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THE IMPACT OF ORAL MICROBIOTA ON SYSTEMIC AND ORAL HEALTH: A LITERATURE REVIEW OF RECENTLY PUBLISHED PAPERS

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Abstract: In recent years we have seen an exponential growth in scientific research aimed at characterising the structure and composition of the microbiota, which colonises various organs and systems. These investigations were supported by the development of very recent microbiological analysis techniques, most of which include molecular methods. In more recent times, however, scientific research has focused more on the study and characterization of relationships between the microbiota and systemic diseases. The purpose of this review is to present the scientific evidence, published from April 2019 to March 2020, on the relationships between oral microbiota and systemic pathologies.

Keywords: Oral microbiota, Systemic diseases, Oral diseases, Narrative Review.

INTRODUCTION

The human microbiome is the collection of microbial genomes resident in humans[1] while the term "microbiota" more precisely expresses the concept of all microbial species which make up the microbial community of a particular organ, system or biological fluid[2]. They include: skin, mammary glands, placenta, seminal fluid, uterus, ovarian follicles, lung, saliva, oral mucosa, conjunctiva, biliary tract, and gastrointestinal tract. Even if the majority of scientific reports focus exclusively on bacteria, other components of the microbiota include other kingdom members, such as: archaea, fungi, protists and viruses.

It has been known for many years that the oral cavity represents a biological niche for bacterial colonisation. As early as 2016, over 700 species had been isolated from the human oral cavity and of these over 30% were previously uncharacterised species. Subsequent studies have further confirmed these results showing that a healthy individual is capable of hosting over 300 different species in the oral cavity[3].

The oral microbiota (OM) is a unique and specialised microbial niche, based on this knowledge various scientific studies have focused on the relationship between the oral microbiota

and systemic diseases. The aim of this review is to present the scientific evidence, published from April 2019 to March 2020, on the relationships between the oral microbiota and systemic pathologies. The electronic search was performed on PubMed and retrieved 537 results, from which only 28 papers were included as reported in the flow diagram (Figure 1).

The evidence from the review was divided into four main topics:

1. Oral Microbiota and Central Nervous System Diseases;
2. Oral Microbiota and Gastro-Intestinal Diseases;
3. Oral Microbiota and Oral and Autoimmune Diseases;
4. Oral Microbiota and Oncological Diseases.

In Table 1 a summary of all the included studies is given.

ORAL MICROBIOTA AND CENTRAL NERVOUS SYSTEM DISEASES

Among central nervous system (CNS) diseases, some studies investigated the role that the oral microbiota could have in autism spectrum disorders (ASD)[4,5]. In their review, Olsen and Singhrao[4] argue that the oral microbiota can affect the brain through two main mechanisms: inflammation and metabolic alterations. The authors report that in previous studies cytokines and chemokines were found to be elevated in the cerebrospinal fluid of ASD patients. From this evidence the

