The emerging role of oral microbiota: A key driver of oral and systemic health

Domenico Azzolino, PhD, **Alessia Felicetti**, BSc, **Luigi Santacroce**, MD, **Tiziano Lucchi**, MD, **Franklin Garcia-Godoy**, DDS, MS, PhD,PhD & **Pier Carmine Passarelli**, DDS

Abstract: Purpose: To describe the existing literature on the emerging role of the oral microbiota in shaping both oral and systemic health. **Methods:** A narrative review was performed. PubMed, EMBASE and Scopus databases were searched for relevant articles published in the English language. **Results:** The oral microbiota plays a crucial role in both oral and systemic health, yet its composition and functions have been underexplored compared to the gut microbiota. The oral cavity harbors a diverse range of microorganisms, including bacteria, fungi, viruses, archaea, and protozoa, which interact within biofilms to influence oral health. The microbiome is influenced by various factors such as diet, oral hygiene, smoking, alcohol consumption, socioeconomic status, pregnancy, and genetics. Dysbiosis in the oral microbiota has been linked to a range of oral diseases, including dental caries, periodontal diseases, oral candidiasis, and even oral cancer. Additionally, oral bacteria can impact systemic health, with emerging associations to cardiovascular disease, respiratory conditions, and various cancers. Effective management of oral dysbiosis involves strategies such as mouthwashes, dietary modifications, and supplementation with probiotics and prebiotics, which can modulate the microbiota, enhance immune responses, and reduce pathogenic growth. (*Am J Dent* 2025;38:111-116).

Clinical significance: Oral microbiota dysbiosis, beyond its role in mediating oral diseases, is emerging as a driver of a range of systemic health conditions, including cardiovascular disease, respiratory conditions, and various cancers. A holistic approach combining regular oral hygiene, balanced nutrition, and microbiome-targeted interventions is essential for maintaining oral health and potentially preventing associated systemic diseases.

✉: Dr. Alessia Felicetti, Department of Medical and Surgical Sciences, Magna Graecia University, 88100 Catanzaro, Italy. E-✉: felicettialessia21@gmail.com

Introduction

Overview of oral microbiota composition

In recent years, there has been an exponential increase in research focused on the role of gut microbiota as a determinant of human health. However, the role of oral microbiota has been largely overlooked.

The oral cavity hosts both hard and soft tissue surfaces (e.g., tongue, lips, cheeks, teeth, and palate) that are constantly moistened by saliva and gingival fluid, creating an environment favoring microbial colonization.[1] Over 700 bacterial species, as well as fungi, viruses, archaea, and protozoa, constitute the oral microbiome.[2] The Figure shows the main relative phyla of oral microbiota.

The Human Oral Microbiome Database (eHOMD)[3] is a leading resource for understanding the composition of the human oral microbiota. The oral cavity is home to both Gram-positive (Gram+) and Gram-negative (Gram−) bacteria, each playing roles in both oral health and disease.[4]

Gram-positive bacteria like Streptococcus spp. are the most abundant in the oral cavity. Among these, *Streptococcus mutans* is particularly associated with dental caries due to its ability to produce acids and form dental plaque. Other Streptococcus species such as *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus anginosus* are also prominent in the oral microbiome, where they perform different roles in oral and systemic health.[5-8] Some Staphylococcus species, especially *Staphylococcus aureus*, are found in the saliva and gingival areas, often in immunocompromised individuals.[6,8] Lactobacillus spp. are also present, typically in low numbers, but their proliferation is linked to the presence of caries due to their ability to thrive in acidic conditions.[3,7,9] Other opportunistic pathogens, such as Propionibacterium spp. and Corynebacterium spp., can contribute to oral diseases like gingivitis.[3,7,9]

Gram-negative bacteria like Porphyromonas spp. (especially *Porphyromonas gingivalis*) and *Treponema denticola* are key players in periodontitis, a serious gingival infection. These anaerobic pathogens can spread throughout the body, potentially leading to systemic diseases.[6,7,10,11] Additionally, Archaea, particularly Methanobrevibacter species, have been found in the oral microbiota, especially in patients with periodontitis.[6,12]

Protozoa, such as *Entamoeba gingivalis* and *Trichomonas tenax*, are found in the oral cavity, particularly in individuals with poor oral hygiene and gingival inflammation. While these protozoa are generally non-pathogenic, their presence is linked to nutrient availability and the accumulation of bacterial debris.[3,13,14] Fungi, mainly Candida spp., also exist in the oral microbiome, though they typically represent a small percentage of the microbial population.[11]

Biofilms, complex communities of microorganisms embedded in a matrix of extracellular polysaccharides, are a major feature of the oral microbiome.[15] Initially, after birth, the oral cavity is colonized by early settlers like Streptococcus spp., which modify the oral environment to create conditions favorable for the growth of secondary settlers.[15-18] As the primary and permanent teeth erupt, new surfaces for bacterial colonization are created, leading to the development of dental plaque, a biofilm of microbial communities attached to the teeth.[15]

Plaque can be categorized into supragingival plaque (above the gum line) and subgingival plaque (below the gum

