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Oral biofilm: Systemic and psychiatric implications

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ABSTRACT

The oral cavity, being an excellent residence for a plethora of microbes, forms biofilm in various compartments. Acting as a preferable habitat with rich nutrients and other facilities, it hosts an array of bacteria, along with members of fungi, archaea, protozoa, and viruses that naturally or accidentally reside in the oral cavity. The dysbiosis of oral microbiota induces diseases and disorders in various physiological systems, including cardiovascular, respiratory, digestive, excretory, reproductive, immune, and neurological systems, leading to various diseases and even cancer. Neurological and other disorders contribute to several psychiatric ailments. Hence, oral ill health not only leads to diseases such as periodontitis and tooth loss but might also result in unpredictable diseases, including carcinogenesis. Oral problems also lead to cognitive dysfunction, dementia, and other psychosocial embarrassments. The induction of these deadly diseases might be predicted by analyzing the oral microbial composition; therefore, the overabundance of microbes such as *Porphyromonas gingivalis* and *Fusobacterium* in the oral microbiome might be used as the bioindicator of various diseases, proving the unequivocal role of oral biofilm in the onset of various systemic and psychiatric ailments.

Keywords: systemic; psychiatric; biofilm; oral microbiota; dysbiosis; periodontal pathogen

1. INTRODUCTION

The oral cavity harbors a diverse oral microbiota in its various microhabitats, developing a dynamic ecosystem that hosts different types of microbes including bacteria, archaea, fungi, protozoa, and viruses. Following the digestive tract, it constitutes the second-largest collection of microbiota in the body. The oral cavity, encompassing both soft and hard tissues such as the tongue, teeth, gingival sulcus, cheeks, tonsils, hard palate, and soft palate irrigated by saliva, provides an excellent surface for the growth of a multitude of microbes (Zhao et al., 2017), forming a biofilm. The favorable conditions of temperature, pH, nutrient supply, and other factors facilitate their flourishing. The composition of the biofilm, along with its relationship with the host, plays a key role in maintaining good oral health (Samaranayake and Matsubara, 2017). The dysbiosis of this equilibrium marks the collapse of overall health. The oral cavity, as the gateway of microbial entry, may invite pathogenic microbes that take part in successional change in the composition of oral biofilm.

Beyond the onset of oral diseases such as caries, gingivitis, periodontitis, and tooth loss, the disseminated microbes from the biofilm may translocate to different body parts, triggering various systemic and psychological diseases (Arweiler and Netuschil, 2016).

As human microflora is found to be one of the root causes of seemingly unrelated diseases in many cases, diagnosis becomes challenging. In recent years, information about the oral microflora and oral biofilm has gained widespread importance and drawn considerable attention from researchers. This focus aims to encourage advancements in disease detection and subsequent therapeutic activities (Jia et al., 2018).

Systemic diseases, which impact the entire body and disrupt the biofunction of physiological systems, may be

initiated by the mechanistic activities of the oral microbiota. These activities, in turn, can affect the proper functioning of the neurological system, potentially leading to various psychiatric disorders.

Given the well-established association between chronic diseases and biofilm-bound microbes, understanding the role of periodontal biofilm-mediated bacteria in the progression of various systemic, neurological, and psychological diseases is crucial. In many cases, periodontitis has been linked to various systemic and psychiatric diseases, revealing a bidirectional relationship. This raises a debate on whether the periodontal microbiota acts as the initiator or just a bystander of these systemic and psychiatric diseases (Kriebel et al., 2018).

The present review involves a literature survey to explore the link between oral biofilm and various systemic and psychiatric diseases, aiming to understand the exact role of these microbes in causing such widespread abnormalities.

2. BIOFILM FORMATION IN ORAL CAVITY

The oral cavity provides an ideal environment for microbial growth, where various species thrive in the moist, nutrition-rich conditions to form biofilms.

Oral biofilms can form at the supra- and sub-gingival areas, on the dental surface, in tooth-associated spaces, and even on the implant surface, with dental plaques being the major type. It has been found that about 2×10^{11} bacteria remain present in just one gram of dental plaque, containing about 800 distinct types of microbes (Niswade, 2022). These microbes include both bacterial and nonbacterial organisms, such as mycoplasma, yeasts, viruses, and protozoa. The diversity of microbes contributes to metabolic variations in oral biofilms and adopting an exclusive living strategy as biofilm matrix-bound communities. This enables them to adapt to adverse environmental changes through alteration in gene expression. In addition, biofilm could protect them from immune reactions and the stress imposed by antimicrobial agents (Hall-Stoodley and Stoodley, 2002).

The oral cavity, acting as a gateway, regularly encounters the external microbes that, upon entry, may adhere to the buccal surface and join others to form a complex community. These microbes can exist in a free-floating planktonic form or coalesce to form a biofilm. In the biofilm state, they remain in a sessile form, shielded by extracellular polymeric substances. Biofilm formation is a dynamic process, involving multiple phases. During the dispersion stage, virulent cells often emerge from the biofilm matrix, causing infection in the host by inducing dysbiosis in the oral microbiota. As a result, plaque develops on the dental surface, between teeth and gingival crevice, extracting nutrition from the gingival fluid and making it more challenging to remove. (Donlan and Costerton, 2002). Dental plaque is a precursor to dental caries, and if left untreated, it can lead to periodontitis and tooth loss. Furthermore, dysbiosis of the oral microbiome may contribute to the development of oral cancer (Sarkar et al., 2021).

