Review Article

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Oral Microbiome: A Gateway to Systemic Diseases Insights

Dentistry Section

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ABSTRACT

The human mouth is said to be a mirror of a person's health and serves as a host to an array of microorganisms that play a crucial role in both disease and health. Different sites in the oral cavity harbour distinct genera of microorganisms, which have been meticulously explored over the years and thoroughly investigated to meet the needs of scientific organisations and research centres in establishing the association between oral microbiomes and systemic diseases. Systemic diseases are often linked to disruptions in the microbial population, and certain conditions appear to be related to oral bacteria. These processes may impact or reflect overall human health. Systemic pathophysiology can broadly be governed by immune and inflammatory factors, virulence factors of pathogens, and systemic dissemination. The oral microbiome, on one hand, acts as a protective barrier by reducing the population of pathogenic bacteria; on the other hand, it can itself function as a pathogenic entity, exacerbating or accelerating existing pathologies. Therefore, understanding the dysbiosis of the oral flora and its involvement in systemic diseases is of great importance. The present review highlights the pathways and subsequent impact of the oral microbiome on systemic health and disease.

Keywords: Dysbiosis, Health, Metabolic diseases, Mouth, Microbiology, Periodontitis

INTRODUCTION

The flora present in the human mouth has recently been recognised as the "oral microbiome." This term was proposed by Joshua Lederberg in 2001 to describe the ecological microspheres of symbiotic, commensal, and pathogenic microorganisms [1]. The oral cavity harbours various complex microbial communities such as bacteria, fungi, bacteriophages, protozoa, viruses, and archaea [2]. Approximately 700 species of microorganisms are present in the oral cavity [3].

The oral microbiome is one of the most intricate and essential ecological niches in the human body and has been rightly identified as one of the five key areas of research in the Human Microbiome Project, along with the nasal cavity, vagina, intestine, and skin [4].

Equilibrium in the oral mucosa is maintained through a complex interplay between symbiotic bacteria and the host's defense mechanisms. Disruption of this homeostasis leads to dysbiosis and subsequent disease states characterised by inflammation [5].

In 1891, Miller WD, a pioneer in oral microbiology, hypothesised the focal infection theory, suggesting that microbial infections originating in the oral cavity could spread to other areas of the body and potentially cause diverse systemic diseases [6].

The oral cavity communicates with the entire body through its microbiome [7]. In fact, a focal point of inflammation caused by oral dysbiosis may contribute to sustaining systemic low-grade inflammation [8]. This may aggravate certain intrinsic diseases, resulting in significant morbidity. The human oral microbiome thus plays an intricate role in determining an individual's health status and may contribute to novel therapeutic and preventive approaches in treatment planning. Due to its systemic dissemination, the oral microbiome serves as a mirror of overall systemic health.

The aim of present narrative review is to present how the oral microbiome acts as a gateway, providing insight into various systemic diseases such as diabetes, obesity, breast cancer, rheumatoid arthritis, osteoporosis, Alzheimer's disease, autism spectrum disorders, colorectal cancer, cardiovascular disease, pancreatic cancer, oesophageal cancer, cystic fibrosis, and adverse pregnancy outcomes.

ORAL MICROBIOTA

The oral microbiome is the second-largest microbial reservoir in the human body [9]. The neonatal microbiota may have a prenatal origin, as maternal microbiota significantly influences the neurodevelopment of the foetus before birth [10]. After birth, the newborn comes into immediate contact with the maternal microbiota from the vagina, mouth, and skin [11].

The oral cavity contains various ecological niches, primarily consisting of soft and hard tissues [12]. Saliva plays a major role in shaping the oral microbiome and maintaining homeostasis [13]. Salivary substances such as glycoproteins provide nourishment that supports bacterial growth in the oral cavity [14]. These bacteria work synergistically, even at minimal levels, to maintain a delicate equilibrium. An inadequate salivary flow can easily result in dysbiosis [15].

Brief Pathophysiology of Dysbiosis of Oral Microbiota

Dental plaque consists of both organic and inorganic matter, as well as anaerobic and aerobic microorganisms that adhere to the surfaces of the teeth and oral mucosa. Bacteria in the oral cavity exist in two different states: planktonic (in saliva) and biofilm (in dental plaque). Bacteria found in planktonic form are able to move freely within the oral environment [16].

