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# The Interaction between the Oral Microbiome and Systemic Diseases: A Narrative Review

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**Abstract: Background**: The human being is defined as a 'superorganism' since it is made up of its own cells and microorganisms that reside inside and outside the human body. Commensal microorganisms, which are even ten times more numerous than the cells present in the body, perform very important functions for the host, as they contribute to the health of the host, resist pathogens, maintain homeostasis, and modulate the immune system. In the mouth, there are different types of microorganisms, such as viruses, mycoplasmas, bacteria, archaea, fungi, and protozoa, often organized in communities. The aim of this umbrella review is to evaluate if there is a connection between the oral microbiome and systematic diseases. **Methodology**: A literature search was conducted through PubMed/MEDLINE, the COCHRANE library, Scopus, and Web of Science databases without any restrictions. Because of the large number of articles included and the wide range of methods and results among the studies found, it was not possible to report the results in the form of a systematic review or meta-analysis. Therefore, a narrative review was conducted. We obtained 73.931 results, of which 3593 passed the English language filter. After the screening of the titles and abstracts, non-topic entries were excluded, but most articles obtained concerned interactions between the oral microbiome and systemic diseases. **Discussion**: A description of the normal microbial flora was present in the oral cavity both in physiological conditions and in local pathological conditions and in the most widespread systemic pathologies. Furthermore, the therapeutic precautions that the clinician can follow in order to intervene on the change in the microbiome have been described. **Conclusions**: This review highlights what are the intercorrelations of the oral microbiota in healthy subjects and in subjects in pathological conditions. According to several recent studies, there is a clear correlation between dysbiosis of the oral microbiota and diseases such as diabetes, cardiovascular diseases, chronic inflammatory diseases, and neurodegenerative diseases.

**Keywords:** oral microbiome; oral dysbiosis; systemic diseases



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## 1. Introduction

The human being is defined as a 'superorganism' since it is made up of its own cells and microorganisms that reside inside and outside the human body [1,2].

Commensal microorganisms, which are even ten times more numerous than the cells present in the body [1,2], perform very important functions for the host as they contribute to the health of the host, resist pathogens, maintain homeostasis, and modulate the immune system [3].

In the mouth, there are different types of microorganisms, such as viruses, mycoplasmas, bacteria, archaea, fungi, and protozoa, often organized in communities [3].

These communities colonize all surfaces of the oral cavity, often in the form of biofilms.

The biofilm is formed by different species of microorganisms, which generally exist in harmony with the host, offering important benefits for the health and general well-being of

the host. The microorganisms present in the oral biofilm interact with each other, constituting both synergistic and antagonistic interactions. Maintenance of a healthy and balanced state occurs, for example, through competition between commensal and pathogenic species, through the production of nisin, through the regulation of nitrate metabolism, and through the regulation of pH [4]. The composition of the microbiome is influenced by the oral environment, and changes within this can affect microbial interactions within these communities and determine the risk of diseases such as caries or periodontal disease [3,4].

However, although the oral microbiota is of paramount importance for host health, it also plays an important role in the pathogenesis and development of various oral and systemic diseases [2].

In fact, under conditions, the virulence factors of oral bacteria can reach distant organs or influence the host's immune responses [2,4]. For example, periodontopathogenic bacteria have been found in thrombi from patients with acute myocardial infarction, suggesting a potential role of the oral microbiome in plaque inflammation and instability [5].

Several authors have linked systemic diseases with oral dysbiosis conditions, such as inflammatory bowel disease or degenerative diseases (for example, atherosclerosis and Alzheimer's disease), macular degeneration, and tumors [6,7]. At the same time, however, the oral microbiota can be altered by systemic diseases such as diabetes [8]. On the other hand, in dysbiotic conditions, accumulations of bacteria and other microorganisms can occur, which can induce the development of oral diseases. Indeed, the most common oral diseases such as caries, gingivitis, or periodontitis are caused by microorganisms [8]. Periodontitis is an inflammatory disease of the supporting tissues of the teeth, which leads to the loss of bone and of the periodontal ligament, up to the loss of teeth [2,5]. The etiology of periodontitis includes the presence of microorganisms, and its pathogenesis is known to be based on the host-mediated inflammatory immune response, although the interaction between the oral microbiome, the host response, and the development of periodontitis itself is not fully understood [9–13]. The inflammation of periodontal tissues, together with the dysbiotic phenomena of the periodontal microbiome, would also seem to be involved in the pathogenesis of various systemic conditions and inflammatory, degenerative, and neoplastic pathologies, influencing, in turn, the onset and progression of periodontitis [14].

Recent research, mostly conducted on animal models, has shown that the oral microbiome also influences the intestinal microbiome and the pathologies associated with it.

This may seem obvious as the oral cavity represents the first section of the gastrointestinal tract and the intestine, the last section; however, the presence of oral bacteria in fecal samples from people with colon cancer has strengthened this theory. A set of bacteria, primarily Fusobacterium nucleatum, was observed in the fecal samples of subjects with colorectal cancer [6].

