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Role of Human Oral Microbiome in Diseases

Mansi Upadhyay[1], Anushika Swaroop[1], Vijay Kumar Sinhal[2], Alok Srivastava[2], Sanjay Kumar Garg[2], Vijay Pal Singh[2] and Pankaj Kumar Arora[2]*

[1]Department of Environmental Microbiology, Babasaheb Bhimrao Ambedkar University, Lucknow, Uttar Pradesh, India.
[2]Department of Plant Science, Faculty of Applied Sciences, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India.

Abstract

The human oral microbiome represents a diverse and intricate ecosystem comprising bacteria, fungi, viruses, and protozoa. It plays a vital role in numerous physiological processes, ranging from digestion to immunity. Recent research endeavors have focused on delineating the composition and functions of the oral microbiome. Changes in the oral microbiome have been associated with both oral diseases (such as dental caries, periodontitis, halitosis) and systemic conditions (including cardiovascular disease, diabetes, and cancer). Despite significant advancements, numerous questions about the role of the oral microbiome in health and disease remain unanswered. Further research is imperative to explore the intricate interactions between the oral microbiome and other microbiomes within the body. Additionally, there is a need to develop targeted interventions capable of selectively modulating the oral microbiome without disrupting other beneficial microorganisms. In summary, delving into the study of the human oral microbiome has the potential to revolutionize our comprehension of health and disease, opening avenues for innovative approaches to preventive and therapeutic medicine.

Keywords: Oral Cavity, Microbiome, Periodontal Diseases, Cancer, Gingivitis

***Correspondence:** arora484@gmail.com

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INTRODUCTION

The microbial community present in our body is named Microbiome. First, Joshua Lederberg gave the term microbiome and described the relationship between these microorganisms and humans, such as symbiotic, commensal or parasitic in nature. The microorganisms basically harbour in our buccal cavity or oral cavity represent the Human oral microbiome, oral microflora or oral microbiota.[1-3]

The human microbiome is categorized into a core microbiome and a variable microbiome. The core microbiome, common to all individuals, consists of bacteria, fungi, and viruses essential for the normal health and functioning of the oral cavity. Conversely, the variable microbiome is individual-specific, influenced by lifestyle and physiological differences. The organisms in the variable microbiome vary based on individual factors and the surrounding environment, posing a potential risk of disease if the delicate balance is disrupted.[3,4] The core microbiome remains relatively stable, comprising species crucial for the proper functioning of the human body. In contrast, the variable microbiome is more dynamic, undergoing constant changes in response to environmental factors and lifestyle choices.[3,5] The oral cavity, serving as the gateway to the digestive system, is lined with mucous membranes and encompasses two types of surfaces: the hard surfaces of the teeth and the soft tissues of the oral mucosa.[3]

Our oral cavity is the initial part of the body that comes into contact with any food or beverages. Continual consumption of food and beverages can change the oral environment along with fewer or decreased saliva production, reduced pH levels, periodontal disease, enamel, and cavities.[6] The reduced production of saliva can decrease the defense mechanism of the mouth, because of which bacteria can easily grow. Reduced pH can make the oral environment more acidic, which can later abrade the coating of the teeth and may cause cavities. The interference in the oral environment that can cause periodontal disease followed by inflammation. Bacteria associated with periodontal disease, such as *Porphyromonas gingivalis*, are much more resistant to alcohol-induced stress compared to other oral bacteria.