3. MICROORGANISMS IN ORAL BIOFILM

Dysbiosis of oral microbiota promotes the growth of acid-producing and acid-tolerating bacteria, especially (but not exclusively) mutants streptococci and lactobacilli (Marsh, 2010).

Bacteria in the oral cavity bind to different surface receptors by adhesin to form bacterial colonies, that, over time forms, develop into plaque containing a variety of microorganisms embedded in an extracellular matrix of polymers. Pioneer colonizing bacterial genera soon after birth, invading the oral cavity, may include *Streptococcus*, *Actinomyces*, *Lactobacillus Neisseria*, and *Veillonella*. Analysis based on 16S rRNA clones reveals major oral bacterial phyla in the core microbiome, including *Firmicutes*, *Fusobacteria*, *Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, *Chlamydiae*, *Chloroflexi*, *Spirochaetes*, *Syner-gistetes*, *Saccharibacteria* (TM7), and *Gracilibacteria* (GN02) (Perera et al, 2016; Deo and Deshmukh, 2019). The TM7 phylum lacks cultivable representatives (Aas et al., 2005). Metagenomic analysis revealed that more than 60% of the bacterial flora was the non-culturable type. This variation responds to routine and genotypic determining factors and is exclusive to an individual (Zarco et al., 2012). The oral microbiome, a dynamic entity, shows frequent compositional changes influenced by several factors such as host diet, genetic changes in bacteria due to horizontal gene transfer, and changes in the microenvironment of the various niches of the oral cavity.

Although the composition of the oral microbial community remains relatively stable in healthy individuals, it undergoes variation due to changes in food habits, environment, and overall health. The bacterial genera, particularly in the subgingival area, act as strong markers like fingerprints, enabling the identification of an individual's ethnicity (Mason et al., 2013).

In addition to the bacterial communities belonging to phyla: *Firmicutes*, *Proteobacteria*, *Fusobacteria*, *Actinobacteria*, *Bacteroidetes*, *Gracilibacteria*, *Chlamydiae*, *Chloroflexi*, *Spirochaetes*, *Synergistetes*, and *Saccharibacteria* as major inhabitants, the oral microbiome also includes a minority of fungi, viruses, archaea, and protozoa (Table 1).

4. PATHOGENESIS BY ORAL BIOFILM

The oral microflora is one of the most diversified microbiomes in the human body and plays an important role in health and disease (Wade, 2013). Apart from dental plaque, dental caries, periodontitis, and tooth decay, different types of diseases and disorders are associated with oral biofilm, which might be both systemic diseases and psychiatric disorders.

Microbes always enter the body from the oral cavity, including movable microbiomes that could spread various infections. Apart from dental caries and periodontitis, this microbial migration could lead to various types of systemic diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), atherosclerosis, infective endocarditis, cardiovascular diseases, diabetes, adverse pregnancy outcome, respiratory diseases, even cancer (Kriebel et al., 2018; Wingfield et al., 2021).

Table 1. Microbial residents of the human oral cavity

Microbial type	Microbial genera	References
Bacteria	*Abiotrophia*, *Peptostreptococcus*, *Streptococcus*, *Stomatococcus*, and *Actinobacteria*	Malhotra, 2019; Idris et al., 2017
	Actinomyces, *Bifidobacterium*, and *Corynebacterium*	Contaldo et al., 2021
	Eubacterium, *Lactobacillus*, and *Propionibacterium*	Deo and Deshmukh, 2019
	Pseudoramibacter, *Rothia. Lactobacillus*, *Neisseria* and *Veillonella*, *Porphyromonas*	Avila et al., 2009
	Neisseria, *Veillonella*, *Capnocytophaga, Campylobacter*, *Moraxella*, *Desulfobacter*, *Desulfovibrio*, *Fusobacterium*, and *Hemophilus*,	Dewhirst et al., 2010
	Leptotrichia, Prevotella, Selemonas, Simonsiella, Treponema, Wolinella, Eikenella Bacteroides spp., *Chlamydiae, Chloroflexi*, *Synergistes jonesii, Jonquetella anthropi, Pyramidobacter piscolens*, and *Fretibacterium fastidiosum*	McCracken and Garcia, 2021
Archaea	*Methanobrevibacter oralis*, *Methanobacterium curvum*, *Methanosarcina mazeii*, and *M. smithii*	Nagarajan et al., 2018
Fungi	*Candida spp*, *C. glabrata*, *C. tropicalis*, *C. krusei* and *C. dubliniensis*, *Cladosporium*, *Aureobasidium*, *Saccharomycetales*, *Aspergillus*, *Fusarium* sp., and *Cryptococcus*	Sharma et al., 2018
	Histoplasma capsulatum, *Blastomyces dermatitidis*, *Rhizopus*, *Rhizomucor* and *Absida sp*, *and Geotrichum candidum*	Santosh et al., 2021
Virus	Human herpesvirus and human papillomavirus	Nagarajan et al., 2018; Santosh and Muddana, 2020
Protozoa	*Entamoeba gingivalis* and *Trichomonas tenax*	Nagarajan et al., 2018; Yaseen et al., 2021; Jiao et al., 2022