The specific PCR protocol for 16S ribosomal DNA in combination with the T-RFLP technique allowed taxonomic identifications to be made at the species level without resorting to a pre-enrichment procedure or the isolation and plating of environmental strains. A real-time PCR protocol has also been developed, targeting 16S ribosomal DNA, which has made it possible to increase the sensitivity and speed of the diagnostic test that, starting from DNA, can be performed in about 30 min [14].

Oral microorganisms can form oral biofilm, which is a three-dimensional structure with diverse communities of microorganisms embedded in an extracellular matrix [14]. Bacterial adhesion is preceded by the formation of an acquired film mainly consisting of salivary glycoproteins [14]. In the initial stages, weak physicochemical interactions are formed between the different microorganisms and the acquired film. Subsequently, stronger bonds are established between the bacterial adhesins and the acquired film glycoprotein receptors [15]. The microbial composition gradually increases due to the coaggregation of the late colonizers binding to the receptors of the early bacteria [15]. The adhesion of microorganisms can occur both on biotic and abiotic surfaces such as removable and fixed prostheses that can be easily colonized by bacteria, fungi, and viruses [15–17].

The oral microbiome present on biotic and abiotic structures has been correlated to different pathologies, especially when the patient has dysbiosis or immunosuppression problems.

The purpose of this narrative review is to describe the present relationship between the main systemic conditions and oral pathogens.

## 2. Relevant Sections (Methodology)

The aim of this review is to describe the correlation between the main systemic conditions and the oral pathogens and highlight any clinical precautions or self-care recommendations for oral dysbiosis prevention and periodontal health maintenance.

A literature search was conducted independently by two reviewers (F.D.A.; G.S.) through the PubMed/MEDLINE, the COCHRANE library, Scopus, and Web of Science databases without any restriction. Only articles published up to 1 July 2023 in English have been included. A combination of the following keywords was used for the electronic search:

("oral microbiome" OR "oral microbiota" OR "oral bacteria" OR "oral virus" OR "oral fungi") AND ("systemic disease" OR "systemic disease" OR "diseases").

References were exported and managed using Mendeley Reference Manager.

We obtained 73,931 results, of which 3593 passed the English language filter. After the screening of the titles and abstracts, non-topic entries were excluded, but most of the articles obtained concerned interactions between the oral microbiome and systemic diseases.

Due to the large number of articles included and the wide range of methods and results among the studies found, it was not possible to report the results in the form of a systematic review or meta-analysis.

Instead, the articles that were identified by the search procedure described above were used as the basis for the present narrative review. This review is a narrative review, so it is not based on a statistical analysis or bias reduction through confounding analysis.

## 3. Discussion

### *3.1. Oral Microbiome in Physiologic Conditions*

At birth, the oral cavity is sterile, but in the following hours, the microorganisms, by vertical transmission, are transferred from the mother to the newborn and these settle, together with those coming from the external environment, in the oral cavity [14]. The first to colonize the oral cavity of the newborn, in general, are the bacteria belonging to the streptococcal family, such as *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus oralis*, which colonize the epithelium of the mucosa.

The metabolic processes of these first colonizers of the oral cavity modify the surrounding environment, favoring the colonization by other bacterial species through mechanisms of intracellular cooperation. An example is *S. gordonii*, which, through the production of extracellular polymers from sucrose, forms bonds with other bacterial species, in particular *Actinomyces* spp [16].

It has been observed that, at the age of one year, the oral cavity of the child is colonized by *streptococci*, *staphylococci*, *Neisseria*, and some strictly anaerobic Gram-negative strains. This balance undergoes a substantial change during the eruption phase of the first deciduous tooth as the hard tissues of the dental element and the gingival sulcus represent a new site of bacterial colonization. In particular, the enamel is rapidly colonized by Gram-positive bacteria such as *Streptoccocus mutans*, *Streptoccocus sanguinis*, *Lactobacilli*, *Actinomyces* spp., and *Rozia.* The anaerobic environment of the gingival sulcus, on the other hand, favors the colonization and proliferation of Gram-negative microorganisms such as non-pigmented spp, *Porphyromonas* spp., and *Capnocytophaga* [17–20].

Further modification of the oral microbiome occurs during puberty as hormonal upheavals contribute to the transition to an adult flora composition. These phases of microbiome diversification and growth continue over time until a balance is created between the resident microflora and local environmental conditions. A sort of "microbial homeostasis"

is created, but this can be disrupted due to hormonal changes, dietary changes, or poor oral hygiene, which favor dysbiosis [21].

We have seen that in vertical transmission, the microorganisms are transmitted from mother to child; however, the transmission of microorganisms can also occur through interpersonal contamination, thus we speak of horizontal transmission.

With advancing age and the consequent greater probability of becoming edentulous, there is the last major upheaval in the composition of the oral microflora, which returns to that present in the child before the teeth erupt. Therapeutic devices usually used for the treatment of edentulism again modify the microbial composition [14–16]. In particular, there is evidence of the increased colonization of *Candida* species in patients wearing polymethacrylate prostheses and the increased prevalence of *Staphylococcus aureus* and *Lactobacilli* in people 70 years of age and older [14,15].

Changes in the composition of the bacterial microflora over time are driven by changes in the physical and biological properties of sites in the oral cavity. The presence of anatomical micro niches that provide physicochemical characteristics suitable for the development of a certain type of microflora, such as pH, oxygen, temperature, or redox potential, allows for the establishment of certain microorganisms [16]. Studies in the literature have observed that the function and composition of the human oral microbiome are unique to everyone not only in patients with ongoing disease processes but also among healthy individuals.