The Acquired Exogenous Pellicle (AEP) is an organic film that covers dental surfaces. It serves as a barrier against mechanical and acidic attacks on the teeth but can also modify the tooth surface to promote bacterial adhesion during biofilm formation. Planktonic microorganisms in saliva can attach to the AEP in two ways-reversibly and irreversibly.

Pioneer bacteria, such as *Streptococcus* species, adhere irreversibly to the AEP and begin to multiply, marking the initial stage of biofilm formation. These pioneer organisms facilitate the aggregation of secondary colonisers, which attach reversibly [17]. As the biofilm matures, a balance is established among the microorganisms. However, a gradual shift toward specific bacterial profiles can lead to dysbiosis, which may contribute to both local and systemic diseases.

Previous studies have demonstrated a relationship between certain systemic diseases and an imbalance in the oral microbiota [18]. It has been proposed that pathogenic oral microbes may enter the

bloodstream, causing complications at distant sites in the body. The key virulence factors involved in this pathophysiology include teichoic acid, flagellin, and Lipopolysaccharide (LPS), which play a role in immune system activation [19]. These bacterial components act as persistent sources of infection and inflammation, contributing to oral microbial dysbiosis.

ORAL MICROBIOME AND SYSTEMIC PATHOLOGY

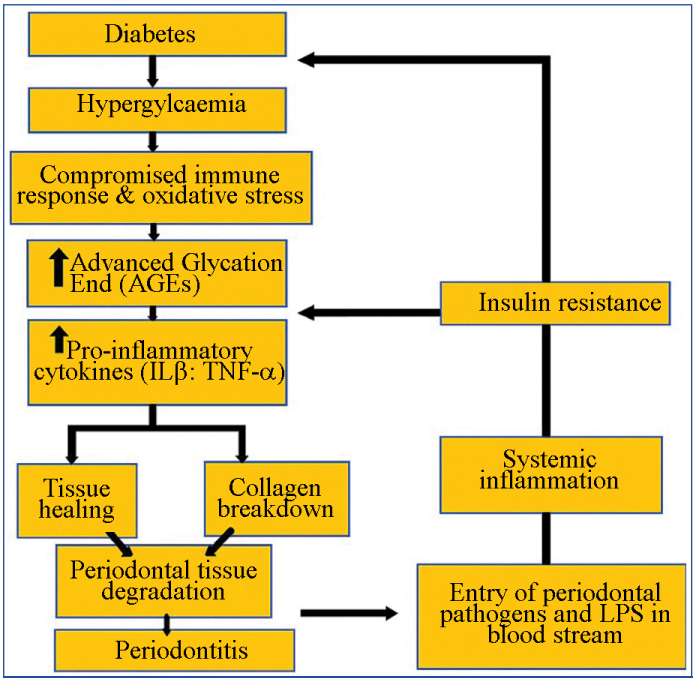
Diabetes

Diabetes is a metabolic disorder resulting from endocrine dysfunction of the pancreas, characterised by insulin deficiency or insulin resistance. It is defined by a hyperglycemic state caused by insufficient insulin secretion due to autoimmune destruction of pancreatic β-cells in Type 1 diabetes, or by uncontrolled insulin resistance in Type 2 diabetes.

In 2019, approximately 463 million people were diagnosed with diabetes globally, accounting for 6% of the world's total population [20]. Despite efforts to combat risk factors, the prevalence of diabetes has continued to rise exponentially. This increase may be partly attributed to dysbiosis of the gut or oral microbiome.

Patients with diabetes mellitus are more prone to periodontal inflammation, and uncontrolled diabetes is considered a major risk factor for periodontal disease. Periodontitis is recognised as the sixth major complication of diabetes. The incidence of chronic periodontitis among diabetic patients is two to three times higher compared to non diabetic individuals [21].

A bidirectional relationship exists between diabetes and periodontitis, as illustrated in [Table/Fig-1] [22].



[Table/Fig-1]: Two-way relationship between diabetes and periodontitis [22].
IL-β : Interleukin- beta and TNF-α : Tumour necrosis factor-alpha

Oral microbes play a significant role in the progression of diabetes through systemic immune mechanisms, stimulating the production of inflammatory mediators such as IL-6, TNF-α, and IL-1β [23]. The entry of these inflammatory mediators into circulation leads to substantial changes in blood vessels and tissues. This subsequently inhibits the gene expression of proteins involved in the insulin signaling pathway, such as Glucose Transporter type 4 protein (GLUT4) [24].