5. SYSTEMIC DISORDERS

Cumulative evidence supports the connection (Figure 1) between the oral microbiota and systemic diseases in humans (Graves et al., 2019). The active oral biofilm collaborates with the host to reveal information on immunological status and metabolism through bidirectional communication along the oral cavity and systemic organs (Peng et al., 2022). Once detached from oral biofilm, microbial cells disseminate from the oral cavity to systemic organs through blood vessels by metastatic movement, metastatic injury caused by oral microbial toxin, or immunological damage by oral microorganisms (Li et al., 2000). Virulent strains from the oral cavity travel to the intestine through the digestive tract or blood, resulting in many systemic diseases (Li et al., 2019). Hence, periodontal disease is considered to be an initiation factor for a variety of systemic diseases (Falcao and Bullón, 2019). On the other hand, systemic diseases such as diabetes, RA, and systemic lupus erythematosus (SLE) in turn, can increase vulnerability to periodontal diseases (Graves et al., 2019).

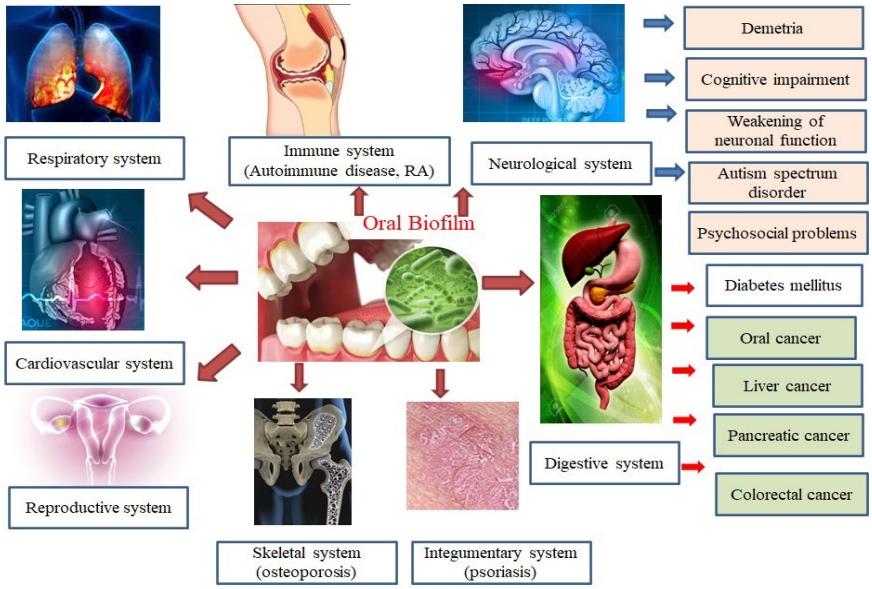

Figure 1. Association between oral biofilm and various physiological systems of the human body

5.1 Diseases of the cardiovascular system

A meta-analysis from about eighty-six thousand patients indicated that individuals with periodontal disease had a higher chance of developing coronary heart disease (CHD) (Bahekar et al., 2007). An interrelationship was observed between the formation of subgingival biofilm with periodontal pathogens and the development of acute myocardial infarction (Nikolaeva et al., 2019). *Streptococcus sanguinis,* typically remains present in dental plaque, was associated with CHD, whereas *Streptococcus mutans* were found to produce biofilm on heart valves, contributing to the development of infective endocarditis. Hence, dental caries and periodontitis were found as potential contributors to acute myocardial infarction (Kaisare et al., 2007).

Evidence strongly supports a close association between oral bacterial diseases and coronary artery disease, an inflammatory disorder characterized by the narrowing of coronary arteries due to atherosclerotic plaque formation (Chhibber-Goel et al., 2016). It was found that DNA from periodontitis-causing bacteria like *P. gingivalis*, *A. actinomycetemcomitans*, *Prevotella intermedia*, and *T. forsythia*, were found in the atherosclerotic plaques of humans, revealing the fact that these oral biofilm-forming bacteria disseminate from the oral cavity and move through the blood vessels to a distant part of the body and take residence in cardiac tissue. Dysbiosis of the oral microbiome is implicated several chronic diseases in the body, including endocarditis (Li et al., 2000). Many epidemiological studies strongly suggest that periodontitis might be a risk factor for CHD (Beck et al., 1999). *P. gingivalis*, the main causative agent of periodontitis, could induce platelet aggregation in human blood, leading to thrombus formation. Similarly, mice infected with *P. gingivalis* and *Treponema denticola* were found to suffer from alveolar bone loss and aortic atherosclerosis (Chukkapalli et al., 2014).

Several studies confirmed that periodontitis may be a risk factor for cardiac diseases. Generally, the most causative microbial genera for inducing coronary diseases are *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia*, *Eikenella corrodens*, *Fusobacterium nucleatum* and *Campylobacter rectus*, *Porphyromonas endodontalis*, *Prevotella intermedia*, *Prevotella nigrescens*, but only *P. gingivalis* expresses virulence factors that could induce platelet aggregation and clot formation (Bui et al., 2019). The increased presence of periodontal bacteria, through direct colonization of the arterial walls, enhances the chance of developing CHD and consequent cardiac arrest.