To identify the microorganisms present in the oral cavity, a microscope was first used, capable of determining the morphology of a bacterium.

Today, however, a correct and precise recognition of the microorganisms present in the oral cavity is possible thanks to genetic analysis, based on the sequencing of the 16S ribosomal RNA gene.

The most widely used technique for RNA gene sequencing is bacterial PCR, which is used for detecting and identifying bacteria based on gene sequence highly conserved 16S-rRNA [16].

This diversity can be found in factors such as smoke, diet, alcohol, environment, the genetic component of the host, and early exposure to microorganisms [17,18,21].

Smoking is recognized as an important risk factor for both oral and systemic diseases. In the case of periodontal disease, it has been recognized as one of the risk factors for assessing the severity of the disease [17–19].

Several studies have demonstrated the negative health impacts of tobacco on systemic pathophysiological changes that can lead to disease, associated with the chemicals, heavy metals, particles, and other constituents of tobacco [20].

Smoking is one of the most important environmental factors that influence the oral microbiome. The toxic components and bacteria present in cigarettes act directly or indirectly on the oral bacterial flora through immunosuppression, oxygen deprivation, biofilm formation or other potential mechanisms, leading to the loss of beneficial oral species and the colonization of pathogens, and finally to the disease [20]. Despite different sampling sites or laboratory methodologies, certain genders have been shown to be predominant in smokers compared to non-smokers. Culture results from smokers showed lower amounts of *Neisseria or Branhamella* species [20].

Mason et al. highlighted how the microbial profiles of subgingival plaque samples from 200 systemically and periodontally healthy smokers and nonsmokers were different at all taxonomic levels. Smokers have demonstrated a highly diverse, pathogen-rich, commensal-poor, anaerobic microbiome that is more closely aligned with a disease-associated community in clinically healthy individuals, suggesting that it creates a harm-prone environment that is primed for a future ecological catastrophe [21].

Emerging studies have linked the role of the gut–brain axis among individuals with alcohol use disorder with or without alcoholic liver disease. Bacterial products penetrate the compromised intestinal barrier and cause central inflammation; changes in the intestinal microbiota impair the enterohepatic circulation of bile acids; and alcohol abuse causes the deficiency of vital nutrients such as thiamine [22].

The proper stages of the colonization and formation of the oral microbiome are critical for the development and maintenance of host health. Animal studies have been conducted where it was seen that mice lacking oral microorganisms had a higher incidence of immune disorders, indicating a dynamic correlation between them [19]. Specific microbes that help restore a healthy, natural microbiota to a given habitat are known as probiotics.

### *3.2. Oral Microbiome in Local Pathologic Conditions*

Some conditions can determine a change in the ecosystem of the oral cavity, often causing conditions predisposing to pathologies (Figure 1).

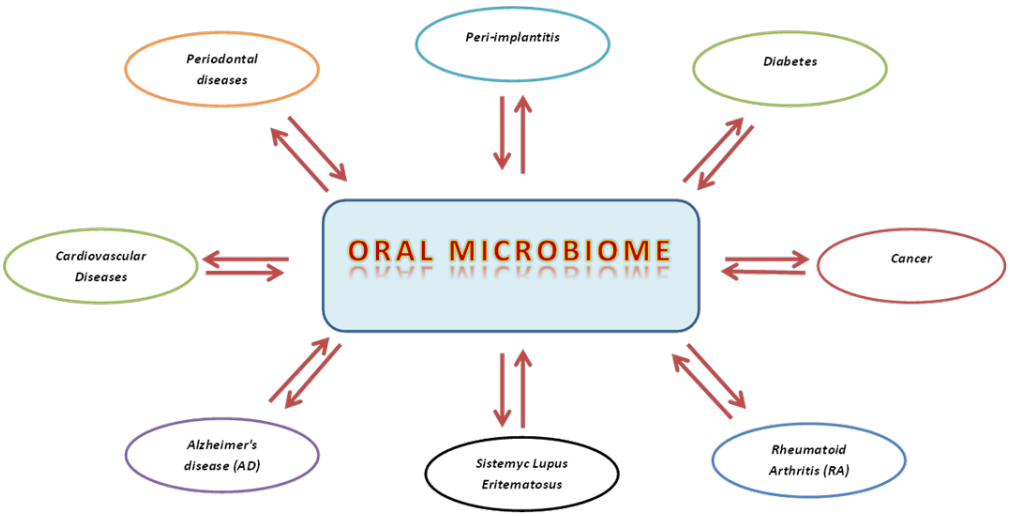


**Figure 1.** The relationship between oral microbiome and systemic diseases as described in the present review.

#### 3.2.1. Oral Microbiota in Periodontal Diseases

Poor oral hygiene, for example, is a habit that causes an accumulation of plaque, with a consequent change in the bacterial species present in the gums.

