal of Clinical Medicine. 10. 780.

Deo, P.N. and Deshmukh, R. (2019). Oral microbiome: Unveiling the fundamentals Priya. Journal of Oral and Maxillofacial Pathology. 23(1): 122-128. https://doi.org/10.4103/jomfp.JOMFP_304_18.

Dey, A.; Khan, A.S.; Eva, F.N.; Islam, T. and Hawlader, M.D.H. (2024). Self-perceived halitosis and associated factors among university students in

Dhaka, Bangladesh. BMC Oral Health. 24: 909. https://doi.org/10.1186/s12903-024-04586-y.

Dilley, M. and Geng, B. (2022). Immediate and Delayed Hypersensitivity Reactions to Antibiotics. Clinical Reviews in Allergy & Immunology. 62: 463-475. https://doi.org/10.1007/s12016-021-08878-x.

Dominika, M.; Malwina, P.; Jagoda, A. and Maciej, B. (2023). Dietary Habits and Oral Hygiene as Determinants of the Incidence and Intensity of Dental Caries-A Pilot Study. Nutrients. 15: 4833. https://doi.org/10.3390/nu15224833.

Dong, J.; Li, W.; Wang, Q.; Chen, J.; Zu, Y.; Zhou, X. et al. (2022). Relationships Between Oral Microecosystem and Respiratory Diseases. Frontiers in Molecular Biosciences. 8: 1–17. https://doi.org/10.3389/fmolb.2021.718222.

Favier, H.; Khanafer, N.; Chaux, A.; Fabris, M. and Farges, J. (2019). Evaluation of Professional Practices in Antibiotic Prescribing Conducted in the Dental Emergency Services of a French University Hospital. Medicine and Infectious Diseases. 49(4): S54. https://doi.org/10.1016/j.medmal.2019.04.138.

Fischer, R.G.; Lira Junior, R.; Retamal-Valdes, B.; Figueiredo, L.C.; Malheiros, Z.; Stewart, B. et al. (2020). Periodontal disease and its impact on general health in Latin America. Section V: Treatment of periodontitis. Brazilian Oral Research. 34(1): 1-9. https://doi.org/10.1590/1807-3107bor-2020.vol34.0026.

Gao, Z.; Chen, X.; Wang, C.; Song, J.; Xu, J.; Liu, X. et al. (2024). New strategies and mechanisms for targeting *Streptococcus mutans* biofilm formation to prevent dental caries : A review. Microbiological Research. 278: 127526. https://doi.org/10.1016/j.micres.2023.127526.

Garrido, L.; Lyra, P.; Rodrigues, J.; Viana, J.; Mendes, J.J. and Barroso, H. (2023). Revisiting Oral Antiseptics, Microorganism Targets and Effectiveness. Journal of Personalized Medicine. 13(9): 1332. https://doi.org/10.3390/jpm13091332.

Georges, F.M.; Do, N.T. and Seleem, D. (2022). Oral dysbiosis and systemic diseases. Frontiers in Dental Medicine. 3: 1-7. https://doi.org/10.3389/fdmed.2022.995423.

Hajishengallis, G. (2015). Periodontitis: From microbial immune subversion to systemic inflammation. Nature Reviews Immunology. 30-44. https://doi.org/10.1038/nri3785.

Inchingolo, A.D.; Malcangi, G.; Semjonova, A.; Inchingolo, A.M.; Patano, A.; Coloccia, G. et al. (2022). Oralbiotica / Oralbiotics : The Impact of Oral Microbiota on Dental Health and Demineralization : A Systematic Review of the Literature. Children. 9: 1014. https://doi.org/10.3390/children9071014.

Jakubovics, N.S. (2015). Intermicrobial Interactions as a Driver for Community Composition and Stratification of Oral Biofilms. Journal of Molecular Biology. 427(23): 3662-3675. https://doi.org/10.1016/j.jmb.2015.09.022.

Jakubovics, N.S.; Goodman, S.D.; Mashburn-Warren, L.; Stafford, G.P.; Cieplik, F. et al. (2021). The dental plaque biofilm matrix. Periodontology. 86: 32–56. https://doi.org/10.1111/prd.12361.

