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The Oral Microbiome: A Gateway to Systemic Health

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Abstract: Since the turn of the millennium, the field of oral microbiology has witnessed remarkable advancements, shedding light on the pivotal role of microorganisms in the oral cavity and their complex interactions in maintaining the balance between health and disease. Understanding the composition and functional dynamics of these microbial communities in both healthy and diseased states has become a central focus in oral microbiology, especially given their significant influence on systemic health. The oral microbiome is intricately linked to various systemic conditions, including cardiovascular diseases, liver diseases, metabolic disorders such as diabetes mellitus and malignancies like oral cancer. Furthermore, lifestyle factors—including tobacco use, alcohol consumption and dietary choices—profoundly shape the oral microbial environment, often tipping the balance toward dysbiosis and disease. The oral and gastrointestinal systems are closely interconnected, as evidenced by the daily ingestion of saliva, which facilitates a continuous exchange between oral and gut microbiota, further influencing overall health. Recent innovations, such as probiotic-based oral care products, aim to restore and maintain this delicate microbial equilibrium, underscoring the importance of fostering a symbiotic relationship within the oral cavity. This review integrates these emerging insights, highlighting the complex interplay between the oral microbiome, oral and systemic health, lifestyle factors and therapeutic advancements.

Keywords: Oral Microbiome, Gut Microbiome,Respiratory disease,Infective Endocarditis, Diabetes Mellitus, Oral Cancer

Introduction:

Different parts of the human body—such as the gut, skin, lungs, and oral cavity—are colonized by a diverse range of commensal, symbiotic, and pathogenic microorganisms, including bacteria, archaea, fungi, protists, and viruses. The human microbiota, often referred to as ‘‘the hidden organ,’’ contributes over 150 times more genetic material than the human genome. The term *microbiota* refers to the community of microbes in a specific environment, whereas *microbiome* encompasses the microbes, their genomes, and the surrounding environment. Recent advances in microbiome research have revealed that the microbiome actively influences the immune, metabolic, and endocrine systems, thereby impacting the host’s physiological functions.

The oral mucosa is exposed to a huge array of microorganisms that collectively comprise the oral microbiome. The presence of several distinct habitats, including the hard tooth surfaces in the oral cavity, presents unique microbial niches that can communicate oral microbiome changes at micron-scale gradients with each other for both short and long-range microbial

interactions.[1]The second largest and most varied microbiome after the gut is the oral microbiome, which includes about 700 species of bacteria, fungi, virusesand protozoa, which have been identified by cultivation or the advancing culture independent molecular approaches.The relationship between oral health and ailments in other parts of the body seems to be related to the dysbiosis of the human oral microbiome, as well as systemic spread of the oral microbiome inhabitants.[2,3]These species attach and form biofilms on the mouth's soft and hard tissue surfaces in a structurally organized matrix, inducing a dynamic equilibrium with the immune-inflammatory response of the host. Despite the similarities between the core microbial composition within the oral cavities, the type of species may vary depending on diet and nutrition, genetic susceptibility, antibiotic usage, hormonal factors, tobacco and alcohol exposure and recurrent pathogenic infections of the host. This disturbance to the equilibrium results in oral dysbiosis altering oral and systemic health through several pathophysiological processes linked to disease. Dysbiosis has reportedly been involved in oral diseases such as periodontitis, caries and oral cancer.[3]

Oral Microbiota, Gut Microbiota and Systemic Diseases:

The human body hosts trillions of microorganisms throughout many diverse habitats with different physico-chemical characteristics. Among them, the oral cavity and the gut harbour some of the most dense and diverse microbial communities.The oral cavity hosts the second largest and most diverse microbiome after the gut, containing over 700 bacterial species.At stable oral conditions an average temperature of 37 °C and salivary pH of 6.5–7—support microbial growth.In health, a core set of microorganisms is almost universally present in the oral cavity.This core microbiome in the oral cavity includes members of the phyla Firmicutes (Streptococcus spp., Veillonella spp., and Granulicatella spp.), Proteobacteria (Neisseria spp., Campylobacter spp., and Haemophilus spp.), Actinobacteria (Corynebacterium spp., Rothia spp., and Actinomyces spp.), Bacteroidetes (Prevotella spp., Capnocytophaga spp., and Porphyromonas spp.) and Fusobacteria (Fusobacterium spp.).Although these two sites are physiologically distinct, they are directly connected and can influence each other in several ways.[4]The oral and gut microbiota interact in a complex and dynamic manner, with microbial transfer between the two being more prominent in patients than in healthy individuals.The oral-gut microbiome axis denotes the intricate relationship between the microbial ecosystems of the oral cavity and the gastrointestinal (GI) tract. This bidirectional axis underscores the dynamic interactions and mutual influence between oral and gut microbiota, as well as their collective implications for systemic health. The connection is predominantly facilitated by saliva, which harbours a diverse consortium of oral microorganisms that are continuously introduced into the gastrointestinal environment through ingestion. The oral microbiota from an open or closed sites (caries, periodontal pockets, periapical infections, unerupted teeth, infected pulp tissue) can have a profound impact on systemic health through its ability to invade and influence distant regions of the body, particularly the intestinal tract and systemic circulation. The direct migration of oral microorganisms into the gastrointestinal tract via the oesophagus can lead to an imbalance in the intestinal microbial ecosystem, contributing to digestive system dysfunction. Fusobacterium nucleatum, a well-known oral bacterium, can colonize the colorectal tract through blood circulation and is associated with colorectal cancer. Similarly, pathogenic bacteria from periodontitis, such as Porphyromonas gingivalis, can enter the systemic circulation via periodontal blood vessels, affecting multiple organs and systems.

The metabolites of the oral microbiota also enter the bloodstream, inducing a persistent low-grade inflammatory state that promotes the development of various chronic diseases, particularly those affecting the digestive system. P. gingivalis is a key bacterium implicated in the progression of diseases such as colon cancer, inflammatory bowel disease (IBD), and diabetes. It disrupts the innate host defence and induces microbial dysbiosis, exacerbating inflammation by impairing the interaction between the host's microbiota and mucosal tissues.

One of the ways P. gingivalis exerts its pathogenic effects is by targeting immune signalling pathways. It can interact with the complement C5a receptor 1 (C5aR1) and Toll-like receptor to activate the PI3K signalling pathway, which inhibits phagocytosis and promotes inflammation. This mechanism disrupts normal immune responses and contributes to a pro-inflammatory environment, fuelling systemic inflammation and disease progression. Certain periodontal bacteria are now being linked to cancer through their role in the oral microecosystem.These findings underscore the significant role of oral microbiota in modulating systemic health and highlight potential therapeutic targets for managing oral and systemic diseases (Figure 1).[5]

Oral Microbiota, Immune System and Inflammatory Diseases:

The host microbiota, consisting of various microorganisms in different body parts, interacts with the immune system, helping to train immune cells to detect pathogens or promote tolerance. This process involves microbe-associated molecular patterns (MAMPs) that interact with pattern recognition receptors (PRRs) on immune cells like mast cells, macrophages and dendritic cells. These interactions can influence immune responses and inflammation, with some immune cells being trained to respond more effectively to pathogens. Commensal microbiota also interacts with T cells and B cells in the adaptive immune system, influencing both cell-mediated and humoral responses. This microbiota contributes to the host's immune system by producing metabolites that influence immune reactions, organ development and metabolism. For instance, bacterial metabolites like short-chain fatty acids (SCFAs) can modulate immune responses and allergic reactions.

Oral microbiota plays a significant role in inflammatory diseases. Oral dysbiosis has been linked to systemic inflammation, affecting conditions like colorectal cancer, HIV and Crohn's disease. Studies suggest that oral bacteria can migrate to the gut, influencing diseases such as inflammatory bowel disease (IBD). For example, bacteria like *Klebsiella*, originally found in the mouth, have been shown to promote Th1 responses in the intestine, contributing to inflammation. Oral dysbiosis and chronic periodontitis are also linked to neurodegenerative diseases like Alzheimer's disease. Chronic periodontitis induces the release of inflammatory mediators, which may contribute to neuroinflammation and cognitive decline. Research indicates that periodontitis might accelerate Alzheimer's progression by raising inflammatory markers such as C-reactive protein and IL-6, suggesting a potential therapeutic approach in managing periodontitis to slow disease progression. Furthermore, oral bacteria, particularly *Porphyromonas gingivalis*, are associated with cardiovascular diseases, including atherosclerosis. These bacteria can enter the bloodstream, causing bacteraemia, which may lead to further cardiovascular complications. Studies have found that these bacteria and inflammatory mediators like IL-6 are elevated in patients with both periodontitis and cardiovascular disease.[21]