Particularly at the subgingival level, conditions of the absence of oxygen can be created, which allow for an increase in Gram-negative bacteria, such as *Prevotella* and *Selenomonas*. These bacteria are the species associated with both the production of inflammation mediators such as Il-1a, Il-1b, and crevicular lactoferrin and the clinical signs of gingivitis [20,22]. A considerable change in the composition of the subgingival bacterial species has been observed in cases of periodontitis, which has been associated with an abundant presence of *Porphyromonas Gingivalis* (*P. gengivalis*), *Treponema denticula* (*T. denticula*), and *Tannerella Forsthia* (*T. Forsthia*) belonging to the Socransky red complex [22]. The pathogenetic mechanism consists of the ability of these bacterial species to evade the host's immune defenses, leading directly, through the production of toxins, or indirectly, by inducing an inflammatory response, to tissue damage with the consequent progression of the disease [23]. As the number of bacterial species belonging to the 'red complex', i.e., the aggregate of *T. forsythia*, *P. gingivalis*, and *T. denticola*, i.e., the main bacteria responsible for periodontal disease, increases, there is a decrease in species such as *Actinomyces* spp., *Rothia* spp., and *S. sanguinis*, abundant in healthy periodontal conditions [24]. There is, however, also an increase in the microorganisms of the orange complex, consisting of *F. nucleatum*, *P. intermedia*, and *Parvimonas micra*, as well as *Actinobacillus actinomycetemcomitans*, *Campylobacter rectus*, *Eikenella corrodens*, *Bacteroides forsythus*, *Filifactor alocis*, *Peptoanaerobacter stomatitis*, *Firmicutes phylum*, *Methanobrevibacter oralis*, *Archeon phylotype Thermoplasmata*, *C. Albicans*, *Citomegalovirus* (CMV), and *Epstein–Barr Virus* (EBV) [23,24].

#### 3.2.2. Oral Microbiota in Tongue

A change in the microbiome of other areas of the oral cavity has also been reported in the literature, such as the tongue and tonsils in the case of gingivitis and periodontitis. Due to its macro- and micro-anatomical structure, the dorsum of the tongue represents a reservoir for the bacteria implicated in periodontitis, contributing to the recolonization of subgingival sites after treatment with causal therapy. It is also true that the lingual microbiome is influenced by the interdental microbiome, which has an abundance of Fusobacteria, especially *F. periodonticum* [25]. Ultimately, the microbial composition of the tongue differs significantly under pathological conditions compared to the microbiome under healthy conditions, harboring larger colonies of *F. nucleatum* ssp. *polymorphum* and *F. nucleatum* ssp. *Vincentii*, empirically emphasizing the role of the bacteria that make up the interdental microbiome in the composition of the lingual and subgingival biofilm [26].

#### 3.2.3. Oral Microbiota in Peri-Implantitis

In peri-implantitis, which is a pathology that affects dental implants, specific bacterial or microbial species of this pathology have not been identified that are not present in healthy tissues [27]. A high microbial diversity consisting mainly of aerobic Gram-positive and anaerobic Gram-negative bacteria has been observed. A high prevalence of *T. denticola*, *P. intermedia*, *C. rectus*, and *Staphylococcus warneri*, as well as *Bacteroidetes* spp., *Actinomyces* spp., and *Campylobacter* spp., was found in the peri-implant sites [28].

### *3.3. Oral Microbiome in Systemic Pathologic Conditions*

#### 3.3.1. Oral Microbiota and Diabetes

Some medical conditions are caused by an increase in inflammation in the body [29]. Some authors have pointed out that among these pathologies, the most frequent are periodontal disease, diabetes, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).

People with increased susceptibility to inflammation have an increased risk of developing periodontitis and have higher blood sugar levels, meaning a greater risk of developing SLE and RA.

The increase in inflammation in these diseases influences the oral microbiota, causing substantial changes.

Systemic diseases have a significant impact on periodontal health, and diabetes mellitus is one of the most correlated factors.

Diabetes is a metabolic disorder and can be divided into two main types: type 1 and type 2 (T1DM and T2DM) [30]. At the basis of this metabolic disorder, there is an inflammatory response; in fact, the introduction of the same bacteria into the connective tissues of diabetic animals causes a more intense inflammatory response than in controls with normal blood glucose levels [31]. Diabetes can influence several factors that contribute to increased inflammation, and this is very often found at the level of the oral microbiome and especially in the periodontal tissues. These include elevated glucose levels, the increased formation of advanced glycation end products, and the increased expression of cytokines, such as tumor necrosis factor (TNF) [30]. In diabetic patients, neutrophils and monocytes/macrophages show elevated cytokine expression in response to stimuli and are less effective at fighting bacteria [32]. Elevated blood glucose levels also affect host mesenchymal cells, such as periodontal ligament cells, osteoblasts, and osteocytes, which increase RANKL expression, resulting in a reduction in bone formation and hence loss of tooth support tissue [30].

Cause-and-effect relationships have been established, demonstrating that blocking the formation of advanced glycation end products (AGEs) reduces levels of inflammatory cytokines (including TNF), matrix metalloproteinase expression, and bone loss in the gums [33]. The various forms of diabetes, in particular T1DM, are associated with complications related to the increase in the degree of inflammation, as in the case of cardiovascular diseases, neuropathies, nephropathies, and periodontal diseases. Both types of diabetes increase the inflammatory response to the presence of bacteria [31]. This must, therefore, be

considered during dental maneuvers that could induce bacterial spread, such as extractions, endodontic treatments, and alveolar curettage [34].