Previous studies have reported that the diabetic oral cavity exhibits a significant increase in pathogenic bacteria, including *Aerococcus, Enterobacteriaceae*, *Enterococcus*, and *Staphylococcus* [25]. The LPS of Gram-negative bacteria inhibit the transduction of insulin receptor–initiated signaling pathways, contributing to the development of insulin resistance [26].

Furthermore, doxycycline therapy, when combined with scaling and root planing, has been shown to reduce Glycated Haemoglobin (HbA1c) levels by upto 10% in diabetic patients [27].

Obesity

Obesity is associated with several chronic diseases, including type 2 diabetes, hypertension, cardiovascular diseases, and dyslipidemia. The pathogenesis of obesity is a complex interplay involving physical activity, calorie utilisation, and appetite regulation, and is influenced by genetic, environmental, and socioeconomic factors.

Researchers have identified differences in the composition of the oral microbiome between obese individuals {Body Mass Index (BMI) ≥30 kg/m^2} and normal-weight individuals (BMI 18.5–24.9 kg/m^2), with an increase in certain genera and species among obese subjects, such as *Peptostreptococcus, Solobacterium, Selenomonas noxia, Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythia* [28].

According to Suvan J et al., the severity of periodontitis is greater in obese individuals than in normal-weight individuals, regardless of oral hygiene practices [29]. Pathogens such as *P. gingivalis, T. forsythia, S. sanguinis, and C. ochracea* have been found to be increased in obese individuals with periodontitis [30].

Literature also confirms a higher prevalence and severity of periodontitis in males compared to females [31], although the extent and significance of this relationship remain subjects of debate.

Breast Cancer

Breast cancer is the most prevalent malignancy worldwide, primarily affecting post-pubertal females, according to the World Health Organisation (WHO). In 2020, more than two million women were diagnosed with breast cancer, resulting in 684,996 deaths globally [32].

The term "oncobiome" refers to the interaction between the microbiome and cancer. Certain oral bacteria and chronic inflammatory markers may enter systemic circulation and contribute to cancer progression at distant body sites.

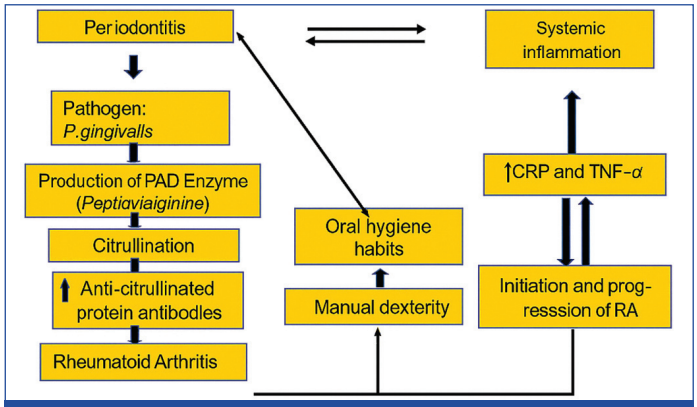
In murine models, *Fusobacterium nucleatum* has been detected in cancerous human breast tissue, where it appears to promote breast cancer progression [33]. A higher risk of breast cancer has been reported in women with periodontal disease caused by bacteria from the red complex (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia*) and the orange complex (*Fusobacterium nucleatum, Prevotella intermedia, Prevotella nigrescens, Streptococcus constellatus, Peptostreptococcus micros, Eubacterium nodatum, Campylobacter showae, Campylobacter rectus, and Campylobacter gracilis*) [34].

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic, inflammatory, autoimmune disease that primarily affects the joints and is associated with the development of autoantibodies. The periodontal microbiome has been extensively studied in relation to rheumatoid diseases, with evidence suggesting that individuals with RA are more likely to develop periodontal disease.

Periodontitis and rheumatoid arthritis share common risk factors, such as genetic polymorphisms of specific receptors and immune mediators including interferon-gamma, B lymphocytes, Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL), and Th17 (T-helper cells expressing IL-17 profiles) [35]. The presence of *Porphyromonas gingivalis* in the synovial fluid and elevated levels of inflammatory markers in the blood (e.g., C-reactive protein) are common to both conditions [36].