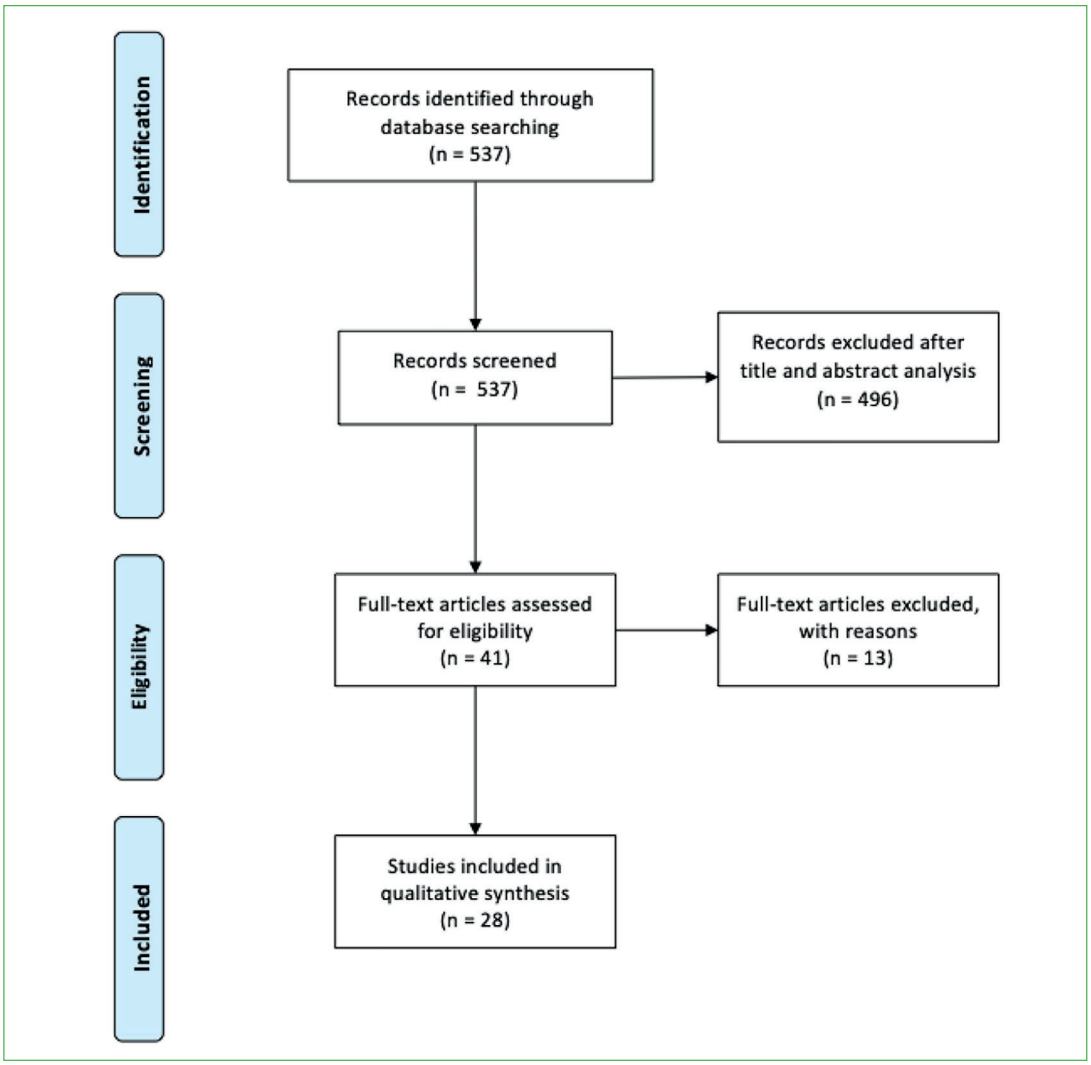

Figure 1. Flow chart of the search strategy.

authors argue that the chronic inflammatory state generated by bacterial pathogenicity factors (especially LPS) can alter the functioning of the synapses and the activity of the microglia, critical elements for the generation and progression of ASDs[4]. Regarding the metabolic alterations there are also evidence that increased levels of acetate and propionate, as well as decreased levels in butyrate are involved in the development of ASD; in fact, a study of oral microbe transcription that enrolled 346 children (among them 180 had ASD) identified ASD-specific changes in pathways involving lysine degradation. Lysine is a precursor to the neurotransmitter glutamate that has been identified as a key factor in ASD pathogenesis as well as the abovementioned acetate, propionate and butyrate[6]. Some additional information was added by Kong et al[8] that, in their article, detected differences in both gut and oral microbiota between ASD and control subjects. In fact they confirmed the results reported in previous reports about the amounts of *Bacilli* in gut microbiota of subjects with ASD, which is expected to be higher than controls[7]. The hypothesis of the authors is that the overgrowth of *Bacilli* in the oral cavity could be connected with the same dysbiosis in the gut thus favouring the onset of the ASD.

In contrast to the situation with ASD, further studies are needed to better investigate the relationship between oral microbiota and Parkinson's disease as the unique paper published in the time-frame of the present review found that levels of *Lactobacillus reuteri* were higher in subjects with Parkinson's disease compared with controls; this evidence seems to potentially counter-intuitive as multiple other studies have demonstrated a strong beneficial role of this bacterium[9].