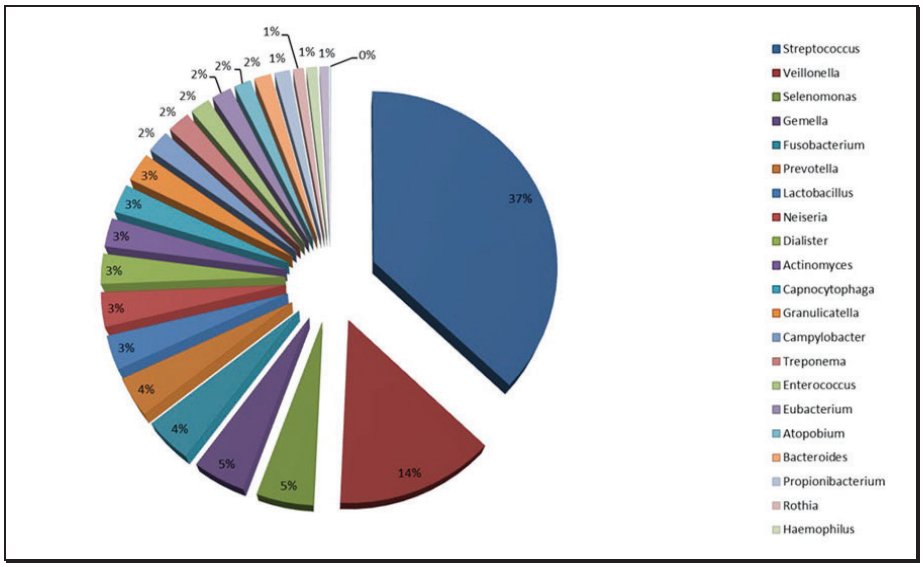

Figure. The main relative phyla of oral microbiota. Reproduced from Santacroce et al[4] under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed. Source: HOMD, http://www.homd.org/.

line). The plaque composition varies depending on the location on the tooth and whether the area is exposed to saliva or remains more anaerobic. Regular oral hygiene is essential, as it prevents plaque buildup, which can lead to gum disease, cavities, and other oral health issues.[15,17-20]

The composition of oral microbiota is influenced by various factors such as age, diet, alcohol use, smoking, socioeconomic status, medications, pregnancy, and genetics.[21]

Diet plays a significant role in shaping the oral microbiota. Fermentable carbohydrates (e.g., simple sugars and starch) are the energy substrate for bacterial metabolism.[22] Excessive alcohol consumption can alter the microbiome by increasing Gram-positive bacteria like *Streptococcus mutans* while inhibiting Fusobacteria.[23,24] Smoking introduces foreign bacteria such as Bacillus spp. and Clostridium spp. and reduces bacteria such as *Neisseria subflava* and *Corynebacterium*, while also increasing acidity in saliva and promoting anaerobic bacterial growth.[23,25] Environmental factors such as temperature, pH, and oxygen levels play a significant role in the growth and survival of oral microbiota communities.[6,26,27] The oral cavity provides both aerobic and anaerobic niches, allowing for a diverse range of microorganisms to thrive. For example, the pH of the mouth can fluctuate after eating, with a drop in pH occurring due to acid production from carbohydrate metabolism, which favors bacteria like Lactobacillus and Streptococcus mutans that contribute to dental caries.[28-30] A diet high in carbohydrates, particularly sugars, can exacerbate the growth of these bacteria and increase plaque formation.[30,31] On the other hand, chewing stimulates salivary flow, which helps wash away bacteria and neutralize acids.[15,32]

The oral microbiome also varies by socioeconomic status. People from lower socioeconomic backgrounds tend to have lower microbiome diversity and higher concentrations of certain bacteria, such as *Aggregatibacter segnis*, whereas wealthier individuals tend to have more diverse microbiomes with higher levels of species like *Veillonella* and *Fusobacterium*.[23,33] Antibiotics, particularly azithromycin and amoxicillin, can reduce certain bacterial populations, such as *Actinobacteria*.[34]

Pregnancy also alters the oral microbiome, with increased presence of bacteria like *Porphyromonas gingivalis* and Candida during different stages.[35] The colonization of the microbiota begins before birth, with microbial species forming on the skin, oral cavity, and other body sites in early life.[35] Early childhood is dominated by Streptococcus species, particularly *Streptococcus salivarius*, which helps protect against pathogenic bacteria.[36]

Factors such as gestational age, mode of delivery, feeding method (breastfeeding vs. formula), and maternal health all influence the infant's oral microbiota.[37,38] Breast milk provides beneficial microbes and supports immune system development. By age three, the microbiome begins to resemble the adult composition, and diet plays a key role in maintaining a healthy microbiome, particularly through antioxidants found in fruits and vegetables.[37,38]

Oral and gut microbiota are interconnected through various communication pathways (e.g., oral/lung, gut/lung), and the health of one microbiota can influence others.[5,39,40] Oral bacteria can translocate to the lungs, affecting lung health, and similarly, gut bacteria like *Bifidobacteria* and *Escherichia coli* play a protective role in both the gut and oral microbiomes, helping to prevent the proliferation of harmful bacteria.[5,39,40]

Oral microbiota and oral health

Dental caries

Dental caries, or tooth decay, is caused by the demineralization of dental structures due to acids produced by bacteria fermenting dietary sugars.[41,42] These bacteria form dental plaque, a type of biofilm on the teeth, which lowers the pH of the plaque within minutes. This acidic environment accelerates enamel erosion. Saliva helps counteract this by neutralizing acids and aiding remineralization, but when the loss of minerals exceeds the rate of remineralization, caries

develops.[43-45] Certain areas of the mouth are more prone to plaque buildup, influenced by tooth anatomy and saliva flow. *Streptococcus mutans*, long believed to be the main cause of caries, is now known to be associated with the initial stages of decay, especially in areas like white spot lesions. However, caries progression involves other bacteria like Lactobacillus spp., which thrive in acidic conditions. The overall microbial diversity in the mouth decreases in areas affected by caries.[41,46]