The increased inflammation of the gums observed in T1DM and T2DM could be attributable to the damage caused by bacteria colonizing the tooth surface.

According to a consensus report by the European Federation of Periodontology and the American Academy of Periodontics, there is no direct evidence that diabetes directly affects the oral microbiota. In fact, it is still not clear whether the destruction of the periodontium in diabetic patients is caused exclusively by an impairment of the host immune response or if there is a change in the pathogenicity of the bacteria that leads to an increase in inflammation and damage [35].

As a result, there are still no clear conclusions from human studies examining the impact of diabetes on the oral microbiome. However, some studies have instead shown alterations in the oral microbiome in association with high blood sugar levels. For example, increases in *Capnocytophaga* levels have been observed in patients with diabetes mellitus [36], as well as increases in *P. gingivalis* and *T. forsythia* [37,38], and in *Capnocytophaga*, *Pseudomonas*, *Bergeyella*, *Sphingomonas*, *Corynebacterium*, *Propionibacterium*, and *Neisseria* in hyperglycemic subjects [39]. However, these results contradict other studies which showed that some bacterial species such as *Porphyromonas*, *Filifactor*, *Eubacterium*, *Synergistetes*, *Tannerella*, and *Treponema* decreased in diabetic patients [40].

Thus, current studies have shown conflicting results on the influence of diabetes on the oral microbiome.

Furthermore, it has been suggested that differences in the oral microbiome may be more pronounced between normoglycemic and diabetic individuals than between healthy and diseased sites within the same location [39].

The lack of a general consensus could be attributable to several reasons, such as statistical reasons based on a large number of oral microorganisms that could generate false positives, insufficient samples that could lead to false negatives, confounding factors such as the degree of hyperglycemia, duration of illness, and medication intake, technical limitations such as the lack of unbiased approaches for identifying oral bacteria, and a limited number of longitudinal studies.

#### 3.3.2. Oral Microbiota and Rheumatoid Arthritis (RA)

RA is a systemic condition of an autoimmune nature characterized by long-lasting inflammation [41]. Some pathogenetic mechanisms underlying periodontal disease share common features with those leading to the development and progression of rheumatoid arthritis. The main mechanism is the dysregulation of the inflammatory process, resulting in the destruction of bone tissue. It has also been shown that periodontitis can trigger RA through the production of enzymes that generate compounds such as malondialdehyde-acetaldehyde, citrullinated adducts, and carbamylates, which increase self-antigenicity and trigger an autoimmune response [41]. Animal studies have also been conducted, showing that, in rodents in which an inflammatory process was induced at the joint level, bone loss was observed at the level of the alveolar processes [42,43]. The use of oral antiseptics, used with the aim of lowering the amount of bacterial load in the oral cavity, has been correlated with less bone destruction related to the inflammatory processes of rheumatoid arthritis, indicating that the oral microbiome plays a role [44]. These data suggested a model involving two factors: the first represents the oral microbiota, and the second concerns the impact of systemic disease on local inflammation. RA can modify, by upregulation, the inflammatory response at the periodontal level, which in turn induces a change in the microbiota [45]. Synergistically, the chronic systemic inflammation present due to the pathogenetic mechanisms of rheumatoid arthritis may influence the levels of inflammatory cytokines in oral tissues, inducing greater disease progression [46]. In fact, it was observed that, in the oral cavity of rodents with RA, there was an increased concentration of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-17 [44]. RA patients also show increased concentrations of IL-17, TNF-α, and IL-33 in saliva, very similar to what is

observed in the case of SLE [42]. IL-17 has been associated, in several studies, with other diseases that have shown a correlation with alterations in the microbiota, as in the case of LAD-1 (leukocyte adhesion deficiency 1) and oral lichen planus [47]. There is, in rodents with rheumatoid arthritis, a change in both the qualitative and quantitative composition of the oral microbiome. In fact, higher levels of *P. micra*, *Selenomonas noxia*, and *Veionella parvula* are found in mice with RA than in the control group [42]. In the case of humans, the microbiome associated with RA shows significant differences from that of healthy subjects. Increasing in the oral microbiota of RA patients are anaerobic bacterial species, such as *Lactobacillus salivarius*, *Atopobium*, *Leptotrichia*, *Prevotella*, and *Cryptobacterium curtum*, while a decrease in oral health-associated species such as *Corynebacterium* and *Streptococcus* was observed [48].