TABLE 1. SUMMARY OF ALL INCLUDED STUDIES. EVERY FIRST AUTHOR OF THE INCLUDED STUDIES IS GIVEN ALONG WITH THE MAIN AND SPECIFIC TOPIC ON WHICH ITS RESEARCH FOCUSED.

First Author	Main Topic	Specific topic
Olsen I[4]	Central nervous system diseases	Autism spectrum disorders
Kong X[8]	Central nervous system diseases	Autism spectrum disorders
Mihaila D[9]	Central nervous system diseases	Parkinson's disease
Zhang Y[13]	Gastro-intestinal diseases	Various types of gastro-intestinal cancer
Iwauchi M[10]	Gastro-intestinal diseases	Gut microbiota dysbiosis
Mameli C[12]	Gastro-intestinal diseases	Obesity
Komiya[14]	Gastro-intestinal diseases	Colorectal cancer
Wang Q[15]	Gastro-intestinal diseases	Oesophageal squamous cell carcinoma
Kageyama S[16]	Gastro-intestinal diseases	Various types of gastro-intestinal cancer
Ji Y[11]	Gastro-intestinal diseases	Helicobacter pylori infection
Tong[27]	Oral and autoimmune diseases	Rheumatoid arthritis
Stehlikova Z[23]	Oral and autoimmune diseases	Recurrent aphthous stomatitis
Wang Y[17]	Oral and autoimmune diseases	Early childhood caries
Grevich S[28]	Oral and autoimmune diseases	Rheumatoid arthritis
Liu Y[21]	Oral and autoimmune diseases	Cheilitis granulomatosa
Lundmark A[20]	Oral and autoimmune diseases	Oral and Autoimmune Diseases
Li Y[25]	Oral and autoimmune diseases	Oral lichen planus
Decsi G[22]	Oral and autoimmune diseases	Oral potentially malignant disorders
Sembler-Møller ML[24]	Oral and autoimmune diseases	Sjögren Syndrome
Vieira AR[18]	Oral and Autoimmune Diseases	Caries
Kazemtabrizi A[19]	Oral and Autoimmune Diseases	Caries
Carvalho MFMS[26]	Oral and Autoimmune Diseases	Oral lichen planus
Correa JD[29]	Oral and Autoimmune Diseases	Rheumatoid arthritis
Zhang Z[31]	Oncological Diseases	Oral squamous cell carcinoma
Gruffaz M[32]	Oncological Diseases	Kaposi's sarcoma
Zhang L[30]	Oncological Diseases	Oral squamous cell carcinoma
Wang L[33]	Oncological Diseases	Throat cancer

ORAL MICROBIOTA AND GASTRO-INTESTINAL DISEASES

A line of research that has sparked particular interest over the past year is the ability of some bacterial species to migrate from the oral to the gastrointestinal region. Iwauchi et al[10] investigated this phenomena by enrolling two groups of patients: 29 elderly subjects (age, 80.2 ± 9.1 years) and 30 younger adults (age, 35.9 ± 5.0 years) and analysing oral samples from sub-gingival plaque and tongue-coating and faecal samples. The results of their analysis revealed that bacteria found in oral samples were higher in prevalence in the faeces of the elderly group than the young adult group. Thus confirming the hypothesis of bacterial translocation between different niches and giving more confidence in all interventions aimed at the preservation of oral health in the elderly as they could result in an improvement in general health[10].

On the other hand research that have focused on the capacity of oral cavity to be a reservoir for *Helicobacter pylori* reflux from the stomach have been less convincing. Ji et al[11] showed that *H. pylori* was present commonly in the oral cavity with no clear relation to *H. pylori* infection of the stomach; the same article, however, demonstrated that *H. pylori* eradication therapy seems to be effective both against bacterial colonies residing in oral cavity and in gut.