Periodontal diseases

Periodontal diseases, such as gingivitis and periodontitis, result from the accumulation of dental plaque and tartar due to poor oral hygiene. Gingivitis, an inflammation of the gums, is marked by swollen, bleeding gums and is reversible with proper care.[47] Periodontitis, if untreated, leads to deeper infections and tissue destruction, forming pockets between the teeth and gums.[48] The key pathogens involved include anaerobic bacteria like *Porphyromonas gingivalis* and *Treponema denticola*, which promote inflammation and tissue damage. The "dysbiosis" hypothesis suggests that the balance of bacteria in the mouth shifts in favor of pathogens, like *Porphyromonas gingivalis*, which alter the microbial environment, facilitating bone loss and chronic inflammation.[48,49] Fungal species, such as those from the Ascomycota family, are also implicated in periodontal disease.[50] Furthermore, oral dysbiosis can trigger an "inflammatory dysbiotic cycle," where inflammation exacerbates the imbalance of microorganisms.[42] Recent studies[51] suggest that a balanced diet with whole grains, omega-3s, vitamins, and antioxidants may help reduce periodontal inflammation.

Oral candidiasis

Oral candidiasis, or thrush, is a fungal infection caused by overgrowth of Candida spp., particularly *Candida albicans*.[50] Normally present in small amounts in the oral cavity, Candida can proliferate in conditions like salivary dysfunction, use of certain medications, or a high-carbohydrate diet.[52,53] Risk factors for candidiasis include smoking, diabetes, cancer, and immunosuppression.[50,52,53] The treatment focuses not on eliminating Candida entirely, but on restoring a healthy balance between the microorganism and the host, often through improved oral hygiene and dietary adjustments.[50,54]

Oral cancer

Oral cancer is a complex, multifactorial disease. The presence of human papillomavirus (HPV), especially type 16, along with *Candida albicans*, has been linked to an increased risk of oral squamous cell carcinoma.[55,56] Additionally, studies have found that specific bacteria, including *Porphyromonas gingivalis* and *Tannerella forsythia*, as well as fungal species like Candida and Hannaella, may contribute to malignant cell transformation in the oral cavity.[55,56] The composition of the oral microbiota could serve as a diagnostic biomarker for early detection of oral cancer, highlighting the potential of microbiome analysis in cancer prevention and diagnosis.

Oral microbiota and systemic health

Dysbiosis in the oral cavity can impact other organs, with or without causing systemic effects. Oral bacteria have been implicated in a variety of systemic diseases, including lichen planus, leukoplakia, mucositis, cardiovascular disease, lower respiratory tract conditions, rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, cirrhosis, Alzheimer's disease, polycystic ovary syndrome, obesity, diabetes, HIV infection, and extra-oral cancers such as those of the esophagus, colon, and pancreas.[57-63] Recent research has found *Porphyromonas gingivalis* in cancerous tissues of esophageal cancers. Other bacteria, including *Peptostreptococcus*, *Fusobacterium*, *Peptococcus*, *Catonella*, and *Parvimonas micra*, have also been linked to esophageal cancers like adenocarcinoma and squamous cell carcinoma.[59,63]

Certain oral microbiota species, such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Gemella haemolysans*, may also play a significant role in cardiovascular disease.[64-66] *Streptococcus mutans*, primarily associated with dental caries, has been shown to contribute to atherosclerosis by affecting the function of epithelial cells.[64-66] *Porphyromonas gingivalis* promotes the production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and prostaglandin E2 (PGE2), which influence the cells in atheromatous plaques, exacerbating atherosclerosis.[67,68] Bacteria like *Campylobacter rectus*, *Porphyromonas gingivalis*, *Porphyromonas endodontalis*, and *Aggregatibacter actinomycetemcomitans* have been strongly associated with the development of coronary artery disease.[67,68]

As the microbiota composition changes along the path of the lower airways compared to the oral cavity, the relationship between the oral and lung microbiota has been explored, particularly with the advancement of polymerase chain reaction technology. Dysbiosis in the oral microbiota may therefore be linked to certain lower airway conditions, such as pneumonia, cystic fibrosis, chronic obstructive pulmonary disease, and lung cancer.[40,69]

Strategies to prevent oral dysbiosis

The role of mouthwashes

Mouthwashes play a crucial role in preventing oral inflammation, infections, and the development of dental caries. Chlorhexidine gluconate mouthwash, for instance, has broad antibacterial activity, particularly against Streptococcus species, and can persist on both soft and hard tissues after use. This persistence is partly due to chlorhexidine's positive electrostatic charge, which allows it to bind to the negatively charged microbial cell membranes, ultimately destroying them. It also inhibits microbial enzymes like glycosyltransferases and phosphoenolpyruvate phosphatase.[70]