Pregnancy:

Pregnancy is driven by a series of immunological, hormonal and metabolic changes that are essential for the normal foetal development and successful delivery. These changes alter the microbiota of the mother in various locations of the body including the gut, vagina and oral cavity. A study by Fujiwara et al. compared the oral microbiota composition in pregnant and non-pregnant Japanese women. They showed that the number of microorganisms identified in pregnant women's saliva samples was significantly higher than non-pregnant women and that, P. gingivalis, A. actinomycetemcomitans, Streptococci, Staphylococci and Candida species were significantly higher in the pregnant women especially during the first and second trimesters. Periodontal diseases like gingivitis and periodontitis are linked to systemic inflammation and adverse pregnancy outcomes, including low birth weight, preterm birth, preeclampsia and miscarriages.Two different mechanisms have been proposed to explain this relationship: the first mechanism proposed that periodontal bacteria originating in the gingival biofilm can translocate from the unhealthy oral cavity and cross the placenta, reaching the intra-amniotic fluid and foetal circulation and thus directly affecting the fetoplacental unit resulting in bacteraemia. The second mechanism proposed that the systemic dissemination of endotoxins and/or inflammatory mediators derived from the periodontal disease and secreted by the subgingival inflammatory site are carried to the fetoplacental unit which can cause an inflammatory response and in turn affect foetal development, lead to a spontaneous abortion, or trigger early labour and delivery.[17]

Respiratory Health and Disease:

The oral cavity serves as a reservoir for respiratory pathogens, influencing respiratory health through microbial infiltration, immune responses and systemic inflammation. A well-functioning airway epithelium and immune defences typically prevent microbial invasion into the lower respiratory tract, but conditions like smoking, diabetes, chronic illnesses and poor oral hygiene can weaken these barriers, increasing the risk of respiratory diseases such as pneumonia, Chronic Obstructive Pulmonary Diseases (COPD), lung cancer and asthma. Pneumonia, particularly in immune com promised individuals and the elderly, is linked to oral bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Porphyromonas gingivalis, Fusobacterium nucleatum* and *Aggregatibacteractinomycetem comitans*, with poor oral hygiene significantly increasing its risk. COPD patients often exhibit poor oral health and periodontitis, with bacterial species like *Johnsonella, Catonella, Campylobacter, Porphyromonas intermedia, Veillonella dispar* and *Prevotellamelaninogenica* contributing to inflammation and compromised lung function. Lung cancer has been associated with oral microbial imbalances, with bacteria such as *Blastomonas, Sphingomonas, Capnocytophaga, Veillonella, Fusobacteriaceae* and *Neisseriaceae* playing potential roles in cancer development, while smoking exacerbates dysbiosis. Asthma patients face increased oral health issues, often due to medications that alter saliva composition, promoting bacterial imbalances with *Lactobacilli, Streptococcus mutans, Prevotella intermedia* and *Candida species* contributing to inflammation and airway complications.[18]

Neurodegenerative Diseases:

Neurodegenerative diseases involve brain deterioration, leading to loss of functions like memory or movement. These include Parkinson's Disease (PD), Alzheimer's Disease (AD), Multiple Sclerosis (MS), and Lewy Body Disease (LBD). Growing evidence links oral dysbiosis to neurodegenerative diseases, especially AD. Most studies focus on the connection between periodontitis and AD. Periodontitis causes inflammation, which may worsen AD-related neuroinflammation; its pathogens release cytokines like IL-1, IL-6, and TNF-alpha. Ide et al. found periodontitis was linked to elevated inflammatory markers and cognitive decline in AD patients, regardless of baseline cognition. Another theory suggests oral bacteria may enter the bloodstream and reach the brain. Franciotti et al. found higher Porphyromonas gingivalis levels in neurodegenerative patients than healthy controls, suggesting oral pathogens might influence disease through immune responses. Though a link exists, the exact mechanism is unconfirmed in animal models. Oral dysbiosis may also contribute to PD through systemic inflammation. Phosphorylated alpha-synuclein aggregates, found in the brain, olfactory bulb, and GI tract, appear early in PD, possibly causing non-motor symptoms like dry mouth and dysphagia. Fleury et al. reported PD patients had distinct oral microbiota, including more Streptococcus mutans, a bacterium forming amyloids that may promote alpha-synuclein aggregation and brain inflammation. Pro-inflammatory cytokines were also higher in PD patients' gingival crevicular fluid, suggesting oral dysbiosis may promote immune activation, inflammation, and PD progression. [19]