Only limited evidence has been reported regarding the relationship between the oral microbiota and obesity; a study by Mameli et al[12] investigated a population made up of children and adolescents. The authors of this paper succeeded in demonstrating significant differences in the salivary microbial diversity between subjects with obesity and normal-weight ones. In particular the largest difference was seen at class level for Gammaproteobacteria and Negativicutes, accounting for the 9% in controls and 6% in cases of the total number.

Research on the relationship between oral microbiota and gastrointestinal cancer has been much more productive with several publications on the topic.

First of all, a review of the literature has helped to outline the possible roles of the oral microbiota in gastrointestinal cancer and the mechanisms by which this relationship can be accomplished. The authors identified them as: chronic inflammation that would cause cancer progression; inhibition of the immune response that would protect cancer cells from defensive immune reactions against them and interference with signaling pathways and the local metabolism of carcinogens that would jointly promote carcinogenesis[13].

Komiya et al[14] focused their attention on the colonization of specific pathogens in colorectal cancer (CRC). In fact, from their study more than 40% of patients suffering from CRC were found to exhibit identical strains of *Fusobacterium nucleatum* in their CRC tissue and saliva samples. This interesting finding sustains the theory that *F. nucleatum* in CRC could originate from the oral cavity. However, the number of patients enrolled is very low so further studies are needed in the field.

Contrasting findings about the role of *F. nucleatum* as risk factor for oncological diseases were highlighted by Wang et al[15]. In a sample of 20 patients suffering from oesophageal squamous cell carcinoma (ESCC) and 21 healthy controls, metagenomic analysis of saliva samples (presenting results at genus level) were conducted and it was found that the high risk of ESCC may be related to *Actinomyces* and *Atopobium*, while *Fusobacterium* and *Porphyromonas* were found in higher concentrations in healthy control group.

The case-control study of Kageyama et al[16] mapped bacterial colonization profiles across the digestive tract of cancer patients by 16S ribosomal RNA gene sequencing. They reported a higher concentration of *F. nucleatum, Porphyromonas gingivalis, Streptococcus sanguinis, Streptococcus parasanguinis I, Streptococcus parasanguinis II, Neisseria spp.* and *Corynebacterium spp.* in salivary specimens of patients suffering from tongue or pharyngeal cancer when compared with healthy subjects. *P. gingivalis, Corynebacterium spp.* and *F. nucleatum* were also higher in oesophageal cancer whereas *P. gingivalis* and *Neisseria spp.* were higher in gastric cancer. In samples from CRC, colonies of *Actynomices odontolyticus, Corynebacterium spp., Neisseria spp., TM7* and *P. gingivalis* were more represented compared to control patients.

ORAL MICROBIOTA AND AUTOIMMUNE AND ORAL DISEASES

The relationship between microbiota and pathologies of the stomatognathic system has been the subject of numerous studies for several years; the aspect that has radically changed in recent years is the use of molecular analysis techniques that have made it possible to characterize the bacterial species involved in diseases with greater specificity. Some studies have analyzed the oral microbiota related to caries, both in adults and in children (known as the Early Childhood Caries - ECC). Wang et al[17] investigated the microbiota of salivary samples of 25 preschool children, affected by severe ECC, and 19 age-matched caries-free children as controls. The authors found higher prevalence of *Prevotella amnii, Shuttleworthia satelles, Olsenella uli,* and *Anaeroglobus geminatus* in the group of children affected by ECC. Adjunctive metabolic analyses highlighted that all bacteria that colonize oral cavities of the ECC group of children demonstrated increased sugar metabolism capability. Vieira et al[18] gave other contributions to the subject by designing a study similar to the one mentioned above but defined *Bacteroides thetaiotaomicron* and *Rothia mucilaginosa* as the most abundant species in children with ECC; while *Staphylococcus epidermidis* was found to be prevalent in the control group of caries-free children. Oral microbiota impact on caries was also investigated through the analysis of carious dentin lesions, biofilm and root canal samples of 30 adult subjects. The study showed that *Prevotella spp.* and *Streptococcus spp.* play a key role in carious dentin and biofilm samples also in adult patients, respectively whereas the higher abundance of bacteria in root lesions was found to belong to *Lactobacillus vaginalis*[19].