Cetylpyridinium chloride, a quaternary ammonium compound, also has antimicrobial properties, though its range of activity is more limited than chlorhexidine's. It is rapidly absorbed into oral surfaces and released more quickly than chlorhexidine.[70] Triclosan, a compound derived from 2,4,4'-trichloro-2-hydroxydiphenyl ether, combined with zinc citrate, offers significant antimicrobial effects, especially against *Streptococcus mutans*, by inhibiting cell membrane functions.[71] Mouthwashes containing phenols and essential oils (such as thymol, eucalyptol, menthol, and methyl salicylate, with up to 26% alcohol) can disrupt plaque biofilm, eliminating most microorganisms responsible for gum inflammation.[72] Some bacterial enzymes and endotoxins from Gram-negative bacteria

have demonstrated anti-inflammatory properties, partly through the blockade of prostaglandin synthetase.[72]

Delmopinol, derived from 2-morpholinoethanol, effectively blocks both plaque formation and gum inflammation.[72] Fluoride mouthwashes have three primary mechanisms for preventing caries: (1) fluoride ions inhibit the metabolism of sugars by bacteria, reducing acid production; (2) fluoride is absorbed intracellularly, where it ionizes, releasing hydrogen ions, which in turn enhance enamel remineralization; and (3) fluoride promotes the formation of apatite crystals, strengthening enamel and reducing solubility in acidic conditions.[73,74]

Xylitol, a sugar alcohol, inhibits the growth of *Streptococcus mutans* by disrupting glucose metabolism. It stimulates saliva production and improves its buffering capacity, which helps reduce caries.[75,76] Studies[75-77] have shown that xylitol reduces the presence of *Streptococcus mutans* in saliva and decreases caries incidence. On the other hand, sorbitol, another sugar alcohol, is less metabolized by oral microorganisms, helping to maintain a higher pH in saliva and prevent acid production, though long-term, frequent use can lead to microbial adaptation and a drop in pH. Sorbitol can also cause gastrointestinal discomfort, a side effect less common with xylitol.[76,78]

Sanguinarine, an alkaloid derived from *Sanguinaria canadensis*, has been shown to affect *Streptococcus mutans*, although its effectiveness is limited by poor bioavailability.[78,79] Povidone-iodine has a broad antimicrobial spectrum against bacteria, fungi, protozoa, and viruses and can be useful for reducing plaque, gingivitis, and mucositis, particularly after radiation therapy.[78,79]

Diet

As mentioned above, some dietary compounds seem to modulate oral microbiota composition and diversity and have been associated with dental caries and periodontitis.[80] Dietary fermentable carbohydrates like simple sugars and starch have long been associated with the development of dental caries.[81] Sugars, for instance, promote the growth of bacteria like *Streptococcus mutans* and *Fusobacterium nucleatum*, while fats and vitamins (particularly vitamin C) favor the growth of Fusobacteria. On the other hand, fiber and dairy products can help maintain a healthy balance of oral bacteria.[2,6,21,23,82] The association of carbohydrate intake with periodontal disease has been less explored.[83] However, emerging evidence suggests that dietary patterns characterized by whole grain consumption in place of refined carbohydrates and simple sugars intake seem to be beneficial also in the context of periodontal disease.[51]

Supplementation with probiotics and prebiotics is gaining growing attention as a strategy to promote oral microbiota health. Probiotics are live microorganisms that, when taken in adequate amounts, confer health benefits to the host.[84] Prebiotics are substances that selectively stimulate the growth or activity of beneficial microorganisms in the host.[85] Prebiotics and probiotics often work synergistically, with prebiotics nourishing beneficial bacteria to enhance their effects. However, while probiotics have been extensively studied for their effects on periodontal health, research on the impact of prebiotics on dental diseases remains limited.[32,86]

Prebiotics are typically carbohydrate-based (such as fructo-oligosaccharides and galacto-oligosaccharides), but may also include non-carbohydrate compounds like polyphenols and polyunsaturated fatty acids.[85] Prebiotics support the growth of beneficial bacteria, such as Lactobacilli and Bifidobacteria, while inhibiting pathogenic microorganisms like Clostridia and *Escherichia coli*.[32,85] Furthermore, prebiotics and probiotics share anti-inflammatory and immunomodulatory properties.[32,84,85]

Probiotics like Lactobacilli and Bifidobacteria can help maintain microbiota eubiosis, modulate the immune system, and produce antimicrobial substances.[87,88] They achieve these effects by competing for adhesion sites, producing antimicrobial compounds, enhancing immune responses (such as increasing Immunoglobulin A production), and by reducing proinflammatory cytokines and matrix metalloproteinases (MMPs). In this way, probiotics can help limit the growth of harmful bacteria and can influence immune response both in the oral cavity and at a systemic level.[87,88] *Lactobacillus acidophilus* supplementation has shown promising effects in the management of periodontal disease, gingivitis, and pregnancy-related gum inflammation.[89] Strains like *Lactobacillus casei*, *Lactobacillus shirota*, and *Lactobacillus reuteri* have been found to reduce gingival bleeding.[89] *Lactobacillus casei* and *Lactobacillus shirota* also reduce the activity of inflammatory markers in gingival crevicular fluid (GCF).[89] *Lactobacillus salivarius* WB21 appears to be effective in reducing gum pocket depth, particularly in smokers.[89] It has also been suggested that daily intake of heat-inactivated *Lactobacillus plantarum* L-137 may reduce periodontal pocket depth,[90] while *Lactobacillus rhamnosus* SP1 supplementation showed no significant difference in periodontal outcomes when compared to a placebo.[91] Additionally, probiotic supplementation has been shown to improve gingival health and reduce harmful bacteria counts, as reported by a randomized placebo-controlled clinical trial testing supplementation with *Lactobacillus rhamnosus* and Bifidobacterium lactis in adolescents.[92] Probiotics can also help reduce halitosis by lowering sulfur gas production from bacteria on the tongue, balancing oral pH, and improving salivation in individuals with xerostomia.[4] However, while the potential of probiotics for oral health is becoming clearer, more clinical trials are needed, particularly to establish the long-term effects of probiotic use for oral diseases.