Jeong, G.; Khan, F.; Tabassum, N. and Kim, Y. (2024). Biofilm Alteration of oral microbial biofilms by sweeteners. Biofilm. 7: 100171. https://doi.org/10.1016/j.bioflm.2023.100171.

Jia, G.; Zhi, A.; Lai, P.F.H.; Wang, G.; Xia, Y.; Xiong, Z. et al. (2018). The oral microbiota - A mechanistic role for systemic diseases. British Dental Journal. 224(6): 447–455. https://doi.org/10.1038/sj.bdj.2018.217.

Jiao, Y.; Tay, F.R.; Niu, L. and Chen, J. (2019). Advancing antimicrobial strategies for managing oral biofilm infections. International Journal of Oral

Science. 11(3): 1–11. https://doi.org/10.1038/s41368-019-0062-1.

Jin, C. and Sengupta, A. (2024). Microbes in porous environments : from active interactions to emergent feedback. Biophysical Reviews. 16: 173-188. https://doi.org/10.1007/s12551-024-01185-7.

Kaan, A.M.; Kahharova, D. and Zaura, E. (2021). Acquisition and establishment of the oral microbiota. Periodontology. 86(1): 123-141. https://doi.org/10.1111/prd.12366.

Kamer, A.R.; Craig, R.G.; Niederman, R.; Fortea, J. and Leon, M.J.D. (2019). Periodontal disease as a possible cause for Alzheimer's disease. Periodontology. 83: 242-271. https://doi.org/10.1111/prd.12327.

Kilian, M.; Chapple, I.L.C.; Hannig, M.; Marsh, P.D.; Meuric, V.; Pedersen, A.M.L. et al. (2016). The oral microbiome - An update for oral healthcare professionals. British Dental Journal. 221(10): 657-666. https://doi.org/10.1038/sj.bdj.2016.865.

Koliarakis, I.; Messaritakis, I.; Nikolouzakis, T.K.; Hamilos, G.; Souglakos, J. and Tsiaoussis, J. (2019). Oral Bacteria and Intestinal Dysbiosis in Colorectal Cancer. International Journal of Molecular Sciences. 20: 4146.

Kozak, M. and Pawlik, A. (2023). The Role of the Oral Microbiome in the Development of Diseases. International Journal of Molecular Sciences. 24(6): 5231. https://doi.org/10.3390/ijms24065231.

Lamont, R.J.; Koo, H. and Hajishengallis, G. (2018). The oral microbiota: dynamic communities and host interactions. Nature Reviews Microbiology. https://doi.org/10.1038/s41579-018-0089-x.

Langella, P. (2017). Dental Biofilm and the Balance of the Oral Microbiota: Key Concepts for Maintaining Oral Health. Paris Descartes University.

Leech, M.T. and Bartold, P.M. (2015). The association between rheumatoid arthritis and periodontitis. Best Practice & Research Clinical Rheumatology. 29(2): 1-13. https://doi.org/10.1016/j.berh.2015.03.001.

Li, X.; Liu, Y.; Yang, X.; Li, C. and Song, Z. (2022). The Oral Microbiota: Community Composition, Influencing Factors, Pathogenesis, and Interventions. Frontiers in Microbiology. 13: 1-19. https://doi.org/10.3389/fmicb.2022.895537.

Lu, S. (2021). Oral Candidosis : Pathophysiology and Best Practice for Diagnosis, Classification, and Successful Management. Fungi. 7(7): 555. https://doi.org/10.3390/jof7070555.

Lu, M.; Xuan, S. and Wang, Z. (2019). Oral microbiota : A new view of body health. Food Science and Human Wellness. 8(1): 8–15. https://doi.org/10.1016/j.fshw.2018.12.001.

Maier, T. (2023). Oral Microbiome in Health and Disease: Maintaining a Healthy, Balanced Ecosystem and Reversing Dysbiosis. Microorganisms. 11(6): 1453. https://doi.org/10.3390/microorganisms11061453.