5.2 Diseases of the respiratory system

Periodontal pathogens can induce various respiratory infections, as the pathogenic bacteria residing in the oral cavity may act as a respiratory pathogen. While bacteria like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae* normally colonize the respiratory tract, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*—known for causing nosocomial pneumonia—are not common residents of the oropharyngeal area. However, they are found in large numbers on the teeth of elderly people or serious patients. The oral biofilm triggers an inflammatory response, which in turn, leads to inflammation of the lung and associated region, paving the way for pathogenic colonization resulting in the actual lung infection (Paju and Scannapieco, 2007). It was found that dental biofilm acts as a reservoir of bacteria causing pneumonia. With the movement of food particles, the pathogenic bacteria manage to enter the oropharynx and thereby move to the lung, where the population of benign bacteria like *Prevotella* spp. and *Veillonella* spp. may be replaced by potentially harmful bacteria such as *P. aeruginosa* and *K. pneumonia*.

5.2.1 Cystic fibrosis (CF)

The oral cavity, especially the dorsal surface of the tongue, acts as a reservoir for bacteria that can cause pneumonia, and the biofilm formed by these bacteria contributes to chronic lung infection in CF (Biswas and Götz, 2022). Key players in the development of CF are *P. aeruginosa*, *S. aureus*, *S. maltophilia*, *A. xylosoxidans*, and *S. marcescens*. The oral cavity is suggested as a potential reservoir for *P. aeruginosa*, allowing initial colonization and subsequent recolonization in CF patients. The oral-lung axis is considered bidirectional in CF.

5.2.2 Chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease characterized by obstructed air flow. Poor dental hygiene has been associated with COPD, linking periodontitis to this respiratory condition. Patients with both conditions showed elevated circulating inflammatory cytokines and mediators such as C-reactive protein, interleukin-8, tumor necrosis factor-α, and matrix metalloproteinase. COPD condition is aggravated by the actions of new strains of bacteria like *Haemophilus influenzae* or *Streptococcus pneumonia* (Sethi et al., 2008).

Oral periodontopathic bacteria may be inhaled, leading to increased release of proinflammatory cytokines in the lower airway epithelium. This exacerbates lung inflammation, contributing to the development of respiratory diseases like COPD and pneumonia. In addition, teeth may serve as a reservoir for colonization of respiratory pathogen, further contributing to the risk of respiratory disorders.

5.3 Diseases of the integumentary system

5.3.1 Systemic sclerosis

Systemic sclerosis, also known as scleroderma, is a group of rare diseases that lead to tightening and toughening of the skin, potentially causing difficulties in the functioning of internal organs and blood vessels (Isola et al., 2017). In a survey involving 50 patients with systemic sclerosis and an equal number of healthy subjects matched for age and sex, their periodontal conditions were evaluated. Logistic regression analysis showed that patients with systemic sclerosis had a notably higher frequency of tooth loss and periodontal problems, compared to their healthy counterparts. Moreover, the severity of periodontal conditions was found to be correlated with the skin problems caused by scleroderma (Isola et al., 2017).

The dysbiotic biofilms produced by pathogenic bacteria associated with chronic periodontal diseases can lead to various dermatological diseases, either directly or by stimulating immunoinflammatory pathways (Macklis et al., 2020).

5.4 Diseases of digestive system

Although the oral cavity is contiguous to the gastrointestinal tract, the composition of natural oral and gut microbiota is

different and unique, due to the existence of an oral-gut barrier. However dysbiosis, or malfunction, of this barrier can lead to the migration of pathogenic microbes from the oral cavity to the intestine and another part of the gut, and vice versa, thereby changing the composition of both microenvironments and triggering various diseases (Park et al., 2021).

IBD, a chronic inflammatory disorder of the colon and small intestine due to dysbiosis of the gut microbiome, can result in Crohn's disease (CD) and ulcerative colitis. The presence of the oral biofilm-forming bacteria in the gut microbiome of IBD patients suggests a potential migration through the oral-gut barrier, directly influencing the pathogenesis of IBD through the oral-gut axis. *Fusobacterium nucleatum*, a common resident of the oral cavity could be rarely found in the guts of healthy individuals (Brennan and Garrett, 2019). But on account of dysbiosis, *F. nucleatum* migrates through the gastrointestinal tract or circulatory pathway and colonizes the intestine. Metabolites produced by *F. nucleatum* can induce the development of chronic inflammatory diseases in the gut (Hashioka et al., 2018; Li et al., 2019). The microbiomes in the digestive tract of IBD patients exhibited reduced diversity, with changes in microbial composition, including the loss of the bacterial phylum *Firmicutes* and increased abundance of *Proteobacteria* and *Bacteroidetes*. These changes depict a loss of natural resistance to different diseases.

Moreover, in patients of CD, oral bacterial pathogens have been observed to colonize the gut of germ-free mice. Among these invaders, *Klebsiella* is the most predominant colonizer, capable of inducing intestinal inflammation, a key event in IBD (Atarashi et al., 2017).

P. gingivalis, the keystone pathogen of periodontitis, when orally administered to C56BL/6 mice, diminished the oral-intestinal barrier function through the downregulation of tight junction proteins. This leads to significant changes in the gut microbiome composition, including an increase in the family *Clostridiaceae* (Flak et al., 2019; Kobayashi et al., 2020). Experimental mice injected with *P. gingivalis* showed intestinal inflammation, presumed to be mediated by the lipopolysaccharide of *P. gingivalis*, an endotoxins (Kobayashi et al., 2020). Both IBD patients and colitis-induced mice showed remarkable alterations in their salivary microbiota compositions, triggering inflammatory responses, and revealing the two-way communication between oral and gut microbiota (Park et al., 2021).