Conclusion

Overall, the oral microbiota is a dynamic ecosystem where bacterial communities interact in complex ways, both cooperatively and competitively. The oral microbiota is influenced by a range of factors throughout life. Diet, oral hygiene, and environmental factors all play a critical role in shaping the microbiome and influencing oral health outcomes. Regular maintenance of oral hygiene, combined with a balanced diet, is essential for supporting a healthy oral and gut microbiota with beneficial effects on both oral and systemic health.

Disclosure statement: The authors declared no conflict of interest.

Dr. Azzolino is a postdoctoral student, Dr. Lucchi is Head, Geriatric Unit, Medical Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. Dr. Felicetti is a Biotechnologist, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy. Dr. Santacroce is Professor, Ionian Department, Microbiology and Virology Laboratory, University Hospital of Bari, Bari, Italy. Dr. Garcia-Godoy is Professor, Department of Bioscience Research, College of Dentistry,

University of Tennessee Health Science Center, Memphis, Tennessee, USA. Dr. Passarelli is Professor and Master Director, Department of Head and Neck and Sensory Organs, Division of Oral Surgery and Implantology, Fondazione Policlinico Universitario A. Gemelli IRCCS, University Cattolica del Sacro Cuore, Rome, Italy.

References

1. Sender R, Fuchs S, Milo R. Revised Estimates for the number of human and bacteria cells in the body. PLOS Biology 2016;14:e1002533.
2. Sultan AS, Kong EF, Rizk AM, Jabra-Rizk MA. The oral microbiome: A lesson in coexistence. PLOS Pathogens 2018;14:e1006719.
3. Chen T, Yu WH, Izard J, Baranova OV, Lakshmanan A, Dewhirst FE. The Human Oral Microbiome Database: A web accessible resource for investigating oral microbe taxonomic and genomic information. Database (Oxford). 2010;2010:baq013.
4. Santacroce L, Passarelli PC, Azzolino D, Bottalico L, Charitos IA, Cazzolla AP, Colella M, Topi S, Garcia-Godoy F, D'Addona A. Oral microbiota in human health and disease: A perspective. *Exp Biol Med* (Maywood). 2023;248:1288-1301.
5. Nobbs AH, Lamont RJ, Jenkinson HF. Streptococcus adherence and colonization. *Microbiol Mol Biol Rev* 2009;73:407-450.
6. Samaranayake L, Matsubara VH. Normal oral flora and the oral ecosystem. *Dent Clin North Am* 2017;61:199-215.
7. Sudhakara P, Gupta A, Bhardwaj A, Wilson A. Oral dysbiotic communities and their implications in systemic diseases. *Dent J* (Basel). 2018;6:10.
8. Cong J, Zhang X. How human microbiome talks to health and disease. *Eur J Clin Microbiol Infect Dis* 2018;37:1595-1601.
9. Zhang Y, Wang X, Li H, Ni C, Du Z, Yan F. Human oral microbiota and its modulation for oral health. *Biomed Pharmacother* 2018;99:883-893.
10. Siqueira JF, Rôças IN. The oral microbiota in health and disease: An overview of molecular findings. *Methods Mol Biol* 2017;1537:127-138.
11. Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: More and more importance in oral cavity and whole body. *Protein Cell* 2018;9:488-500.
12. Poehlein A, Seedorf H. Draft genome sequences of Methanobrevibacter curvatus DSM11111, Methanobrevibacter cuticularis DSM11139, Methanobrevibacter filiformis DSM11501, and Methanobrevibacter oralis DSM7256. *Genome Announc* 2016;4:e00617-16.
13. Rashidi Maybodi F, Haerian Ardakani A, Fattahi Bafghi A, Haerian Ardakani A, Zafarbakhsh A. The effect of nonsurgical periodontal therapy on trichomonas Tenax and Entamoeba Gingivalis in patients with chronic periodontitis. *J Dent* (Shiraz). 2016;17:171-176.
14. Baker JL, Bor B, Agnello M, Shi W, He X. Ecology of the oral microbiome: Beyond bacteria. *Trends Microbiol* 2017;25:362-374.
15. Fux CA, Stoodley P, Hall-Stoodley L, Costerton JW. Bacterial biofilms: A diagnostic and therapeutic challenge. *Expert Rev Anti Infect Ther* 2003;1:667-683.
16. Palmer RJ. Composition and development of oral bacterial com-munities. *Periodontol 2000* 2014;64:20-39.
17. Rendueles O, Ghigo JM. Multi-species biofilms: How to avoid unfriendly neighbors. *FEMS Microbiol Rev* 2012;36:972-989.
18. Lemos JA, Abranches J, Koo H, Marquis RE, Burne RA. Protocols to study the physiology of oral biofilms. *Methods Mol Biol* 2010;666:87-102.
19. Mason MR, Chambers S, Dabdoub SM, Thikkurissy S, Kumar PS. Characterizing oral microbial communities across dentition states and colonization niches. *Microbiome* 2018;6:67.
20. Li H, Xiao B, Zhang Y, Xiao S, Luo J, Huang W. Impact of maternal intrapartum antibiotics on the initial oral microbiome of neonates. *Pediatr Neonatol* 2019;60:654-661.
21. Li X, Liu Y, Yang X, Li C, Song Z. The oral microbiota: Community composition, influencing factors, pathogenesis, and interventions. *Front Microbiol* 2022;13:895537.
22. Jurtshuk P Jr. Bacterial metabolism. In: Baron S, editor. *Medical Microbiology*. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 4.
23. Dagli N, Dagli R, Darwish S, Baroudi K. Oral microbial shift: Factors affecting the microbiome and prevention of oral disease. *J Contemp Dent Pract* 2016;17:90-96.