Patients with periodontitis are more likely to develop rheumatoid arthritis, and conversely, individuals with rheumatoid arthritis have a greater risk of periodontitis. Thus, there exists a bidirectional relationship between periodontitis and rheumatoid arthritis [Table/Fig-2] [37-39].



[Table/Fig-2]: Bidirectional relationship between rheumatoid arthritis and periodontitis [37].
PAD: Peptidylarginine deiminase; TNF-α: Tumour necrosis factor-alpha

Osteoporosis

Osteoporosis is characterised by a generalised and sustained loss of bone mineral density, resulting in increased fracture susceptibility and bone fragility, even during routine daily activities or following minor traumatic injury. Liang W et al., (2013) were the first to investigate the association between osteoporosis and oral bacteria [40].

In a large-scale study, Brennan RM et al., examined the correlation between oral bacteria and oral bone loss in 1,256 postmenopausal women and identified eight subgingival bacterial species associated with bone loss: *Tannerella forsythensis, Prevotella intermedia, Streptococcus sanguis, Eubacterium saburreum, Capnocytophaga species, Porphyromonas gingivalis, Campylobacter rectus, and Fusobacterium nucleatum* [41].

They found a strong positive correlation between specific periodontopathogens and the severity of bone loss in patients with periodontitis. Health care professionals should be aware of this interplay between bone health and oral microbiota and should encourage large-scale, longitudinal studies to further explore this area of research.

Alzheimer's Disease

Alzheimer's disease is a debilitating neurodegenerative disorder of progressive nature. Approximately 60–80% of dementia cases worldwide are attributed to Alzheimer's disease. About 2–5% of patients have familial or genetically inherited Alzheimer's disease, whereas more than 95% suffer from sporadic or late-onset Alzheimer's disease.

Histologically, Alzheimer's disease is characterised by the accumulation of senile (amyloid) plaques, caused by extracellular deposition of beta-amyloid peptide, which is cytotoxic to nerve cells. Additionally, the accumulation of hyperphosphorylated tau proteins (formerly referred to as tubulin-associated unit proteins) leads to degeneration of neuronal fibers [42].

Environmental risk factors and non modifiable genetic factors contribute to the onset and consolidation of late-onset Alzheimer's disease, which is heterogeneous and sporadic in nature. Oral microbiota dysbiosis is believed to contribute either directly, by inducing amyloid protein production, or indirectly, by promoting neuroinflammation due to bacterial invasion [43].

Cognitive impairment in Alzheimer's disease leads to reduced oral motor skills—such as impaired lip movements and swallowing—resulting in poor oral hygiene and a higher prevalence of oral diseases compared to healthy individuals.

Chronic inflammation triggers immune activation, free radical production, apoptosis, and amyloid-beta deposition [44]. Viral infections such as Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV), and Cytomegalovirus (CMV) have also been implicated in Alzheimer's disease pathology, primarily through amyloid-beta accumulation and hyperphosphorylation of tau proteins in the brain [45].

Oral microbiota can be transported from the mouth to the brain via the bloodstream during brushing, flossing, chewing, or toothpick use in patients with periodontitis, leading to bacteremia [46]. An increase in pro-inflammatory responses may weaken the Blood-Brain barrier (BBB), facilitating the penetration of bacteria, Lipopolysaccharides (LPSs), and other toxic products [47].

The LPSs of *P. gingivalis* have been detected in 12-hour postmortem brain tissue from Alzheimer's disease patients [48]. In elderly individuals, periodontitis has been found to be associated with cognitive impairment and an immunoglobulin response against P. gingivalis [49]. Serum IgG levels against several oral bacteria—*Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Fusobacterium nucleatum, P. gingivalis, P. intermedia, Tannerella forsythia, and Treponema denticola*—were also found to be elevated in Alzheimer's disease patients [50].

Autism Spectrum Disorders

Autism Spectrum Disorders (ASD) are characterised by persistent deficits in language, communication, and attention, along with restricted interests and repetitive behaviors [51].

The prevalence of ASD has been continuously increasing over the past decade. Approximately 1% of the general population is affected by ASD [52].