Observational facts reveal that inhabitant oral bacteria migrate to the alimentary canal primarily through enteral routes. They colonize and contribute to the development of various diseases such as CD, IBD, colitis, and even colon cancer. However, the reason behind such ectopic colonization and consequent pathogenicity is still elusive.

5.5 Cancer

There is much evidence that confirms the direct or indirect contribution of oral microorganisms in the induction of cancer. (Zhou et al., 2018). Oral microorganisms could either secrete polysaccharides or apply their flagella to adhere to the surface of tumor cells in large numbers. This brings about chronic inflammation and induces the secretion of cytokines which directly promotes the growth of tumor cells (Peng, et al., 2022). Major oral pathogens, like *P. gingivalis* and *F. nucleatum*, could endorse pathways that trigger carcinoma development. Since in the human body the microbiota works synergistically, more research is required to find out the complex mechanisms behind the impact of bacterial microbiota on cancer development.

5.5.1 Oral cancer

Oral squamous cell carcinoma (OSCC), representing 90% of all human cancers, is a common cancer of the head and neck area. Dysbiosis in the oral microbiome leads to inflammation that drives OSCC through the direct metabolism of carcinogens (Chattopadhyay et al., 2019). Chronic inflammation, prompted by biofilm-mediated infections, has a significant effect on multistage carcinogenesis, namely, induction, progression, invasion, and metastasis (Grivennikov et al., 2010). Since the periodontal pathogenic bacteria, *P. gingivalis* and *F. nucleatum,* play an important role in the development of cancer (Tuominen and Rautava, 2021). Biofilm-forming bacteria are known to be the main starting factor for oral carcinogenesis (Perera et al., 2016).

5.5.2 Pancreatic cancer

Among cancer-associated deaths worldwide, pancreatic cancer is the fourth major fatal malignant disease (Fu et al., 2018) and it maintains a connection between oral dysbiosis and the enhanced danger of pancreatic and liver diseases. Elevated numbers of certain oral bacteria, particularly *P. gingivalis* (Öğrendik, 2017), along with high levels of blood serum antibodies, against this bacterial species, reveal the involvement of these pathogens with the occurrence of pancreatic cancer and cirrhosis of the liver (Mohammed et al., 2018).

High-throughput genomic sequencing studies have identified the presence of *P. gingivalis* in the human pancreatic duct in patients with high risk of pancreatic cancer. Similarly, many experimental observations have revealed that individuals with higher titers of circulating antibodies against various oral bacteria are at a greater risk of pancreatic cancer (Mohammed et al., 2018).

Another study reveals the presence of dense polyspecies bacterial biofilm, comprised of various genera of oral bacteria, in the pancreatic duct. This biofilm may include *P. gingivalis*, *A. actinomycetemcomitans*, *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola. P. gingivalis*, in particular, can attack the host immune system, disrupting signaling pathways through cytokine and receptor degradation. Additionally, both *P. gingivalis* and *A. actinomycetemcomitans* are capable of initiating Toll-like receptor (TLR) signaling pathways, a crucial promoter of pancreatic cancer in animals (Ramadan et al., 2020).

5.5.3 Liver cirrhosis and hepatic cancer

Liver cirrhosis is the histological transformation of hepatic tissue into nodular tissue. Clinical cases demonstrate an association between periodontitis with liver cirrhosis, hepatocellular carcinoma, and pre-cirrhotic non-alcoholic fatty liver disease (NAFLD). In mice, *P. gingivalis* was found to promote NAFLD towards non-alcoholic steatohepatitis (Albuquerque-Souza and Sahingur, 2022).

The microbial composition of the oral cavity is more diversified in patients with liver cancer than in healthy people. The abundance of *Haemophilus*, *Streptococcus*, and *Pseudomonas* is much lower, compared to the *Bacillus*, *Leptotrichia*, *Actinomyces*, and *Campylobacter* (Lu et al.,

2016). Researchers have identified various bacteria including *Fusobacterium*, *Veillonella*, *Streptococcus*, *Lactobacillus*, and *Megasphaera* strains, originating mostly from the mouth, that use the oral route to invade the gut, contributing to the development of liver cirrhosis (Qin et al., 2014).

A significant change in microbial composition on the tongue covering in liver cancer patients has been identified, and this change in tongue microbiota may serve as a new technique for detecting liver carcinoma (Lu et al., 2016).

A large number of oral microbes, including *Veillonella*, *Streptococcus*, *Prevotella*, *Haemophilus*, *Lactobacillus*, and *Clostridium* are generally found in the intestine of patients with liver cirrhosis (Peng et al., 2022). The intrusion of *P. gingivalis* into the intestine can bring about a change in the composition of the gut microbiome, increase the permeability of the intestinal mucosa, facilitate the spread of intestinal bacteria to the liver, and upsurge the content of triglycerides in liver tissue.