Our oral cavity is a very indispensable and spirited environment of the human body which harbours more than 774 species of bacteria. However, only 14% are cultured but they are still not named, whereas 32% are not cultivated, yet, and 54% are known and cultured. The oral bacteria are responsible for numerous systemic diseases like endocarditis, chronic respiratory disease, bone infection in children, preterm birth, and coronary artery disease.[7] The major component of the oral microbiota is bacteria. The oral bacterial group is made up of six main phyla— *Bacteroidetes, Firmicutes, Fusobacteria, Spirochaetes, Proteobacteria*, and *Actinobacteria.*[8]

The human body harbors its most concentrated microbial density in saliva, dental plaque, and oral mucosa. This is because saliva has a lot of nutrients, which feed bacteria. The dental plaque is adherent so it assembles on teeth and gives space to the bacteria to grow. There are approximately 774 bacteria and around 100 species of fungus are assumed to reside in the oral cavity. Various research studies investigate that there is a possible relationship between the oral microbiome and systemic disease. As a result, the importance of oral health should not be missed, as it can have collision with the overall well-being.[9,10]

Our oral cavity is the main entrance of the human body.[11,12] This is because the mouth contains a variety of microbial communities that can spread to other parts of the body and cause disease. Additionally, the oral cavity contains mucus membranes that can be penetrated by bacteria and viruses, allowing them to enter the body and cause infection. The oral cavity, or mouth, contains a diverse population of microorganisms that can cause infection when entering the bloodstream. These microorganisms produce toxins and enzymes that can damage tissues and organs of the body, leading to a variety of conditions such as cavities, gum disease, and even systemic diseases.[12,13]

Development of the oral microbiome

The development of microbiome begins when the mother's microbiome is passed on to the fetus through the mother's saliva and placenta, and this microbiome affects the development of the fetus's immune system and how it should response to the mother's microbiome.[14] The fetus womb is normally aseptic and this helps the infant build up its own microflora, which is essential for healthy development. The mother's microflora is thought to provide the infant with beneficial bacteria and also help protect it from potentially harmful bacteria in the environment. Usually, the oral cavity of the newborn is aseptic and in malice of the probability of the contamination. At any time, the first feeding is started, the microorganisms injected into the mouth of the newborn, and the addition of residential oral microflora begins.[3,15] *Fusobacterium nucleatum* is the most ordinary easily cultivable microorganism detected in passing time; the microbial configuration of our oral cavity changes due to lifestyle such as diet, hygiene practices, and host immunity. As time passes the community of microbial species increases, which creates a firm microbial environment in the oral cavity.[15,16]

Oral bacterial associations in health and disease

The mouth ports a diversity of microbes in the body, which have bacteria, viruses, fungi, and even protozoa. Although most of the disease are caused by the bacteria like: periodontal disease, tooth decay etc.[17] The microbiome is group of each microorganism that specifically lives in the environment and in human mouth. The oral microbiome is certainly important to human health, as it may lead to systemic infections.[4]

Some of the most common diseases caused by oral microbiome are given below:

1. Periodontal disease
2. Dental caries
3. Dysbiosis
4. Gingivitis
5. Oral cancer

Periodontal disease

Periodontal disease is an oral inflammatory infection which is caused by a buildup of plaque, which consists of bacteria along with other food particles. The bacteria builds toxins that inflame the gums and can cause damage to tissues and also to the periodontium. This occurs because gingivitis is caused by plaque buildup on the gums, whereas periodontitis is caused by a bacterial inflammation that affects the inner layers of the gums and the bone maxilla and mandible. Periodontitis is caused by the accumulation of bacteria that trigger an inflammatory response in the body. This inflammation is caused by a buildup of bacteria in the mouth, which can lead to gum disease. Bacteria can enter the veins, causing the body to release inflammatory chemicals that can damage the gums and form pockets. These pockets can collect more bacteria, leading to further damage and potential tooth loss.[18] The bacteria secrete toxins that destroy the tissues of the host, while the immune response results in infection and further tissue damage. Smoking affects the host's immune response, making it more difficult for the body to fight the bacteria. This in turn leads to sites with deep probing depths, mobility, and bleeding upon probing. Additionally, the bacteria can cause the teeth to move around in their sockets, leading to pathologic migration.[19] Periodontal disease is an infection of the tissues that support your teeth. It is caused by bacteria in plaque, a sticky film that forms on your teeth. Plaque is made up of food debris, saliva, and bacteria. These bacteria produce toxins or poisons that irritate the gums. This irritation causes the body to produce inflammation.[20]