Manos, J.I.M. (2022). The human microbiome in disease and pathology. Journal of Pathology. Microbiology and Immunology. 130: 690-705. https://doi.org/10.1111/apm.13225.

Marchesi, J.R. and Ravel, J. (2015). The vocabulary of microbiome research: a proposal. Microbiome. 3(1): 1-3. https://doi.org/10.1186/s40168-015-0094-5.

Martínez, C.J.H.; Silva, P.F.; Salvador, S.L.; Messora, M. and Palioto, D.B. (2023). Chronological analysis of periodontal bone loss in experimental periodontitis in mice. Clinical and Experimental Dental Research. 9: 1009-1020. https://doi.org/10.1002/cre2.806.

Meuric, V. (2016). From Bacteria to Microbiomes. Clinic: S4–S10.

Milho, C.; Silva, J.; Guimar, R.; Ferreira, I.C.F.R.; Barros, L. and Alves, M.J. (2021). Antimicrobials from Medicinal Plants : An Emergent Strategy to Control Oral Biofilms. Applied Sciences. 11: 4020. https://doi.org/10.3390/app11094020.

Mohammed, H.; Varoni, E.M.; Cochis, A.; Cordaro, M.; Gallenzi, P.; Patini, R. et al. (2018). Oral Dysbiosis in Pancreatic Cancer and Liver Cirrhosis : A Review of the Literature. Biomedicine. 6: 115. https://doi.org/10.3390/biomedicines6040115.

Muhammad, M.H.; Idris, A.L.; Fan, X.; Guo, Y.; Yu, Y.; Jin, X. et al. (2020). Beyond Risk : Bacterial Biofilms and Their Regulating Approaches. Frontiers in Microbiology. 11: 1-20. https://doi.org/10.3389/fmicb.2020.00928.

Müller-renno, C. and Ziegler, C. (2024). The Contribution of Scanning Force Microscopy on Dental Research : A Narrative Review. Materials. 17: 2100. https://doi.org/10.3390/ma17092100.

Nautiyal, A.; Bali, S.; Pradeepkumar, V; Aggarwal, P. and Sharma, V.R. (2022). Dental Abscess A diagnostic enigma. Journal of Pharmaceutical Negative Results. 13(6): 239-243. https://doi.org/10.47750/pnr.2022.13.S06.035.

Netter, F.H. and Scott, J. (2019). Atlas of Human Anatomy. Elsevier H. Elsevier Health Sciences.

Pamoukdjian, F.; Caillet, P.; Gogly, B.; Ebadi, N.A.; Obraztsova, A.; Merbah, S. et al. (2016). Oropharyngeal candidiasis in elderly patients. Journal of Geriatrics. 41(8): 453-459.

Patel, M. (2022). Oral Cavity and *Candida albicans*: Colonisation to the Development of Infection. Pathogens. 11: 335. https://doi.org/10.3390/pathogens11030335.

Patini, R. (2020). Oral microbiota: Discovering and facing the new associations with systemic diseases. Pathogens. 9(4): 313. https://doi.org/10.3390/pathogens9040313.

Pietiainen, M.; Liljestrand, J.M.; Kopra, E. and Pussinen, P.J. (2018). Mediators between oral dysbiosis and cardiovascular diseases. European Journal of Oral Sciences. 126(1): 26–36. https://doi.org/10.1111/eos.12423.

Rosa, G.R.M.L.; Gattuso, G.; Pedullà, E.; Rapisarda, E.; Nicolosi, D.; Salmeri, M. et al. (2020). Association of oral dysbiosis with oral cancer development (Review). Oncology Letters. 19: 3045-3058. https://doi.org/10.3892/ol.2020.11441.

Sampaio-Maia, B.; Caldas, I.M.; Pereira, M.L.; Pérez-Mongiovix, D. and Araujo, R. (2016). The Oral Microbiome in Health and Its Implication in Oral and Systemic Diseases. Advances in Applied Microbiology. https://doi.org/10.1016/bs.aambs.2016.08.002.

Sedghi, L.; DiMassa, V.; Harrington, A.; Lynch, S.V. and Kapila, Y. L. (2021). The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontology. 87(1): 107-131. https://doi.org/10.1111/prd.12393.