5.5.4 Colorectal cancer

Oral microbiota stimulates ectopic colonization and produces microbial metabolites to disturb immunologic balance and thereby bring about the development of colorectal cancer and adenomas (Ito et al., 2015). *Fusobacterium* from the oral cavity is found to be the pioneer bacterium for the induction of colorectal cancer. Pathogenic biofilm-forming bacteria of the oral cavity such as *Porphyromonas*, *Fusobacterium*, *Faecalibacterium*, *Treponema*, *Streptococcus*, and *Rothia* play important roles in the development of colorectal carcinogenesis. Hence these bacteria might act as noteworthy diagnostic tools for colorectal cancer (Zhang, et al., 2020).

5.5.5 Lung cancer

Yan and co-workers were the first to demonstrate the connection between buccal microbiota and lung cancer, as they share a similar pathogenesis of oral microbiota dysbiosis (Yan et al., 2015). Some oral bacteria are found to be potential biomarkers for lung cancer. It was found that some bacteria, like *Blastomonas* and *Sphingomonas,* were found to be significantly higher in the oral microbiota of lung cancer patients, while *Acinetobacter* and *Streptococcus* were higher in the healthy subjects (Pu et al., 2020).

From the above discussion, it is clear that the most prominent oral pathogens showing carcinogenic effects include *Porphyromonas gingivalis* and *Fusobacterium nucleatum* along with other bacteria like *Streptococcus* sp., *Prevotella* sp., *Capnocytophaga gingivalis*, and *Peptostreptococcus* sp. It was found that their carcinogenicity on human cells is accomplished through one of three mechanisms: chronic inflammation, stimulation of cellular growth through activation of NF-κB along with prevention of apoptosis, or production of carcinogens (Karpiński, 2019).

5.6 Other systemic diseases

Both immune and endocrine systems play important role in regulating the dynamics of oral microflora. In the oral cavity, the immune system not only harmonizes with the ecology of commensal bacteria, fungi, and viruses but also defends against pathogenic microbes (Idris et al., 2017).

Again, the sex steroid hormones secreted into saliva and entering the oral cavity can initiate physiological responses from oral tissues, with potential clinical implications, such as gingival inflammation and bleeding. These hormones and their changes affect not only oral host cells but also oral microorganisms (Cornejo et al., 2021), leading to various systemic disorders.

5.6.1 Diabetes mellitus

Numerous studies indicate that diabetic patients are more susceptible to periodontitis-like oral complications. Conversely, the chance of periodontitis increases by two to three folds in people with diabetes, indicating a bidirectional relationship between periodontitis and diabetes (Preshaw and Bissett, 2019). Experimental observations with animal models of periodontitis have elucidated the mechanisms by which periodontitis could enhance insulin resistance, leading to glucose intolerance/DM (Barutta et al., 2022).

There is a clear relationship between the degree of hyperglycemia and the severity of periodontitis as it is associated with higher glycated hemoglobin HbA1c levels. Hyperglycaemia brings about the disbalance of oral microbial equilibrium, with a notable enhancement in the population of bacterial genera of *Staphylococcus*, *Leptotrichia*, *Bulleidia*, and *Catonella* imparting alveolar bone loss (Wang et al., 2019). It was found that oral administration of periodontal pathogens like *P. gingivalis* and *Actinobacillus actinomycetemcomitans* can induce insulin resistance and glucose intolerance in mice fed with a high-fat diet (Tian et al., 2020).

5.6.2 Autoimmune diseases

Autoimmune disease is the disease caused by the failure of the body to discriminate between self and non-self and consequent destruction of self-tissue. Recently, researchers have discovered the association between autoimmune disease and microbiomes, and dysbiosis as a biomarker for autoimmune diseases (Zorba et al., 2020). Microbiome analysis technology indicates the association of microbiomes with different autoimmune diseases like SLE, RA, psoriatic arthritis, ankylosing spondylarthritis, giant cell arteritis, CD, Type 1 diabetes, psoriasis, Behcet disease, Sjögren's syndrome, and Kawasaki disease (Coit and Sawalha, 2016).

There is significant evidence to advocate that the periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are regarded as autoimmunity triggers for RA. On the other hand, patients with RA are found to have a higher incidence of periodontitis compared with healthy individuals (Fuggle et al., 2016).

It is evident that the dysbiosis of oral microbiota has a direct influence on the development of major auto-immune diseases and in-depth researches reveal that oral pathogens affect the host immune system through molecular mimicry, epitope spreading, TLRs, and antigen persistence, although the exact mechanism is yet to be established (Zorba et al., 2020).

5.6.3 Chronic kidney disease (CKD)

Periodontal therapy can reduce the systemic inflammatory burden in CKD patients. On the contrary, CKD exerts an overall negative impact on the patient's oral health. It could be inferred that there remains a bidirectional relation between CKD and oral biofilm-mediated periodontal disease (Wahid et al., 2013).

5.6.4 Osteoporosis

Osteoporosis is considered a systemic disease developed due to the microarchitectural deterioration of bone tissue. This gradually leads to bone brittleness and ultimately bone loss with a greater risk of fracture (Contaldo et al., 2020).

5.7 Menstruation and pregnancy

A compositional variation of the oral microbiome during the menstrual cycle was found which is further influenced by the plasma level of estradiol as oral, microbiota composition could be regulated by estrogen levels (Bostanci et al., 2021).

Estrogen receptor-beta has been detected in the oral mucosa and salivary glands (Valimaa et al., 2004), and for estrogen deficiency in menopausal women, there is a significant change in the oral microbiome (Vieira et al., 2017).