Liver Diseases:

Recent studies have found that both gut microbiota and the imbalance of oral microbiota are closely related to liver disease. The diversity of oral microbiota in patients with liver cancer was higher than that of healthy people, and the composition of the microbiota in patients with liver cancer was also significantly different from that of healthy people. Among them, Clostridium, Oribacterium, Ciliate, Actinomycetes and Campylobacter have high abundance, whereas Haemophilus, Streptococcus and Pseudomonas have low abundance. Clostridium and Oribacterium are biomarkers that can distinguish between patients with liver cancer and healthy people, as well as assist in the diagnosis of liver cancer. Similar to patients with liver cancer, patients with cirrhosis exhibit an imbalance of oral microbiota, reduced abundance of oral symbiotic bacteria, and increased abundance of potential pathogenic bacteria (e.g., Enterobacteriaceae and Enterococcus). Researchers compared the gut microbiota of patients with cirrhosis and healthy people, and they found that the intestinal microbiota of patients with cirrhosis is enriched with a large number of oral-derived microorganisms, including Weirong, Streptococcus, Pasteurella genus, Haemophilus, Lactobacillus and Clostridium. These researchers speculated that oral microbes invade gut microbiota of patients with cirrhosis(5). Many studies have also demonstrated that P. gingivalis or A. actinomycetemcomitans can worsen Non-alcoholic fatty liver disease (NAFLD).[6]

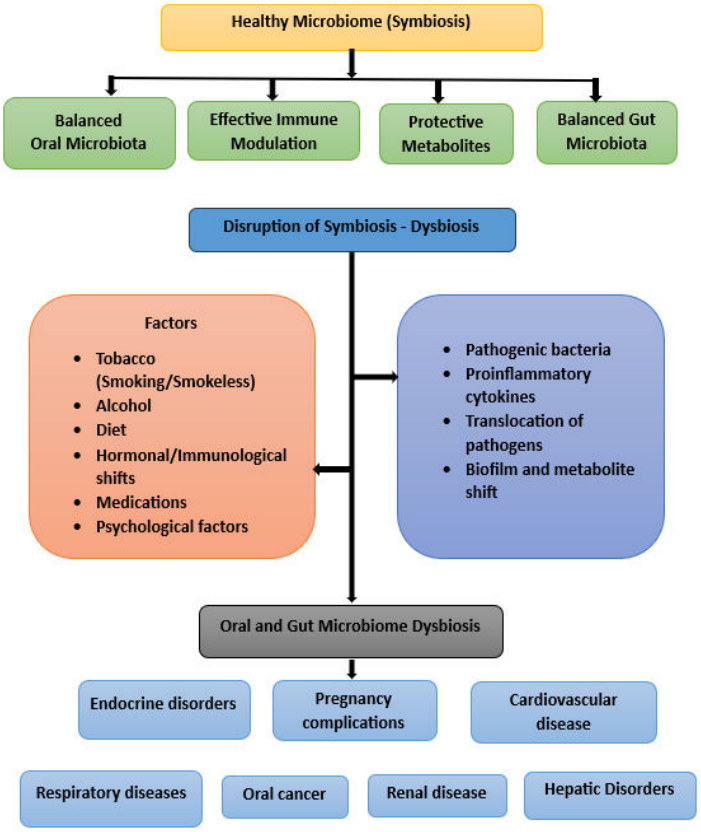

Figure 1. Mechanistic Pathway from Oral and Gut Microbiome Symbiosis to Dysbiosis and Its Systemic Health Implications

Infective Endocarditis:

Infective endocarditis is an uncommon but severe inflammatory disease of the endocardium caused by complex interplay of different factors that cause certain microorganisms to adhere to the cardiac endothelium and trigger an inflammatory process. Disintegration of a bacterially colonized surface, such as the mucous membrane, which harbours numerous commensals but also opportunistic pathogens can cause transient bacteraemia and affect the endocardium. This condition can affect individuals having congenital heart disease, valvular heart disease, hypertrophic cardiomyopathy, rheumatic heart disease, heart valve replacement, pacemaker, immunocompromised patients, etc. While up to 90% of IE are caused by gram-positive *Staphylococcus sp.* (species), *Streptococcus sp.* and *Enterococcus sp.*,Streptococcal infections by the oral viridans group (e.g., *S. mutans*, *S. mitis*, *S. anguinis*) cause almost 20% of infective endocarditis.[7]

Diabetes Mellitus:

The microbiota composition is closely related to Type 2 Diabetes Mellitus. Research shows that even if there is no oral problem, the composition of oral flora and its metabolites in patients with T2DM have changed compared with healthy people,such as *Porphyromonas gingivalis* and *Prevotellamelanogeneica* are significantly enriched.[8]There has recently been

much emphasis on the 'two-way' relationship between diabetes and periodontitis. That is, not only is diabetes a risk factor for periodontitis, but periodontitis could have a negative effect on glycaemic control. Accumulation of AGEs in the periodontal tissues is likely to play a role in upregulating periodontal inflammation in individuals with diabetes. Binding of AGE to its receptor (RAGE) results in the upregulated production of inflammatory mediators such as IL-1β, TNF-α and IL-6. AGE formation results in the production of ROS and enhances oxidant stress, and the subsequent endothelial cell changes that occur contribute to the vascular injury implicated in many diabetes complications. AGEs also enhance the respiratory burst in PMNs, which has the potential to significantly increase local tissue damage in periodontitis. Furthermore, AGEs have detrimental effects on bone metabolism, leading to impaired repair and bone formation and decreased extracellular matrix production. Both type 1 and type 2 diabetes mellitus are associated with elevated levels of systemic markers of inflammation. Elevated serum levels of IL-6 and TNF-α have been demonstrated in diabetes, and serum levels of IL-6 and C-reactive protein (CRP) have been shown to predict future occurrence of type 2 diabetes mellitus. Elevated levels of CRP are also associated with insulin resistance, type 2 diabetes mellitus and cardiovascular disease. TNF-α and IL-6 are the main inducers of acute-phase proteins, including CRP, and both have been shown to impair intracellular insulin signalling, potentially contributing to insulin resistance. Serum levels of IL-6 and CRP are also raised in patients with periodontitis, with IL-6 levels correlating with the extent of disease. The systemic inflammation that is associated with periodontal disease may therefore enhance the diabetic state. [9]

Renal Disease:

Chronic Kidney Disease (CKD) is characterized by a gradual decline in kidney function; however, the changes in oral microbiota and its association with CKD progression has not been widely studied. Oral bacteria, particularly *Porphyromonas gingivalis*, *Treponema denticola*, and *Streptococcus mutans*, are key contributors to periodontal disease and dental caries. These bacterial infections can lead to tooth loss and spread throughout the body, worsening other diseases, including chronic kidney disease (CKD). Study by Ysuno et. al. demonstrated higher rates of periodontal disease in CKD patients, especially those in advanced stages. The bacteria linked to periodontal disease, including the "red complex" (*Porphyromonas gingivalis*, *Tannerellaforsythia*) and "orange complex" (*Fusobacterium nucleatum*), vary depending on CKD stage. CKD stage 5D, requiring renal replacement therapy, showed increased levels of *Streptococcus*, linked to caries. CKD patients have weakened immunity, which increases their susceptibility to infections, including those from periodontal bacteria, potentially leading to renal damage.[20]

Oral Cancer:

Microorganisms have been shown to have a complex association with cancer development. While cancer is typically attributed to a combination of genetic and environmental factors, microbes are estimated to be involved in approximately 20% of human cancers. Crosstalk between microbial species also influences cancer pathology, acting on DNA stability, microenvironment composition, tumor promotion, and activation or avoidance of cancer immunity. Oral microbiota significantly contributes to tumor growth, invasion, and spread. Similarly, the diverse gut microbiota influences overall cancer progression and also impacts

how patients respond to chemotherapy, radiotherapy, and immunotherapy. The interactions between the oral and intestinal microbiota are complex, unstable, and interconnected.In the 1990s, the relationship between bacteria and carcinogenesis was first established by demonstrating the causative role of *Helicobacter pylori* in gastric cancer. As far as oral cancer is concerned, evidence is emerging, for the carcinogenicity of the periodontal bacteria *Porphyromonas gingivalis*and *Fusobacterium nucleatum*.[12]Both Gram-negative anaerobic pathogens could stimulate tumorigenesis via direct interaction with oral epithelial cells through Toll-like receptors (TLR) and augmented signalling via the IL-6-STAT3 axis. Infection with *F. nucleatum* induced key molecular players, such as cyclin D1 and matrix metalloproteinase-9 (MMP-9), which are involved in oral tumour growth and invasiveness. STAT3 signalling promotes initiation and progression of cancer by controlling genes responsible for suppressing apoptosis and driving proliferation, angiogenesis, metastasis and invasion. *F. nucleatum* affects many of the accepted hallmarks of cancer and can induce genomic instability by causing DNA damage; sustain proliferative signalling via LPS/TLR4 and FadA/E-cadherin signalling pathways; downregulate and silence tumour suppressor genes; avoid immune destruction by inhibiting T-cell and NK cell activities; generate pro-tumour inflammation by activating NF-κB signalling; and cause invasion and metastasis by inducing EMT.[13]

P. gingivalis has been shown to inhibit apoptosis at different levels, including activation of JAK1/STAT3 and PI3K/Akt signaling pathways, suppression of proapoptotic BCL-2-associated death promoter, blocking activity of caspase-3 and caspase-9, upregulation of microRNA-203, and prevention of ATP-dependent $P2X_7$-mediated apoptosis. [12]Tumor-colonized S. mutans stimulates the production of high levels of Kynurenic Acid (KYNA) by OSCC cells via its surface adhesion protein PAc, and then KYNA activates the Aryl Hydrocarbon Receptor and promotes the expansion and infiltration of neutrophils characterized with highly immune suppressive features in the TME, which further increases the production of IL-1β and promotes CD8 + T cell exhaustion and OSCC progression. Such interaction axis of oral bacteria-oncometabolite-neutrophil expansions -immune exhaustion induces a poor responsiveness against PD-1/PD-L1 blockade immunotherapy in OSCC rat models and is linked with poor survival of OSCC patients. [14]

Effect Of Environmental and Lifestyle Factors on the Oral Microbiome:

Cigarette smoking induces significant dysbiosis within the oral microbiome. Studies report increased Streptococcus spp., which downregulate pro-inflammatory cytokines and facilitate biofilm maturation. The hypoxic environment favours obligate and facultative anaerobes, including Prevotella, Veillonella and Actinomyces. Actinomyces modulates the prevalence of various Gram-negative taxa. Reduced redox potential and acidity promote colonization by periopathogenic anaerobes such as *Fusobacterium nucleatum*, *Treponema denticola*, and *Porphyromonas gingivalis*, contributing to periodontitis. [15]

Smokeless tobacco similarly perturbs the oral ecosystem and Nicotine enhances *Streptococcus mutans*, increasing caries risk. Streptococci also produce carcinogenic acetaldehyde. *Fusobacterium*, enriched in users, is acid-resistant and linked to colorectal and head and neck carcinomas via chronic inflammation and immune modulation.[15]

Alcohol alters oral microbiota directly and indirectly. Microbial alcohol dehydrogenase generates acetaldehyde, while ethanol disrupts antioxidant defences and enhances

inflammation. Chronic intake reduces commensals like *Moryella*, *Selenomonas*, *Bulleidia* and *Catonella*, while enriching periodontitis-associated taxa (*Filifactor*, *Lactobacillus*, *Dialister*). Alcohol also increases *Actinomyces*, *Leptotrichia*, *Cardiobacterium* and *Neisseria*, correlating with elevated salivary IL-1β, a cytokine linked to epithelial proliferation and oncogenesis. Diet strongly influences microbial dynamics as antioxidants and trace elements aid immune and microbial regulation. Fermentable carbohydrates promote biofilm and acid production. Sucrose is highly cariogenic due to its role in exopolysaccharide synthesis. Polyols like xylitol inhibit *P. gingivalis* and *A. actinomycetemcomitans*, reducing periodontal pathogenicity.[14]