Patient's medical history can help to know about these risk factors can help the dentist determine the most appropriate treatment plan and develop strategies to help the patient reduce the likelihood of developing periodontitis. Additionally, having the patient's medical history on record can help the dentist more accurately diagnose the patient's condition. These parameters provide information about the severity of periodontal disease, the extent of tissue destruction, the presence of deep pockets, the degree of attachment loss, the presence of mucogingival deformities, and the ability of the tooth to resist occlusal forces.[19]

Dental caries

Bacteria in the mouth produce acid that breaks down the tooth enamel, leading to cavities. These bacteria can also spread to other parts of the body, leading to infections that can cause systemic diseases. Additionally, cavities can be very painful and expensive to treat.[21] Dental caries, or tooth decay, is a condition in which the enamel of the tooth breaks down and a hole forms in the tooth. Caries can be caused by bacteria, sugary drinks, and acidic foods. Diet plays an important role in the progression of dental caries because the bacteria in the mouth feed on the sugars found in food and drinks. When bacteria break down the sugars, they produce an acid that can dissolve the enamel of the teeth, leading to caries. However, if the foods and beverages consumed are low in sugar and plaque is regularly removed from the teeth, the caries process can be reversed. Preventive strategies such as regular dental hygiene, avoiding sugary and acidic foods, and regular visits to the dentist can help to prevent the disease from developing in the first place and can reduce the severity of the symptoms. Additionally, preventive strategies cost significantly less than surgical intervention and can be carried out continuously.[22]

The lactic acid produced by the microorganisms lowers the pH of the oral environment, thus creating an acidic environment that causes minerals in the teeth to dissolve. Fluorides present in saliva and toothpaste help to restore the mineral balance and thus reduce the risk of cavities.[22] Toothpaste helps to deliver fluoride to the teeth, which is important since fluoride helps to strengthen the enamel and prevent cavities. Fluoride also helps to re-mineralize early lesions, which can help prevent cavities from forming.[22]

Dysbiosis

Dysbiosis occurs when there is a shift in the relationship between the microbiome and the host, resulting in a decrease in beneficial microorganisms and an increase in the pathogenic potential, leading to an imbalance within the human body. This imbalance is commonly referred to as dysbiosis, and in the context of oral health, it serves as a gateway to periodontitis and related diseases.

The primary cause of dysbiosis in the oral cavity is inadequate oral hygiene. Other significant contributors include poor dietary habits, gingivitis, smoking, genetic variations, and disorders of salivary glands affecting salivary protein activity. Dysbiosis involves the disruption of the normal microbiome balance, allowing pathogenic organisms to flourish.[23]

Recent research suggests a shift in understanding oral diseases – rather than being solely attributed to external infections, they are now thought to be primarily caused by variations in the oral microbiome. In a healthy host, pathogens are naturally present in limited numbers at healthy sites. However, dysbiosis leads to a substantial overgrowth of infectious bacteria, particularly on the biofilm surface, accompanied by alterations in neutral components. Oral dysbiosis is closely linked to dietary patterns and poor oral hygiene, giving rise to various oral health issues, including gingival inflammation, periodontitis, dental caries, dysbiosis itself, and even oral cancer. It underscores the importance of maintaining proper oral hygiene and making positive lifestyle choices to prevent dysbiosis-related complications.[24]

Gingivitis

Gingivitis is an inflammation of the soft tissues of the gum that surrounds the teeth that develops due to the interaction between the plaque microbiota and the host tissues. When the bacteria in the plaque buildup, they produce substances that irritate the gums, causing inflammation. This inflammation can lead to gum disease and decay, which can cause the gums to recede and loosen from the teeth, leading to tooth loss.[25] Gingivitis is the mildest form of periodontal disease. The bacteria in the plaque produce toxins that can irritate the gums, causing them to become inflamed and easily bleed. If left untreated, the bacteria can cause the gums to recede, creating pockets that can become filled with more plaque and bacteria, leading to more serious forms of periodontal disease.[26] It is believed that the bacterial components of these pathogens, such as the lipopolysaccharide (LPS) of *P. gingivalis*, can induce the release of pro-inflammatory cytokines and other mediators that can trigger an inflammatory response in the surrounding tissue, leading to an increased risk of periodontal diseases.[27]