During pregnancy, due to immunologic and hormonal changes, a change in oral microbiota occurs. Researchers found a close association between periodontitis and pregnancy-associated oral dysbiosis (Ye and Kapila, 2021). It is found that the composition of the oral microbiota experiences a pathogenic change during pregnancy, which is mediated by female steroids like oestradiol and progesterone (Lin et al., 2018). In pregnant women oral microbiota is dominated by genera *Porphyromonas*, *Neisseria*, and *Treponema* (Ye and Kapila, 2021).

It was proven from a study that maternal periodontal disease could bring about premature childbirth with low birth weight (Alves and Ribeiro, 2006). On the other hand, oral bacteria could be detected in the uterus of women experiencing miscarriage or stillbirth (Mitchell-Lewis et al., 2001). Hence, periodontitis might be a risk factor for pregnant women (Priyanka et al., 2019).

Although the mechanism involved in the transmigration of periodontal pathogens to extraoral spots and the development of diseases there is yet to be clearly understood, it is clear that the oral cavity-borne pathogens attack different systems to give rise to various systemic diseases, some of them might be fatal (Table 2).

6. PSYCHIATRIC DISORDERS

Recent findings revealed the fact that dysbiosis of the oral microbiome causes various neurological and psychiatric disorders since these microbial communities maintain bidirectional communications between the gut microbiome and the central nervous system (CNS) and are responsible for evoking significant neuroimmune chemical response (Bowland and Weyrich, 2022).

It was found that *Streptococcus mutans*, an oral cavity-dwelling dental caries-causing bacteria with collagen-binding ability enters the blood vascular system from the oral cavity and finally reaches the brain, damaging the blood-brain barrier. In the brain, they bind the collagen of blood capillaries of the brain, leading to cerebral hemorrhage (Watanabe et al., 2016).

Similarly, another normal oral bacteria, *Porphyromonas gingivalis*, reaches the brain, forms a biofilm, and secrete gingipains, a neurotoxic protease that disrupts amyloid precursor protein (APP), resulting in the formation of abnormal amyloid plaques in the brain promoting neuronal death, which might result in extreme mental fatigue (Dominy et al., 2019).

This bacterium could directly promote disease development through the disruption of APP, causing subsequent Aβ accumulation (Bulgart et al., 2020).

After screening the alpha and beta diversity of salivary microbiota of healthy individuals and patients with major depressive disorder, it was found that there is a clear distinction between the microbial composition between these two. It was reported that in depressive patients, the salivary microbiota contains a few unique species like *Prevotella nigrescens* and *Neisseria* spp (Wingfield et al., 2021).

A link between oral community changes and initiation of mental health disorders, like anxiety and depression, was reported, contributing by the differential abundance of specific bacterial taxa, including *Spirochaetaceae*, *Actinomyces*, *Treponema*, *Fusobacterium*, and *Leptotrichia* spp (Simpson et al., 2020). They even reported the plausible connection between microbiota composition (not diversity) and mood change, which is further affected by C reactive protein and cortisol hormone. The change in microbiome, especially the inclusion of a few exclusive species is so obvious in patients with anxiety and depression, that oral microbial composition, might be considered as a potent biomarker for the diagnosis of several psychological disorders (Wingfield et al., 2021).

Scientists realized the existence of the oral-microbiota-brain axis (OMBA) since the oral microbiome is intimately related to the development of neuropsychiatric disorders (NPDs). The oral pathogens play key roles in the development of oral microbe-associated dysbiosis and oral disease and play critical roles in the production of pro-inflammatory cytokines. Systemic inflammation could induce alterations in neurovascular functions, increasing the blood-brain barrier permeability. Hence neuroinflammatory response bridges the oral microbes and the CNS by bringing about neuronal loss and synaptic deficits, which ultimately cause cognitive impairment (Bowland and Weyrich, 2022).

It was found that smoking-induced dysbiosis of the oral microbiome causes alteration in functional connectivity of the brain through modification of neurotransmitter signaling pathways, which include tyrosine metabolism and the production of glutamate-glutamine and glutamatergic synapse. It weakens the functional network connectivity between networks involved in cognitive control and information processing in smokers (Lin et al., 2019).

Table 2. Probable relationship between oral pathogens and various systemic and psychiatric diseases