Oral bacteria can reduce the antioxidative capacity of the brain, leading to decreased mitochondrial energy production in individuals with ASD [53]. According to the direct mechanism, bacteria may reach the brain via the olfactory nerve through the oral cavity. In the indirect mechanism, oral bacteria enter the brain through the blood–brain barrier, perivascular spaces, and circumventricular organs. Leakage of Lipopolysaccharides (LPS) through the blood–brain barrier can lead to inflammation of the central nervous system. Elevated levels of LPS have been found to correlate with higher levels of IL-6 a pro-inflammatory cytokine [54].

Qiao Y et al., compared the oral microflora of children with ASD to that of healthy controls using sequencing methods. *Haemophilus* and *Streptococcus* were significantly more abundant in saliva and dental plaque, respectively, whereas *Prevotella*, *Porphyromonas,* and *Fusobacterium* were decreased [55]. Thus, the bacterial profile in patients with ASD did not establish a definite relationship.

Colorectal Cancer

Colorectal Cancer (CRC) is an aggressive tumour occurring in the human body [56]. Clinical studies have reported that *Fusobacterium species* are closely associated with colorectal cancer [57]. *Fusobacterium* binds to the epithelial receptor E-cadherin through adhesin FadA on the surface of cancer cells, promoting tumour cell invasion and proliferation [58]. Fusobacterium adhesin protein 2 (Fap2), another adhesin expressed by *Fusobacterium nucleatum*, inhibits the activity of immune cells, preventing the destruction of tumour cells [59]. It also affects autophagy and promotes tumour development.

The ten most common genera found in CRC include *Haemophilus, Streptococcus, Neisseria, Fusobacterium, Prevotella, Leptotrichia, Veillonella, Porphyromonas, Rothia, and Actinomyces*. These genera are also found in the oral cavity, as reported in previous studies [60]. The overall bacterial profiles in colorectal cancer patients were significantly different from those of healthy individuals.

Cardiovascular Diseases

Cardiovascular Diseases (CVDs) comprise a group of disorders affecting vascular circulation, arteries, veins, and the heart—namely endocarditis, myocardial infarction, and coronary heart disease. Atherosclerosis is closely related to the proliferation of vascular endothelial cells, which causes functional alterations. It is characterised by the deposition of lipids within the vascular endothelium, leading to the formation of atherosclerotic plaques that narrow the vessel lumen.

Research has established that periodontitis is a risk factor for cardiovascular diseases. In periodontitis, epithelial attachment breaks down through two mechanisms: one due to collagenases produced by host cells and bacteria, and another through phagocytosis of collagen fibres. Bacteria can then enter the bloodstream via connective tissue, leading to bacteremia or ectopic colonisation at distant sites. These bacteria damage immune cells, compromise both cellular and humoral immunity, and, along with the release of inflammatory mediators, damage the vascular endothelium and cause oxidative stress. This attracts macrophages, leading to foam cell formation and the eventual development of atherosclerotic plaques [61].

Porphyromonas gingivalis can colonise and invade atherosclerotic plaques. Chiu CJ et al., studied microorganisms in carotid endarterectomy tissues from 76 patients with cardiovascular disease and reported a 42% detection rate of *P. gingivalis* [62]. Evidence indicates that patients with periodontal inflammation have a greater risk of developing coronary heart disease.

Animal studies have shown that inoculation of *Porphyromonas*, a periodontal pathogen, into the oral cavity of mice led to an increase in *Bacteroides* and a decrease in *Firmicutes*, both associated with endotoxemia and inflammatory reactions [63].

Lactobacillus and *Streptococcus* species, which are early colonisers in dental plaque, show the highest detection rates in patients with infective endocarditis [64]. These bacteria can enter the bloodstream during oral hygiene practices or tissue injury. Their interaction with platelets leads to the formation of microthrombi, promoting bacterial attachment to damaged valve surfaces. Therefore, individuals with pre-existing cardiovascular conditions are more prone to endothelial damage, which facilitates bacterial colonisation and biofilm formation, ultimately leading to infective endocarditis [65].

Pancreatic Cancer

Pancreatic cancer is a fatal disease with a five-year survival rate of around 6% [66]. A systematic review demonstrated that both pathologies are linked and that the presence of periodontitis can worsen the prognosis of pancreatic cancer [67].