The influence of the oral microbiota on chronic periodontal disease was investigated in salivary samples by Lundmark et al[20] According to the findings, a large amount of bacteria, such as: *Eubacterium saphenum, Tannerella forsythia, Filifactor alocis, Streptococcus mitis/ parasanguinis, Parvimonas micra, Prevotella spp., Phocaeicola spp.* and *Fretibacterium spp.* were more present in subject affected by periodontitis compared with healthy controls. In contrast, species more abundant in healthy patients were *Campylobacter concisus* and *Veillonella spp*.

The research group of Liu et al[21] carried out a clinical control trial with the aim of evaluating the role of bacteria in the genesis of Cheilitis granulomatosa (CG), an inflammatory disease of the lips. Saliva samples from 15 patients affected by GC and from as many healthy controls were collected. Analysis revealed that CG patients are colonized by a particular microbiota in which there is a higher abundance of: *Prevotella, Alloprevotella, Porphyromonas, Actinomyces, Rothia, Fusobacterium, Haemophilus,* and *Aggregatibacter*. On the other hand *Streptococcus* and *Campylobacter* were found to be more abundant in healthy controls.

A case-control pilot study assessing the oral microbiota located on oral mucosa of potentially malignant disorders (PMD) revealed that *F. nucleatum* was present in higher abundance in samples taken from PMD areas whereas *Streptococcus mitis* seems to be more concentrated in healthy mucosal sites[22]. In the timeframe of the review only one study was carried out assessing the influence of the oral microbiota on recurrent aphthous stomatitis (RAS). In recent years, RAS has been associated with bacterial and fungal dysbiosis. In order to better evaluate this association the authors investigated eventual microbial communities changes during RAS manifestation in three sites (an ulcerated lesion, its surroundings and an unaffected site) and compared them with healed mucosa in RAS patients and healthy controls for a total of five sample sites per patient. Bacteria belonging to the genus *Selenomonas* were found to have higher prevalence in areas of healed mucosa of RAS patients; on the other hand genera *Lachnoanaerobaculum, Cardiobacterium, Leptotrichia* and *Fusobacterium* were found to be prevalent in active ulcer areas. Thus, this study clearly demonstrated that changes in the oral microbiota connected with ulcer generation could persist even when the ulcer is healed[23].

Scientific research about autoimmune disorders and oral microbiota mainly focused on Oral Lichen Planus (OLP), Sjögren Syndrome (SS) and rheumatoid arthritis (RA).

Evidence drawn by the analysis of salivary oral microbiota in SS patients reported no differences between SS-affected and healthy control patients[24]; however further research is needed to better evaluate this aspect since the number of enrolled patients was low.

Relating to OLP, the authors' search retrieved two results. A case-control study published by Li et al[25] analysed the salivary oral microbiota of patients affected by reticular and erosive OLP comparing it with healthy patients. In reticular OLP the authors found a higher concentration of the fungi *Candida* and *Aspergillus* whereas higher abundance of *Alternaria* and *Sclerotiniaceae* were identified in erosive OLP when compared to healthy subjects.

The publication of Marques Silva de Carvalho et al[26] provided more information although the study reported on a very small sample size, only 4 samples. Patients were enrolled if they suffered from OLP or from oral non-specific inflammatory lesions (NSIL). A higher abundance of *Firmicutes*, *Actinobacteria*, *Campylobacter rectus, F. nucleatum* and *Neisseria mucosa* were found in OLP group whereas *Proteobacteria* were found to be more prevalent in the NSIL group. In the same group, also a greater abundance of *Haemophilus parahaemolyticus, Haemophilus parainfluenza, Neisseria oralis, Streptococcus oralis, Streptococcus salivarius and Streptococcus sanguinis* was retrieved.