Pharmaceuticals alter microbial composition via various mechanisms. Broad-spectrum antibiotics reduce diversity, enabling overgrowth of *Candida spp.*Xerogenic drugs—antihypertensives, immunosuppressants, chemotherapeutics—impair salivary flow and buffering, favouring cariogenic and periodontopathic species. PPIs, by suppressing systemic acid, promote aciduric organisms. Thus, pharmacotherapy is a key factor in oral microbial health, especially in polymedicated or immunocompromised individuals.[24] Psychosocial stress impacts the oral microbiome through immune and neuroendocrine pathways. Elevated cortisol suppresses immunity, lowers salivary IgA, and alters pH and flow, favouring pathogenic taxa. Stress-driven dysbiosis is intensified by pro-inflammatory cytokines like IL-6 and TNF-α, worsening mucosal inflammation and weakening epithelial barriers. Emerging data links stress-related microbial shifts with increased oral carcinogenic potential. [25]

Clinical Significance and Recent Advances:

The knowledge of oral microbiota and its connection to systemic diseases has significant clinical implications, particularly in the areas of prevention, early disease detection, risk assessmentand the development of novel microbial-based interventions. Understanding the role of oral bacteria in conditions like cardiovascular disease, Alzheimer's, renal diseases, etc allows for more proactive approaches in preventing these diseases. Early detection of oral dysbiosis through regular oral health check-ups could serve as an indicator for underlying systemic issues, enabling timely intervention and potentially preventing disease progression. Additionally, oral microbiota can be used to assess an individual's risk for certain diseases, guiding personalized treatment plans. By targeting specific microbial imbalances, novel microbial-based interventions, such as probiotics or antimicrobial therapies, could be developed to modulate the oral microbiome, improving overall health and reducing the burden of systemic diseases linked to poor oral health. This integrated approach emphasizes the importance of oral health as a cornerstone for preventing and managing broader health conditions, highlighting the potential for improved patient outcomes through better oral care.

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[16] Various probiotics (e.g. *Lactobacillus rhamnosus* GG, *L. reuteri*, bifidobacteria, and certain strains of *L. casei* or the *L. acidophilus*-group) are used in probiotic foods, particularly fermented milk products, or have been studied. *Lactobacilli* and *Bifidobacteria* exert benefits mainly through (1) stimulating microbiota eubiosis, (2) immunomodulation, and (3) beneficial metabolic effects. Probiotics also help boost immunity and metabolism. For immunity, strains like *L. acidophilus* and *L. casei* promote Th1-Th2 balance, *L. rhamnosus* aids wound healing, and *Akkermansiamuciniphila* supports immune responses.

Recent studies show probiotic bacteria like *Lactobacilli* can colonize the oral cavity and help restore healthy microbiota when used in products contacting the mouth rather than ingested. However, randomized clinical trials (36 up to 2021) assessing probiotics for reducing gingival inflammation in gingivitis and periodontitis showed inconsistent results. Some reported enhanced pocket closure with probiotic adjunct therapy, while others found no significant added benefit.

Bacteriophage-based therapy is a newer approach to treating oral dysbiosis. Bacteriophages, viruses that target bacteria, may help restore beneficial microbiota and induce immunomodulation. Their specificity can be genetically modified. Studies show they reduce C-reactive protein levels, upregulate IL-10, and downregulate TLR4. Research on their effects on oral microbiota is ongoing. [21]

Conclusion:

The intricate interplay between the oral microbiome, gut microbiome, and systemic health underscores the importance of maintaining microbial balance for overall well-being. The oral cavity, as a gateway to the gastrointestinal tract and systemic circulation, harbours a diverse microbial community that can significantly influence distant body systems. Dysbiosis of the oral microbiome has been implicated in the pathogenesis of several systemic diseases. Understanding the oral microbiome's role as a critical mediator in health and disease paves the way for targeted interventions and personalized medicine.

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