24. Fan X, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Freedman ND, Alekseyenko AV, Wu J, Yang L, Pei Z, Hayes RB, Ahn J. Drinking alcohol is associated with variation in the human oral microbiome in a large study of American adults. *Microbiome* 2018;6:59.
25. Wu J, Peters BA, Dominianni C, Zhang Y, Pei Z, Yang L, Ma Y, Purdue MP, Jacobs EJ, Gapstur SM, Li H, Alekseyenko AV, Hayes RB, Ahn J. Cigarette smoking and the oral microbiome in a large study of American adults. ISME J. 2016;10:2435-2446.
26. Keijser BJF, Zaura E, Huse SM, van der Vossen JMBM, Schuren FHJ, Montijn RC, ten Cate JM, Crielaard W. Pyrosequencing analysis of the oral microflora of healthy adults. *J Dent Res* 2008;87:1016-1020.
27. Faran Ali SM, Tanwir F. Oral microbial habitat a dynamic entity. *J Oral Biol Craniofac Res* 2012;2:181-187.
28. Honda K. Porphyromonas gingivalis sinks teeth into the oral microbiota and periodontal disease. *Cell Host Microbe* 2011;10:423-425.
29. Marsh PD. Dental plaque as a biofilm: The significance of pH in health and caries. *Compend Contin Educ Dent* 2009;30:76-78,80,83-87.
30. Wade WG. The oral microbiome in health and disease. *Pharmacol Res* 2013;69:137-143.
31. Bowden GH, Li YH. Nutritional influences on biofilm development. *Adv Dent Res* 1997;11:81-99.
32. Santonocito S, Giudice A, Polizzi A, Troiano G, Merlo EM, Sclafani R, Grosso G, Isola G. A cross-talk between diet and the oral microbiome: Balance of nutrition on inflammation and immune system's response during periodontitis. *Nutrients* 2022;14:2426.
33. Belstrøm D, Holmstrup P, Nielsen CH, Kirkby N, Twetman S, Heitmann BL, Klepac-Ceraj V, Paster BJ, Fiehn NE. Bacterial profiles of saliva in relation to diet, lifestyle factors, and socioeconomic status. *J Oral Microbiol* 2014;6:10.3402/jom.v6.23609.
34. Almeida V de SM, Azevedo J, Leal HF, Queiroz ATL de, Filho HP da S, Reis JN. Bacterial diversity and prevalence of antibiotic resistance genes in the oral microbiome. *PLOS ONE* 2020;15:e0239664.
35. Saadaoui M, Singh P, Al Khodor S. Oral microbiome and pregnancy: A bidirectional relationship. *J Reprod Immunol* 2021;145:103293.
36. Dzidic M, Collado MC, Abrahamsson T, Artacho A, Stensson M, Jenmalm MC, Mira A. Oral microbiome development during childhood: an ecological succession influenced by postnatal factors and associated with tooth decay. *ISME J* 2018;12:2292-2306.
37. Agostoni C, Kim KS. Nutrition and the microbiome. *Pediat Res* 2015;77:113-114.
38. Mändar R, Mikelsaar M. Transmission of mother's microflora to the newborn at birth. *Biol Neonate* 1996;69:30-35.
39. Santacroce L, Riegel P, Toti S, Ghelardi E. The oral microbiota in oral health and disease: New insights into the human microbiome. *J Oral Microbiol* 2021;13:1875440.
40. Pei Z, Bini E, Yang L, Zhou M, Francois F, LeLeiko N, Shapiro M, Liu Y, Li H, Hayes RB. Bacterial biota in the human distal esophagus. *J Clin Microbiol* 2004;42:42024209.
41. Li J, Liu Y, Ma X, Peng Y, Zhao Y, Zhang Y, Zhao X, Wu Z. Effects of oral probiotics on oral health and gut microbiota: A systematic review and meta-analysis. *BMC Oral Health* 2021;21:1-13.
42. Dipalma G, Inchingolo AD, Inchingolo F, Charitos IA, Di Cosola M, Cazzolla AP. Focus on the cariogenic process: microbial and biochemical interactions with teeth and oral environment. *J Biol Regul Homeost Agents* 2021;35.
43. Barbería E, Maroto M, Arenas M, Silva CC. A clinical study of caries diagnosis with a laser fluorescence system. *J Am Dent Assoc* 2008;139:572-579.
44. Belibasakis GN, Bostanci N, Marsh PD, Zaura E. Applications of the oral microbiome in personalized dentistry. *Arch Oral Biol* 2019;104:7-12.
45. Di Domenico M, Ballini A, Boccellino M, Scacco S, Lovero R, Charitos IA, Santacroce L. The intestinal microbiota may be a potential theranostic tool for personalized medicine. *J Pers Med* 2022;12:523.
46. Struzycka I. The oral microbiome in dental caries. *Pol J Microbiol* 2014;63:127-135.
47. Zinja V, van Leeuwen MBM, Degener JE, Abbas F, Thurnheer T, Gmür R, Harmsen HJM. Oral biofilm architecture on natural teeth. *PLoS One* 2010;5:e9321.
48. Hajishengallis G, Liang S, Payne MA, Hashim A, Jotwani R, Eskan MA, McIntosh ML, Alsam A, Kirkwood KL, Lambris JD, Darveau RP, Curtis MA. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. *Cell Host Microbe* 2011;10:497-506.
49. van der Meulen TA, Harmsen H, Bootsma H, Spijkervet F, Kroese F, Vissink A. The microbiome-systemic diseases connection. *Oral Dis* 2016;22:719-734.
50. Sztukowska MN, Dutton LC, Delaney C, Ramsdale M, Ramage G, Jenkinson HF, Nobbs AH, Lamont RJ. Community development between Porphyromonas gingivalis and Candida albicans mediated by InlJ and Als3. *mBio* 2018;9:e00202-18.
51. De Angelis P, Gasparini G, Manicone PF, Passarelli PC, Azzolino D, Rella E, De Rosa G, Papi P, Pompa G, De Angelis S, Grassi R, D'Addona A. The effect of an optimized diet as an adjunct to non-surgical periodontal therapy