Oral cancer

Oral cancer is multifaceted disease in itself. There are some risk factors involved in causing oral cancer such as HPV, alcohol consumption, smoking, poor oral hygiene, chewing tobacco, sun exposure, diet, betel nuts, family history of mouth cancer, genetic susceptibility are all major risk factor for occurrence of oral cancer.[25]

Recent research shows interrelation between leukemia and periodontitis. Since these reports there has been growing proof of the relation between various cancers and periodontal disease.[28]

Chronic bacterial infections may be the cause of the oral cancer in humans. This is due to the fact that these pathogens are able to use the food sources present in oral cavity to survive and grow rapidly. Bacteria in periodontal disease can enter the bloodstream and cause inflammation in the mouth, which can damage cells in the tissues and cause them to evolve. This can lead to premalignant lesions and oral cancers. The correlation between chronic inflammation and periodontitis and oral cancer has been studied extensively, it is believed to be one of the main causes. However, HPV infection is not a major cause of oral cancer, as it is rarely found in these cases. However, more research is needed to further understand the causal relationship between chronic inflammation and oral cancer.[27]

The tongue, buccal mucosa, supragingival and subgingival surfaces of the teeth, soft and hard palates, and saliva of the oral cavity may represent different ecological niches or habitats.[26] These surfaces provide an ideal environment for the growth of bacteria due to their moist and warm conditions. Bacteria in these areas can also thrive due to the food particles found in saliva and the nutrients present in the oral cavity.[26] Risk factors for oral squamous cell carcinomas (OSCC) include tobacco and alcohol use, poor nutrition, and human papillomavirus (HPV) infection. It is also more common among men than women.[29]

Tobacco-containing products contain harmful chemicals that can damage cells in the mouth, leading to genetic mutations that cause cells to become cancerous. These cancerous cells can then spread to other parts of the body and cause serious health issues. Certain bacteria in the oral microbiome can produce harmful toxins that increase inflammation and irritation in the mouth, leading to the development of oral submucous fibrosis. Additionally, a decrease in beneficial bacteria can cause an imbalance in the oral microbiome, which can also contribute to the development of the condition.[29] Poor oral hygiene habits and diets that are high in sugar and acidic foods can increase the risk of developing oral cancer. Additionally, smoking and drinking alcohol can change the composition of the mouth's microbiome, which can further increase the risk of developing oral cancer.[30]

Biofilm in oral microbiome

Biofilms represent intricate structures created by microbial communities, predominantly bacteria, which adhere to surfaces and become ingrained in a self-generated extracellular matrix.[31] Within biofilms, cells engage in interactions, coexist harmoniously, and exhibit diverse characteristics that distinguish them from independently living cells.[32] In the oral cavity, a substantial array of bacteria contributes to the development of biofilms that envelop oral structures, influenced by the composition and surface attributes of these structures.[33]

The inception of biofilm formation occurs in the salivary pellicle, a thin layer containing proteins and other substances. This initiates essential processes like bacterial adhesion, colonization, cell proliferation, and co-aggregation. The extracellular polymeric matrix of the biofilm, pivotal for providing structural support, comprises proteins, lipids, polysaccharides, and extracellular DNA. This matrix assumes a crucial role in maintaining the stability and integrity of the biofilm.

The intricate environment within the oral cavity supports the maturation of the biofilm. This phase involves the addition of more layers of microbial cells and matrix, leading to a highly organized and stable biofilm structure. Depending on the type of biofilm and its specific conditions, variations in bacterial gene expression may occur. This implies that the bacteria within the biofilm may express different genes compared to when they are in a free-living state.