In patients with RA who do not have periodontitis, an increase in periodontitis-related bacterial species such as *Prevotella* (e.g., *P. melaninogenenica*, *P. denticola*, *P. histicola*, *P. nigrescens*, *P. oulorum*, and *P. maculosa*) and other pathogenic species (*S. noxia*, *S. sputigena*, and *Anaeroglobus geminatus*) can be observed. In addition, subjects with rheumatoid arthritis show a significant decrease in species associated with good health (such as *Streptococcus*, *Rothia aeria*, *Kingella oralis*, *Haemophilus*, and *Actinomyces*). A number of studies have analyzed the composition of the gut microbiome in the onset stages of rheumatic disease and observed differences from the control group of healthy patients; in particular, there is a decrease in *Bifidobacterium* and *Bacteroides* and an increase in *Prevotella* [49]. Similarly, *Prevotella* species show an increase in both saliva [50] and subgingival microbiota of patients with RAL. Interestingly, *Prevotella copri* shows a strong ability to induce Th17-related cytokine production, just as *Prevotella* spp. is associated with Th17-mediated mucosal inflammation [51]. Increased inflammatory mediators in the periodontal tissues of individuals with rheumatoid arthritis and other diseases may create favorable conditions for pathogenic bacterial species and promote the onset and progression of periodontitis [52,53]. Local inflammation, amplified by systemic disease, may influence microbial composition toward an environment conducive to inflammation. The increased inflammation caused by RA, together with alterations in the microbiota, may amplify periodontal inflammation and explain the increased susceptibility to periodontitis observed by several researchers in these patients [41]. Systemic and local inflammatory changes may thus alter the microbial balance and, consequently, increase bacterial pathogenicity and susceptibility to periodontal disease. In contrast, the treatment of RA improves gum status and affects the oral microbiome [50]. Disease-modifying antirheumatic drugs reduce inflammation and RA severity by modifying the gut and oral microbiota [50].

#### 3.3.3. Oral Microbiota and Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune condition characterized by persistent inflammation that causes tissue damage in various organs, including the kidneys, lungs, joints, heart muscle, and brain. Pathogenic causes leading to the onset of SLE include genetic and environmental factors and occur due to an imbalance in microbial composition [42,54]. Regarding the oral cavity, symptoms of SLE are manifested by the occurrence of nonspecific oral ulcers [55], dry mouth, a reduction in saliva production [55], and an increased chance of developing forms of periodontal disease [56,57]. A meta-analysis in the literature showed that there is a 1.76-fold increased risk of developing periodontal disease in SLE patients [58]. This increased risk is associated with changes in the upregulation of both local and systemic inflammatory processes, as indicated by the elevated levels of cytokines (e.g., IL-6, IL-17, and IL-33) present in the saliva of patients with SLE [59]. This dysregulation of inflammatory processes has been associated with an imbalance of the biofilm present at the subgingival level in patients with SLE. These observations have been documented in human studies. However, there are currently no focused studies in the literature that are able to establish a specific link between oral microbiota disturbances, inflammatory processes, and periodontal damage in SLE patients, as is demonstrated in patients with diabetes [60]. Studies have shown that SLE patients have a higher bacterial load than healthy subjects [42], which is associated with

altered bacterial composition. High levels of *lactobacilli* and *Candida albicans* have been found in the oral cavity of SLE patients, which are present in lower amounts in healthy control patients [55]. Subjects with SLE show a reduced microbial diversity and a greater presence of potentially pathogenic bacteria [42]. Bacteria associated with periodontal disease, such as *Prevotella oulorum*, *P. nigrescens*, *P. oris*, *S noxia*, *Leptotrichia*, and *Lachnospiraceae*, occur in higher percentages in SLE patients, even in periodontally healthy areas [42]. On the other hand, bacteria commonly associated with periodontal health, such as *Capnocytophaga*, *Rothia*, *Haemophilus parainfluenzae*, and *Streptococcus*, are in a lower concentration in SLE patients who also have periodontitis. In addition, the presence of pathogenic bacteria correlates with the level of systemic inflammation, as analyzed and measured by the parameter and concentration from serum C-reactive protein [42]. Overall, the onset and development of periodontal conditions correlates with systemic inflammation [42]. Consistent with these findings, periodontal treatment appears to improve response to conventional therapy in patients with SLE by reducing disease activity and progression [61]. Increased inflammation may be a source of nutrients formed as a result of tissue breakdown processes and may alter the environment by promoting the growth of bacteria, particularly anaerobic species [62]. In turn, alterations in the microbiota could contribute to amplifying local inflammation and periodontal tissue damage, worsening the impact of systemic disease on periodontal health. Overall, these data highlight the link between microbiota and SLE, suggesting that a reduction in systemic inflammation due to SLE promotes the formation of a less pathogenic oral microbial profile. It has also been reported that changes in the gut microbiome of patients with SLE occur with greater diversity than in healthy individuals [54]. In mice with lupus, a decrease in *Lactobacilli* and an increase in *Clostridial* species (*Lachnospiraceae*) were observed, associated with an overall increase in bacterial diversity [50].

#### 3.3.4. Oral Microbiota and Cancer

The oral cavity is a unique environment within the digestive tract as it is openly exposed to the external environment. This characteristic differentiates it from other regions of the digestive tract and represents a challenge for the microbiota present in the area, as it must prevent colonization by external pathogenic microorganisms [63,64].

Dysbiosis, an imbalance of the oral microbiome, has been associated with several oral pathologies according to recent studies [64,65]. The most common and expensive chronic oral pathologies are caries and periodontitis. In addition, a link between the presence of oral dysbiosis and oral cancer has been established [66,67]. Several studies showed an association between periodontal disease and an increased risk of cancer affecting distant organs [68].