in subjects with periodontitis: A prospective study. *Healthcare* 2022; 10:583.
52. Akpan A, Morgan R. Oral candidiasis. *Postgrad Med J* 2002;78:455-459.
53. Man A, Ciurea CN, Pasaroiu D, Savin AI, Toma F, Sular F, Santacroce L, Mare A. New perspectives on the nutritional factors influencing growth rate of Candida albicans in diabetics. An in vitro study. *Mem Inst Oswaldo Cruz* 2017;112:587-592.
54. Monea A, Santacroce L, Marrelli M, Man A. Oral candidiasis and inflammatory response: A potential synergic contribution to the onset of Type-2 diabetes mellitus. *Australasian Med J* 2017;10:550-556.
55. Santacroce L, Di Cosola M, Bottalico L, Topi S, Charitos IA, Ballini A, Inchingolo F, Cazzolla AP, Dipalma G. Focus on HPV infection and the molecular mechanisms of oral carcinogenesis. *Viruses* 2021;13:559.
56. Di Cosola M, Cazzolla AP, Charitos IA, Ballini A, Inchingolo F, Santacroce L. Candida albicans and oral carcinogenesis. A brief review. *J Fungi* (Basel) 2021;7:476.
57. La Rosa GRM, Gattuso G, Pedullà E, Rapisarda E, Nicolosi D, Salmeri M. Association of oral dysbiosis with oral cancer development. *Oncol Lett* 2020;19:3045-3058.
58. Chen J, Domingue JC, Sears CL. Microbiota dysbiosis in select human cancers: Evidence of association and causality. *Semin Immunol* 2017; 32:25-34.
59. Graves DT, Corrêa JD, Silva TA. The oral microbiota is modified by systemic diseases. *J Dent Res* 2019;98:148-156.
60. Flemer B, Warren RD, Barrett MP, Cisek K, Das A, Jeffery IB, Hurley E, O'Riordain M, Shanahan F, O'Toole PW. The oral microbiota in colorectal cancer is distinctive and predictive. *Gut* 2018;67:1454-1463.
61. Ballini A, Scacco S, Boccellino M, Santacroce L, Arrigoni R. Microbiota and obesity: Where are we now? *Biology* (Basel) 2020;9:415.
62. Olson SH, Satagopan J, Xu Y, Ling L, Leong S, Orlow I, Saldia A, Li P, Nunes P, Madonia V, Allen PJ, O'Reilly E, Pamer E, Kurtz RC. The oral microbiota in patients with pancreatic cancer, patients with IPMNs, and controls: A pilot study. *Cancer Causes Control* 2017;28:959-969.
63. Gao S, Li S, Ma Z, Liang S, Shan T, Zhang M, Zhu X, Zhang P, Liu G, Zhou F, Yuan X, Jia R, Potempa J, Scott DA, Lamont RJ, Wang H, Feng X. Presence of Porphyromonas gingivalis in the esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. *Infect Agent Cancer* 2016;11:3.
64. Schirinzi A, Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Ciavarella D, Palmieri G, Pozzessere P, Procacci V, Di Serio F, Santacroce L. New insights in laboratory testing for COVID-19 patients: Looking for the role and predictive value of human epididymis secretory protein 4 (HE4) and the innate immunity of the oral cavity and respiratory tract. *Microorganisms* 2020;8:1718.
65. Wang Y, Xue J, Zhou X, You M, Du Q, Yang X, He J, Zou J, Cheng L, Li M, Li Y, Zhu Y, Li J, Shi W, Xu X. Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. *PLoS One* 2014;9:e102116.
66. Lazar V, Ditu LM, Pircalabioru GG, Gheorghe I, Curutiu C, Holban AM, Picu A, Petcu L, Chifiriuc MC. Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Front Immunol 2018;9:1830.
67. Krzyściak W, Jurczak A, Kościelniak D, Bystrowska B, Skalniak A. The virulence of Streptococcus mutans and the ability to form biofilms. Eur *J Clin Microbiol Infect Dis* 2014;33:499-515.
68. Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L, Crean S. Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE-/- mice brains. *J Alzheimers Dis* 2015;43:67-80.
69. Santacroce L, Charitos IA, Ballini A, Inchingolo F, Luperto P, De Nitto E, Topi S. The human respiratory system and its microbiome at a glimpse. *Biology (Basel)* 2020;9:318.
70. Basrani B, Lemonie C. Chlorhexidine gluconate. *Aust Endod J* 2005; 31:48-52.