Segura-Egea, J.J.; Gould, K.; Şen, B.H.; Jonasson, P.; Cotti, E.; Mazzoni, A. et al. (2017). Antibiotics in Endodontics: a review. International Endodontic Journal. 50(12): 1169–1184. https://doi.org/10.1111/iej.12741.

Sekar, K. (2023). Painful Recurrent Ulcers in the Mouth: Aphthous Ulcers. In: Clinicopathological Correlation of Oral Diseases, Tilakaratne, W.M. and Kallarakkal, T.G. (Editors). Springer, Cham. https://doi.org/10.1007/978-3-031-24408-7_35.

Shibly, S.U.A. and Ningthoujam, D.S. (2023). A Review of Human Microbiomes on the Regulation of Body’s Hidden Ecosystem. Microbial Bioactive. 6(1): 1-10. https://doi.org/10.25163/microbbioacts.619374.

Shirsat, S.P.; Tambe, K.P.; Dhakad, G.G.; Patil, P.A. and Jain R.S. (2021). Review on antifungal agents. Research Journal of Pharmacology and Pharmacodynamics. 13(4): 147–154. https://doi.org/10.52711/2321-5836.2021.00028.

Siqueira, J.F. and Rôças, I.N. (2013). Microbiology and treatment of acute apical abscesses. Clinical Microbiology Reviews. 26(2): 255-273. https://doi.org/10.1128/CMR.00082-12.

Ślebioda, Z.; Szponar, E. and Kowalska, A. (2014). Etiopathogenesis of recurrent Aphthous stomatitis and the role of immunologic aspects: Literature review. Archives of Immunology and Experimental Therapy. 62(3): 205-215. https://doi.org/10.1007/s00005-013-0261-y.

Sudhakara, P.; Gupta, A.; Bhardwaj, A. and Wilson, A. (2018). Oral dysbiotic communities and their implications in systemic diseases. Dentistry Journal. 6(2): 1-14. https://doi.org/10.3390/dj6020010.

Thualfakar, H.H. and Al-Harmoosh, R.A. (2020). Mechanisms of antibiotics resistance in bacteria. Systematic Reviews in Pharmacy. 11(6): 817-823. https://doi.org/10.31838/srp.2020.6.118.

Tilotta, F.; Lévy, G. and Lautrou, A. (2018). Dental Anatomy. Elsevier H. Elsevier Health Sciences.

Tomar, K.; Chintamani, Y. and Roy, I. (2024). Orofacial Space Infections in Systemically Compromised Individuals: A Case Series and Review of Literature. Clinics of Surgery. 10: 1-9.

Tsesis, I.; Rosen, E.; Taschieri, S.; Telishevsky S.Y.; Ceresoli, V.; Del Fabbro, M. et al. (2013). Outcomes of surgical endodontic treatment performed by a modern technique: An updated meta-analysis of the literature. Journal of Endodontics. 39(3): 332-339. https://doi.org/10.1016/j.joen.2012.11.044.

Wirata, I.N.; Agung, A.A.G.; Arini, N.W.; Raiyanti, I.G.A.; Aryana, I.K.; and Purna, I.N. (2023). Decrease in the number of *Streptococcus mutans* and *Staphylococcus aureus* bacterial colonies after administration of sentul fruit peel extract gel (*Sandoricum koetjape*) in gingivitis model of white Wistar rats. Bali Medical Journal. 12(3): 2739-2742. https://doi.org/10.15562/bmj.v12i3.4753.

Wu, J.; Peters, B.A.; Dominianni, C.; Zhang, Y.; Pei, Z. ; Yang, L. et al. (2016). Cigarette smoking and the oral microbiome in a large study of American adults. ISME Journal. 10(10): 2435–2446. https://doi.org/10.1038/ismej.2016.37.

Zhang, Y.; Wang, X.; Li, H.; Ni, C.; Du, Z. and Yan, F. (2018). Human oral microbiota and its modulation for oral health. Biomedicine and Pharmacotherapy. 99: 883-893. https://doi.org/10.1016/j.biopha.2018.01.146.