In addition, specific models of dysbiosis of the oral microbiome have been related to different types of cancer. For example, the increased colonization of *T. forsythia* and *P. gingivalis* in the oral microbiome has been associated with esophageal cancer [69], while *P. gingivalis* and *A. actinomycetemcomitans* have been linked to pancreatic cancer [70]. The genera *Fusobacterium* and *Porphyromonas* have been implicated in colorectal cancer [71,72].

#### 3.3.5. Oral Microbiota and Alzheimer's Disease (AD)

AD is the major cause of dementia worldwide and the fifth leading cause of death in people older than 65 years [73–79]. One hypothesis that has emerged is that there may be a contribution from bacteria with neuroinflammation and senile plaque formation [80]. Soluble amyloid beta peptide (Aβ) is normally produced and degraded through enzymatic mechanisms [81,82]. In AD patients, however, the brain performs insufficient degradation, leading to an accumulation of Aβ fragments [80]. Moreover, the presence of these peptides impairs the degradation mechanisms of brain cells [80]. An important role of Aβ peptides in the brain is the antimicrobial function in the case of brain infections. However, the prolonged presence of Aβ peptides, either due to recurrent infections or due to ineffectiveness in degrading them once they are no longer needed, can lead to the destruction of neighboring tissues [83]. A study by Kato et al. showed that the presence of *P. gingi-*

*valis* in mice, one of the red complex bacteria described by Socranski, increases intestinal permeability, whereby it facilitates the transfer of LPS across the intestinal barrier, fueling systemic inflammation [84]. A study by Ilievski et al. showed that the pro-inflammatory mechanism caused by the repeated application of *P. gingivalis* in mice also occurs at the brain level, causing neurodegeneration. Oral pathogens, such as the bacterium *P. gingivalis*, have been studied using human postmortem brain tissue [83]. Similarly, studies have been conducted on animal models, such as ApoE/mice and BALB/c mice that were free of pathogens, as well as on different spirochetes, which have been reported to co-localize with amyloid-beta (Aβ) plaques [80,83,84]. In addition, the dysbiosis of oral and intestinal microbiota might play a role in promoting and accelerating the formation of Aβ plaques and neurofibrillary tangles [85]. As explained above, periodontitis is a dysbiotic immunoinflammatory disease that can directly cause neuroinflammation [86–88]. Several studies support that chronic inflammation associated with periodontitis can induce changes in the gut microbiota, increasing individual inflammatory responses [89]. In addition, periodontitis has been observed to be associated with an increased risk of dementia, including AD, through mechanisms of systemic inflammation [90,91]. Another study argues that the oral microbiota may influence AD risk through systemic access to the brain of the imbalanced strains of oral microbiota and hypothesizes a possible relationship between AD neuropathology and periodontitis through this mechanism [92]. The first study considers the fact that chronic periodontitis is significantly related to an increased risk of developing AD and other age-related dementias [93]. AD patients have also been shown to have a lower diversity of microorganisms in the oral microbiota than healthy subjects, indicating a specific oral dysbiosis associated with AD. In addition, oral pathogens such as *P. gingivalis* may cause an alteration of the gut microbiota, which leads to intestinal inflammation and may be related to the onset and maintenance of neuroinflammation through the translocation of toxic bacterial proteases from the oral/intestinal environment to the brain [92,94,95]. The significant consumption of fish rich in docosahexaenoic acid (DHA) has been reported to significantly reduce the likelihood of developing Alzheimer disease (AD). In addition, a daily intake of 900 mg of DHA may provide neuroprotection during the onset of cognitive deficits associated with early stage dementia [96,97]. DHA is associated with several neuroprotective abilities, such as the inhibition of the signaling cascade between Toll-like receptors and cytokines. It has been found that lipid components of the diet can influence TLR receptor activation and associated immune and inflammatory responses. Recently, evidence has emerged linking TLR receptors to neurodegenerative conditions [98]. A recent study by Ribeiro-Vidal et al. showed that both DHA and eicosapentaenoic acid (EPA) had a significant effect on reducing harmful bacterial strains, including *P. gingivalis*, *A. actinomycetemcomitans*, *F. nucleatum*, and *Veillonella parvula*, among others [92]. In addition, several studies have been conducted on the effect of anthocyanins, a type of polyphenols, on preventing and improving specific clinical manifestations of progressive AD. A review of the literature concluded that the gut microbiota has a significant impact on the pathogenesis of AD, and that anthocyanin administration could clinically delay its development [93–96]. A study conducted in 2020 showed the neuroprotective ability of cyanidin-3-glucoside (C3G) in a mouse model of AD [96]. It is known that oral health status can influence overall health. Therefore, the prevention of oral disease and inhibition of proteases produced by bacteria such as *P. gingivalis* and other bacteria associated with periodontitis and AD may help reduce the neurodegenerative disease [97,98]. Several studies showed that the oral microbiota can easily reach the gut or lungs in people with compromised immune systems, causing systemic health problems and inflammation [8,11,98].