71. Abello R, Buitrago C, Prate CM, DeVizio W, Bakar SK. Effect of a mouthrinse containing triclosan and a copolymer on plaque formation in the absence of oral hygiene. Am J Dent 1990;3 Sp Is:S57–61.
72. Raja M, Saha S, Vamsi K, Reddy, Shafaat M, Kumari M. Mouthwashes – An overview of current knowledge. *Int Jour Oral Health Res & Rev* 2013;1:24-28.
73. Jenkins GN. Review of fluoride research since 1959. *Arch Oral Biol* 1999;44:985-992.
74. Aoba T, Shimazu Y, Taya Y, Soeno Y, Sato K, Miake Y. Fluoride and apatite formation in vivo and in vitro. *J Electron Microsc* (Tokyo) 2003;52:615-625.
75. Machiulskiene V, Nyvad B, Baelum V. Caries preventive effect of sugar-substituted chewing gum. *Community Dent Oral Epidemiol* 2001;29:278-288.
76. Söderling E, Isokangas P, Tenovuo J, Mustakallio S, Mäkinen KK. Long-term xylitol consumption and mutans streptococci in plaque and saliva. *Caries Res* 1991;25:153-157.
77. Corsalini M, Montagnani M, Charitos IA, Bottalico L, Barile G, Santacroce L. Non-surgical therapy and oral microbiota features in peri-implant complications: A brief narrative review. *Healthcare (Basel)* 2023;11:652.
78. Petersen PE, Razanamihaja N. Carbamide-containing polyol chewing gum and prevention of dental caries in schoolchildren in Madagascar. *Int Dent J* 1999;49:226–230.
79. Brecx M, Netuschil L, Reichert B, Schreil G. Efficacy of Listerine, Meridol and chlorhexidine mouthrinses on plaque, gingivitis and plaque bacteria vitality. *J Clin Periodontol* 1990;17:292-297.
80. Scardina GA, Messina P. Good oral health and diet. *BioMed Research International* 2012;720692.
81. Gupta P, Gupta N, Pawar AP, Birajdar SS, Natt AS, Singh HP. Role of sugar and sugar substitutes in dental caries: A review. *International Scholarly Research Notices* 2013;2013:519421.
82. Hansen TH, Kern T, Bak EG, Kashani A, Allin KH, Nielsen T, Hansen T, Pedersen O. Impact of a vegan diet on the human salivary microbiota. *Sci Rep* 2018;8:5847.
83. Millen AE, Dahhan R, Freudenheim JL, Hovey KM, Li L, McSkimming DI, Andrews CA, Buck MJ, LaMonte MJ, Kirkwood KL, Sun Y, Murugaiyan V, Tsompana M, Wactawski-Wende J. Dietary carbohydrate intake is associated with the subgingival plaque oral microbiome abundance and diversity in a cohort of postmenopausal women. *Sci Rep* 2022;12:2643.
84. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506-514.
85. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 2017;14:491-502.
86. Slomka V, Herrero ER, Boon N, Bernaerts K, Trivedi HM, Daep C, Quirynen M, Teughels W. Oral prebiotics and the influence of environmental conditions in vitro. *J Periodontol* 2018;89:708-717.
87. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol* 2013;6:39-51.
88. Santacroce L, Charitos IA, Bottalico L. A successful history: probiotics and their potential as antimicrobials. *Expert Rev Anti Infect Ther* 2019; 17:635-645.
89. Chugh P, Dutt R, Sharma A, Bhagat N, Dhar MS. A critical appraisal of the effects of probiotics on oral health. *Journal of Functional Foods* 2020;70:103985.
90. Iwasaki K, Maeda K, Hidaka K, Nemoto K, Hirose Y, Deguchi S. Daily Intake of Heat-killed Lactobacillus plantarum L-137 Decreases the probing depth in patients undergoing supportive periodontal therapy. *Oral Health Prev Dent* 2016;14:207-214.
91. Morales A, Carvajal P, Silva N, Hernandez M, Godoy C, Rodriguez G, Cabello R, Garcia-Sesnich J, Hoare A, Diaz PI, Gamonal J. Clinical effects of Lactobacillus rhamnosus in non-surgical treatment of chronic periodontitis: A randomized placebo-controlled trial with 1-year follow-up. *J Periodontol* 2016;87:944-952.
92. Alanzi A, Honkala S, Honkala E, Varghese A, Tolvanen M, Söderling E. Effect of Lactobacillus rhamnosus and Bifidobacterium lactis on gingival health, dental plaque, and periodontopathogens in adolescents: A randomised placebo-controlled clinical trial. *Benef Microbes* 2018; 9:593-602.