Fan X et al., studied the oral microbiome of pancreatic cancer patients compared with controls and found that *Porphyromonas* and *Aggregatibacter* were more abundant in patients with pancreatic cancer [68]. Another study that analysed the salivary microbiome of 108 individuals using sequencing technology reported a higher abundance of *P. gingivalis* in subjects with pancreatic cancer [69]. Based on the findings of various studies, an association can be inferred between the salivary oral microbiota and pancreatic cancer.

Oesophageal Cancer

Oesophageal cancer is one of the most commonly detected cancers worldwide [70]. This carcinoma is closely associated with Helicobacter pylori infection; however, a low frequency of tooth brushing increases its risk by nearly one-fold [71]. Poor oral hygiene is a contributing factor to epithelial dysplasia and subsequent oesophageal carcinoma. The microbial imbalance caused by poor oral hygiene may promote the accumulation of carcinogens.

Narikiyo M et al., concluded that periodontitis-causing bacteria such as Treponema may be detected in healthy tissues of subjects with oesophageal cancer and may promote tumour formation through inflammatory mechanisms [72]. Gao SG et al., reported a 61% detection rate of *P. gingivalis* in lesional areas and only 12% in adjacent tissues [73]. The severity of oesophageal cancer was positively correlated with increased levels of *P. gingivalis*. Therefore, colonisation of *Porphyromonas gingivalis* is related to both the occurrence and severity of oesophageal squamous cell carcinoma. Consequently, the salivary microbiome may serve as a biomarker in patients with oesophageal squamous cell carcinoma and may assist in its diagnosis and screening.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder caused by a defect in the transmembrane conductance regulator gene [74]. It is a common genetic disease in the Caucasian population, affecting approximately one in 3,000 newborns in the European Union [75]. Lung infections are common and can develop into severe, chronic, and life-threatening diseases due to impaired clearance of thick mucus.

Various bacteria and fungi are associated with lower airway infections in cystic fibrosis. These include *Pseudomonas aeruginosa*, *Candida albicans, Aspergillus fumigatus, Haemophilus influenzae, Staphylococcus aureus, Stenotrophomonas maltophilia, and Achromobacter xylosoxidans* [76]. Infections typically begin early in life and progressively worsen with age, with *P. aeruginosa* colonising the lungs of up to 80% of patients above the age of 18 years [77]. P. *aeruginosa* does not colonise the airways alone; it is also commonly present in the oral cavity and sputum of patients with cystic fibrosis, suggesting a potential reservoir role of the oral microbiome [78].

Several microorganisms have been linked to higher prevalence and abundance in oral rinse samples from patients with cystic fibrosis compared to healthy controls, including *Microbacterium* [79], *Streptococcus* [80], and *Candida albicans* [81].

Adverse Pregnancy Outcomes

Pregnant women experience physiological, immunological, and hormonal changes that make them more vulnerable to infections, including periodontal and dental disorders [82]. Additionally, variations in oestrogen and progesterone levels influence the oral microbiota, predisposing them to periodontitis and gingivitis. Unlike in non pregnant women, the oral microbiome undergoes a pathogenic shift during pregnancy before returning to a healthy state in the postpartum phase [83].

Fusobacterium nucleatum and *Porphyromonas gingivalis* are the most common species of periodontopathogens found in the foetal placental unit. The enzymes released by *P. gingivalis* can directly or indirectly damage foetal and maternal tissues, leading to systemic inflammatory responses [84]. Dental dysbiosis can increase the risk of adverse pregnancy outcomes such as preterm birth, hypertension, gestational diabetes, and low birth weight, as observed in cases of periodontitis [85].

Dental health professionals play a vital role in reducing the overall microbial load in patients with severe oral or periodontal diseases, educating patients about oral and systemic health, collaborating with medical practitioners to ensure better patient care, and contributing to appropriate treatment planning.

CONCLUSION(S)

The present review highlights a significant relationship between the oral microbiome and the pathogenesis of various systemic diseases, emphasising the impact of microbial dysbiosis on human health. It can be concluded that the delicate symbiosis of the oral microbiome serves as a balancing factor, and dysbiosis shifts this equilibrium from

health to disease. Future research should focus on understanding the functional relationship between the oral microbiota and systemic diseases. Such analyses will aid in developing targeted treatment strategies and personalised medical approaches, ultimately improving treatment outcomes and prognosis.

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