The oral microbiome's microbial populations and the host are known to communicate with one another more and more frequently.[34] Multiple processes, such as the formation of hydrogen peroxide, a signaling molecule as well, are critical in *Streptococci* and several other species related to the temporal and spatial formation of biofilms in the mouth and their persistence. Commensal bacteria, primarily *S. sanguinis* create H_2O_2 through the action of bacterial enzymes including lactate oxidase, L-amino acid oxidase, or pyruvate oxidase.[35] Oral health is enhanced by shifting the scales in favor of increased H_2O_2 production.[35]

Biofilms and Curli Amyloid

Curli amyloid fibers are proteinaceous structures produced by certain bacteria during biofilm formation. Bacteria that carry the curli-specific gene (CSG) cluster produce curli amyloid fibers and produce biofilm.[36] Various bacterial groups, including *Enterobacteriaceae, Bacteroidetes, Proteobacteria, Firmicutes, and Theromosulfobacteria,* are capable of producing curli fibers. Curli fibers can activate the NLRP3 inflammasome (intracellular NLR family Pyrin Domain Containing 3), leading to inflammation. The release of cytokines, such as type I interferons, is associated with the presence of curli fibers.[36,37]

Microorganisms producing amyloid are identified in diseases like systemic lupus erythematosus, reactive arthritis, neurological disorders, and colorectal malignancies. The hope is that understanding these associations could lead to the development of potential treatments for these diseases.[37] Microorganisms in oral biofilms exhibit higher medication resistance, making control challenging. Dental materials play a role in biofilm formation; surfaces with rough textures tend to harbor more germs.[38] Recent developments include dental components that either destroy bacterial cells on contact or release antibacterial compounds. The choice of dental materials can influence biofilm formation; materials with smooth surfaces are less conducive to biofilm growth.[38] Removable dentures can encourage the accumulation of microorganisms and the formation of biofilms, influenced by the unique properties of the materials used.[39] An alternative to mechanically removing biofilms is antimicrobial photodynamic treatment, which involves using light to activate photosensitizing agents that kill bacteria.

Microbial colonization in oral cavity

There is a complex interaction between different bacteria in the mouth, characterized by the production of diverse glycoproteins and polysaccharides. These substances facilitate the sequential adhesion of various microbes, contributing to the formation of biofilms.[40,41] Biofilms are created in the oral cavity through the cooperation of both oxygen-dependent and oxygen-independent bacteria. Gram-positive bacteria, particularly *Streptococcus* and *Actinomyces*, play a significant role in biofilm formation. *Streptococcus* and *Actinomyces* tend to colonize newly cleaned teeth surfaces, with *Streptococcus* spp. being among the first to infiltrate the area.[42] Various *Streptococcus* species, including *Streptococcus gordonii*, *Streptococcus oralis*, *Streptococcus sanguinis*, *Streptococcus mutants*, and *Streptococcus sobrinus*, are involved in the early stages of biofilm development.[43,44] *Streptococci* attach to exposed salivary proteins, specifically slathering and proline-rich protein receptors, to adhere to enamel surfaces. These bacteria then generate high molecular weight polypeptide antigens (160-180 KDa) Extracellular polymeric substances are generated, forming an adhesive bond with enamel surfaces. Salivary agglutinin glycoprotein gp340 interacts with arginine or proline-rich antigens produced by *Streptococci*.[45] Complexes formed by these interactions serve as adhesions and mucins, preparing surfaces for the attachment of microbes, especially Gram-negative bacteria.[46] According to Du and Kolenbrander[47] two large anchoring antigens, SspA and SspB particularly communicate with *Actinomyces* oral T14V and *Actinomyces naeslundii* PK606.