The impact of oral microbiota on the onset of RA was investigated in three different studies. Tong et al[27] analysed salivary samples of 79 patients; among them 29 were defined as at risk of developing RA [since they were positive for anti-citrullinated protein antibodies (ACPA)] but without clinical signs of arthritis, 27 were suffering from RA and 23 were healthy controls. Metagenomic analysis revealed no major changes are detectable when comparing the oral microbiota of RA patients and healthy controls. In contrast, statistically significant differences were seen when comparing individual at risk against controls. Patients with risk factors for RA showed a higher abundance of several *Prevotella spp.*, although *P. gingivalis* was decreased. The evidence from this study seems to suggest that oral microbiota dysbiosis occurs only in the "pre-onset" stage of RA. Contrasting findings were presented by Grevich et al[28] who studied the oral microbiota in subjects affected by juvenile idiopathic arthritis (JIA). Subgingival plaque analysis taken from JIA patients and healthy subjects showed that JIA patients seem to be more easily colonized by *Prevotella, Porphyromonas, Haemophilus* and *Kingella* whereas a low concentration of *Corynebacterium spp.* was found. The findings are in line with the scientific literature reports of recent years that recognized *P. gingivalis* as one of the most important oral pathogens associated with the onset of RA and JIA. The report of Correa et al[29] added further evidence to this topic asserting that *Fretibacterium fastidiosum, Parvimonas micra* and *Anaeroglobus geminatus* are also more frequently found in the oral cavity of RA patients.

ORAL MICROBIOTA AND ONCOLOGICAL DISEASES

The most studied oncological diseases, with the aim outlining their relationship with the oral microbiota, were: oral squamous cell carcinoma (OSCC), Kaposi's sarcoma (KS) and throat cancer.

The hypothetical role of oral microbiota in the onset and progression of OSCC was investigated in oral biopsies of 50 patients comparing oral microbiota composition between tumour sites and adjacent normal tissues in the buccal mucosa. A higher incidence of *F. nucleatum, Prevotella intermedia, Aggregatibacter segnis, Capnocytophaga leadbetteri* and *Peptostreptococcus stomatis* was revealed in the tumour sites suggesting that such species could play a key role in OSCC pathogenesis[30]. Another study, that limited bacterial identification to genus level, conducted a differential analysis between microbiota of cancer tissues, saliva and patients' mouthwashes. The results demonstrated that diversity and richness of microbes of cancer tissues were lower than in saliva and mouthwashes samples. In tissue samples *Acinetobacter spp.* and *Fusobacterium spp.* were predominant whereas *Streptococcus spp.* and *Prevotella spp.* were the major species in saliva and mouthwashes respectively[31].

The relationship between oral microbiota and KS was evaluated by Gruffaz et al[32] through metagenomic analysis of KS lesions and blood specimens. In this study specimens were collected from a cohort of 9 patients HIV infected and suffering from KS, from a cohort of 10 patients without oral KS but infected by Kaposi's Sarcoma Herpes-Virus (KSHV), or from a cohort of 10 patients with neither oral KS nor KSHV infection. No major differences were found between patients with or without clinical manifestations of KS in terms of bacterial diversity but individuals affected by KS were found to have less bacterial communities than patients unaffected.

Similar metagenomic analysis of the previous report was made by Wang et al[33] for the analysis of oral microbiota in patients suffering from throat cancer. Salivary samples from 32 patients suffering from throat cancer and from 29 healthy individuals were evaluated and clearly demonstrated a difference between the compositions of bacterial communities between the 2 groups. Patients affected by cancer were significantly more likely to be colonized by *Aggregatibacter, Pseudomonas, Bacteroides,* and *Ruminiclostridium* when compared with unaffected subjects, thus sustaining the hypothesis that a specific microbiota could be connected with the risk of throat cancer onset.

CONCLUSIONS

During the past year a large amount of scientific studies have been produced with the aim of increasing the knowledge on the relationship between the oral microbiota and oral/systemic health. The advent of molecular analysis methods has made possible to adequately standardize the procedures and, therefore, to effectively compare the results. It is important to note, however, that some studies are still characterized by small samples, some methodological bias and that sometimes they report contrasting evidence. It is therefore necessary to implement the share of studies on this topic in order to further contribute to its knowledge as it is of crucial importance for the maintenance of both oral and systemic health of patients.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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