#### 3.3.6. Oral Microbiota and Cardiovascular Diseases

It has been observed that certain bacteria, including *P. gingivalis*, can potentially increase the risk of developing cardiovascular disease by acting on autoimmunity and in metabolic syndromes, causing alterations in the metabolism of amino acid chains and in the host immune feedback [8]. The cytokine-mediated pro-inflammatory response may

undergo upregulation by the increased *Firmicutes/Bacteroidetes* ratio; this increased response may contribute to the development and progression of cardiovascular disease [95]. Epidemiological studies reported in the literature indicate that various types of bacterial infections, such as *Helicobacter pylori*, *C. pneumoniae*, *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, and *P. intermedia*, and the presence in serum of metabolites from these products, such as lipopolysaccharides, are implicated in the development of atherosclerosis. It has also been observed that inflammatory risk factors associated with myocardial infarction have a similar profile to those involved in periodontitis, suggesting a common pathway of atherogenesis related to systemic inflammation. In addition to oral immunity, the oral microbiome also regulates and modulates the gut microbiome, which can go into dysbiosis, resulting in the disruption of the gut barrier and subsequent systemic inflammation. Studies conducted on nitrates, which are present in large amounts in food products such as meat, vegetables, particularly beets, lettuce, and spinach, and in drinking water, have led to findings showing prebiotic potential for the oral microbiota [10,98,99]. These data were derived from a study examining the cardiovascular benefits of nitrates in foods. In this study, the profiles of the bacteria that make up the oral microbiome were measured, and it was observed that in 65 hypercholesterolemic subjects who had randomly received 250 mL of nitrate-rich beet juice or a placebo juice for 6 weeks, the percentage of two nitrate-reducing bacterial species (*Rothia mucilaginosa* and *Neisseria flavenscens*) was significantly increased. These strains are themselves associated with periodontal and dental disorders. In another study, the microbiome on the tongue of subjects who were subjected to a diet of beet juice enriched in inorganic nitrate for 10 days was analyzed, and then bacterial 16S ribosomal RNA genes were sequenced. It has been observed that nitrate is converted to nitrous oxide, which induces a lowering of blood pressure [98]. Emerging data showed that an increased presence of the oral bacteria *Prevotella* and *Veillonella* is detrimental, while the bacterial strains *Rothia* and *Neisseria* play a beneficial role in the homeostatic maintenance of nitric oxide and for associated rates of cardiovascular disease, as well as improved blood pressure [98–101].

### *3.4. Clinical Considerations*

Considering what has been described, it emerged that it is very important to safeguard the commensal oral microbiome to avoid aggravating or determining local or systemic pathologies.

Antibiotic therapies for dental procedures can further alter the oral microbiome in healthy subjects, but also in those who already have other pathologies.

The most common guidelines on the management of antibiotics and oral antiseptics should be followed to prevent any serious and dangerous infections, especially after routine dental procedures [102–104].

It is very important to have your patients undergo regular check-ups to avoid the onset of periodontal and peri-implant diseases and to avoid the accumulation of bacterial plaque.

In fact, maintaining adequate control of the bacterial biofilm above and below the gums and throughout the mouth helps to avoid the formation of "ecological niches", which can act as a reservoir for pathogenic microorganisms. As highlighted in a recent review, oral hygiene must be maintained daily not only for the teeth but also for prostheses, both fixed on natural teeth and on dental implants, and removable ones [17].

It is necessary to maintain adequate hygiene even in those patients who, for reasons of disability or neurological system diseases, are not able to perform adequate oral hygiene and who may be more susceptible to infections resulting from oral pathogens [80,81,105,106].

It becomes important, especially for these patients, to consider alternative methods that can help maintain correct oral hygiene.

Numerous products have been proposed, found to influence the oral microbiome, such as ozone products and probiotics [11,107,108].

Probiotics are microorganisms, mostly *lactobacilli*, which, administered in certain quantities, confer benefits on the health of the host.

The potential application of probiotics includes the prevention and treatment of various health conditions and diseases, such as some types of infections, gastrointestinal diseases, inflammatory bowel diseases, various tumors, and a reduction in the side effects of antimicrobials. In oral health, they have been proposed for the prevention of dental caries, periodontal diseases, and halitosis problems [11,104].

The use of probiotics has been proposed as adjuvants in the therapy of periodontitis and peri-implantitis based on the dysbiotic etiology of both diseases and their effect on the modulation of host inflammation [11]. Their use can bring benefits even after long antibiotic therapies to restore good bacterial flora [11,102–104].

In recent years, studies have been conducted examining the correlation between the COVID-19 virus and the oral microbiome and the importance of adequate oral hygiene has emerged to avoid greater complications of the viral pathology [109–114].

## 4. Conclusions

This review highlights what are the intercorrelations of the oral microbiota in healthy subjects and in subjects in pathological conditions.

According to several recent studies, there is a clear correlation between dysbiosis of the oral microbiota and diseases such as diabetes, cardiovascular diseases, chronic inflammatory, and neurodegenerative diseases.

The adoption of adequate oral hygiene maneuvers could help to avoid pathologies of the mouth due to the accumulation of bacterial plaque; moreover, it must be kept in mind that the administration of systemic antibiotics, oral antiseptics, probiotics, and other products, such as those based on ozone, could influence the composition of the oral microbiome.

The use of these products must always consider these changes to make the most of only the advantages, limiting the oral microbiome in subjects suffering from systemic diseases and possibly positively influencing the prognosis of systemic diseases.

## 5. Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

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