Streptococci and *Veillonella* have a close metabolic connection that supports their association. This connection likely involves shared metabolic pathways or mutual dependencies on certain nutrients.[46] Aerobic microbial communities provide a specific habitat that permits the presence of anaerobic microorganisms. This interaction may create microenvironments where anaerobic microbes can thrive in the presence of oxygen-producing microorganisms. Microorganisms, including *Fusobacterium*, can associate with *Veillonella* in these microenvironments.[46] *Veillonella* may act as a facilitator for the attachment of other anaerobic microbes, such as *Fusobacterium*. The *Fusobacterium*, described as an obligate anaerobe, plays a role in the microbial community. To attach, *Fusobacterium* releases signaling molecules, indicating a communication mechanism between microorganisms for the formation and maintenance of microbial associations.[48,49] Certain bacteria have related receptors, possibly involved in the recognition and interaction with specific molecules or structures. The RadD receptor in *Fusobacterium notatum* binds with *S. sanguinis*[50] Additionally, *F. nuclear* promotes microorganism development in an anaerobic situation.[51] *Streptococcus, Actinobacteria, Veillonella, Prevotella*, and *Fusobacterium* sequentially aggregate.[51, 52] With a range of cell-cell interactions, *Streptococci* play a crucial role in the co-aggregation among different microorganisms. Additionally, *Streptococcus* generates hydrogen peroxide and bacteriocins, both of which have antibacterial properties and can inhibit the development of certain phylotypes.[53] *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* collaborate and use lactate generated through sucrose metabolism by *Streptococcus gordonii*. *S. oralis* and *Veillonella* species have remarkably similar relationships.[54] Similarly, to this, autoinducer-2 mediated bacterial co-aggregation raises the level of numerous gene expressions.

Yeast colonization starts using a interaction of yeast and other microorganisms. *Candida* species heat-stable mannan receptors engage in interactions with the heat-resistant parts of the *Fusobacterium*. A combination of *Porphyromonas, Veillonella, Fusobacterium, Treponema,* and *Candida* results in extreme tooth cavities. For defining the process by which microorganisms in the oral cavity produce biofilms, several models have been developed. Numerous polysaccharide hydrolyzing enzymes are secreted as a result of bacterial competition for carbohydrates. These hydrolases disassemble the polysaccharide's glycosidic bonds to create a variety of soluble and insoluble sugars. Insoluble sugars help to create the matrix, whereas bacteria use soluble sugars for growth.[55,56]

Additionally, it has been noted that oral bacteria create exo-polysaccharides and the development of biofilms is aided by extracellular polymeric substances (EPS), this act as a scaffold.[40] *Veillonella, Porphyromonas, Fusobacterium*, and *Candida* count rise due to inadequate dental cleanliness in the oral cavity, which promotes the adhesion of additional pathogenic candidates.

CONCLUSION

The oral microbiome, which consists of the diverse community of microorganisms in the mouth, plays a crucial role in maintaining oral health. However, much remains unknown about its complexity and how it influences overall health.

Several factors contribute to the variation in the oral microbiome among individuals. Genetics, diet, hygiene practices, environmental factors, and overall health can all influence the composition and diversity of the oral microbiome. Researchers are working to unravel these complexities and understand why some people have a more diverse oral microbiome than others.

The link between the oral microbiome and oral diseases, such as tooth decay and gum disease, is well-established. However, the specific mechanisms and factors that make some individuals more susceptible to these diseases remain unclear. Research efforts are ongoing to explore these relationships and identify potential risk factors.

The development of predictive models and biomarkers for dysbiosis detection is a promising avenue of research. Early identification of microbial imbalances in the oral microbiome before clinical symptoms arise could significantly improve preventive and therapeutic strategies. Reliable biomarkers would be essential for long-term prognosis and targeted treatment approaches.

As research in this field progresses, it is expected that a more comprehensive understanding of the oral microbiome and its impact on human health will emerge. This knowledge could lead to personalized approaches in oral healthcare, allowing for more effective prevention and treatment strategies tailored to individual microbial profiles and health conditions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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