System affected	Diseases	Relationship with oral bacteria	References
Cardiovascular	Coronary heart disease	*Streptococcus sanguinis*	Martini et al., 2020
	Infective endocarditis	*Streptococcus mutans*	Nakano et al., 2008
	Myocardial infarction	*S. mutans*	Kaisare et al., 2007
	Atherosclerosis	*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Tannerella forsythia*	Chukkapalli et al., 2014
	Internal clot formation	*P. gingivalis,*	Bui et al., 2019
Respiratory	Inflammation of the lung and associated region	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*	Paju and Scannapieco, 2007
	Cystic fibrosis	*P. aeruginosa*, *S. aureus*, *S. maltophilia*, *Achromobacter xylosoxidans*, and *Serratia marcescens.*	Biswas and Götz, 2022
	Chronic obstructive pulmonary disease	*Haemophilus influenzae Streptococcus pneumonia*	Sethi et al., 2008
Integumentary	Systemic sclerosis	*P. gingivalis*	Isola et al., 2017
	Psoriasis	*Streptococcus pyogenes*	Macklis et al., 2020
	Lichen planus	*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola*	Macklis et al., 2020
	Aphthous stomatitis	*Bacteroidales*, *Porphyromonadaceae* and *Veillonellaceae*	Macklis et al., 2020
Digestive	Intestinal bowel disease	*Fusobacterium nucleatum*	Brennan and Garrett, 2019
	Crohn's disease	*Klebsiella sp*	Atarashi et al., 2017
	Intestinal bowel disease and colitis	*P. gingivalis,*	Park et al., 2021
Cancer	Oral squamous cell carcinoma	*P. gingivalis* and *F. nucleatum*	Tuominen and Rautava, 2021
	Pancreatic cancer	*P. gingivalis*	Öğrendik, 2017
	Liver cirrhosis and hepatic cancer	*P. gingivalis*	Mohammed et al., 2018
		Fusobacterium, Veillonella , *Streptococcus*, *Lactobacillus* , *Megasphaera* sp	Qin et al., 2014; Peng et al., 2022
	Colorectal cancer	*Porphyromonas*, *Fusobacterium, Faecalibacterium, Treponema, Streptococcus and Rothia sp*	Zhang et al., 2020
	Lung cancer	*Blastomonas* and *Sphingomonas*	Pu et al., 2020
Other autoimmune nervous and psychiatric diseases	Diabetes mellitus	*P. gingivalis*, *A. actinomycetemcomitans*	Tian et al., 2020
	Rheumatoid arthritis	*P. gingivalis*, *A. actinomycetemcomitans*	Fuggle et al., 2016
	Extreme mental fatigue	*P. gingivalis*	Dominy et al., 2019
	Depression	*Prevotella nigrescens Neisseria* spp	Wingfield et al., 2021
	Depression	Spirochaetaceae, Actinomyces, *Treponema, Fusobacterium* and *Leptotrichia* spp	Simpson et al., 2020
	Autism spectrum disorder	*Prevotella*, *Selenomonas*, *Porphyromonas*, and *Fusobacterium*	Olsen and Hicks, 2020
	Alzheimer's disease	*Fusobacterium nucleatum*	Liu et al., 2023

Recent researches indicate that the detection of a specific relation between oral microbiome and brain circuit function is becoming a prerequisite for reviewing psychiatric disorders. It is found that there is a close association between oral microbiota and autism spectrum disorder (ASD), a neurodevelopmental disorder causing difficulties in verbal and nonverbal communication, restricted interests or activities, and repetitive patterns of behavior. It is confirmed by the fact that the children suffering from ASD possess lower oral bacterial diversity than their normal counterparts. ASD children were found to have a greater number of bacteria associated with periodontal disease, immune activation, and inflammatory response like *Streptococcus* and *Haemophilus*, but a lower number was found in the dental biofilm of children with ASD whereas a relative number of other bacteria such as *Prevotella*, *Selenomonas*, *Porphyromonas*, and *Fusobacterium* become increased. This reveals the role of certain oral microbiota in aggravating ASD symptom. (Olsen and Hicks, 2020). The same afferent signaling pathway coordinates the association between gut microbes and the brain through the oral microbiome via the vagus and trigeminal nerve complex (Bonaz et al., 2018; Goellner and Rocha, 2020).

6.1 Alzheimer's disease (AD)

A neurodegenerative disorder and the most common form of dementia, AD is thought to have some association with the imbalance of the oral microbiome, although the direct connection is yet unclear. A team of researchers from Tufts University has found a correlation between gum disease and *Fusobacterium nucleatum* and AD via a mouse study. Scientists believe their findings might help reduce the progression of both periodontal disease and this form of dementia. Current evidence moderately supports the association between oral bacteria and AD, as pre-clinical evidence reveals the role of oral bacteria in the pathogenesis of AD, while clinical studies show diverse results (Liu et al., 2023).

Accumulated evidence indicates that the OMBA, oral peri pathogens could induce anxiety- and depressive-like behaviors, as well as trauma- and stress-related disorders. Pre-clinical studies reveal the direct role of periodontal bacteria in the development of NPDs, namely major depressive disorder and schizophrenia (Martínez et al., 2022).

6.2 Psychosocial problems

Oral biofilm formation due to poor dental health lowers self-confidence and, in turn, gives rise to various psychological problems (Ray, 2022). Halitosis, a severe problem of bad oral smell, has an immense impact on psychological and social well-being. Oral malodor is generated in an unwashed mouth, as an uncleaned tongue harbors various periodontal microbes like *Porphyromonas gingivalis*, *Fusobacterium*, and *Prevotella intermedius,* producing volatile sulfur compounds that give rise to halitosis. Hence, oral biofilm could affect mastication function, speech, smile, and overall mental condition, thereby deteriorating the quality of life (Mathur and Dhillon, 2018).

7. CONCLUSION

The alteration in the composition of oral microflora is an indicator of the initiation of various diseases, which might involve various physiological systems or even affect the psychology of an individual. The close relation between the oral ecosystem and the homeostasis of the body reveals the irrefutable role of the oral microbiome in orchestrating the physiological and psychological balance of the entire body. Hence, the analysis of the fluctuation of oral microbial composition could be used as a non-invasive diagnostic tool for any future disease in the body. Also, the compositional variation of oral biofilm must be understood for taking proper therapeutic measures and for future targeted drug designing against personalized health care.

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